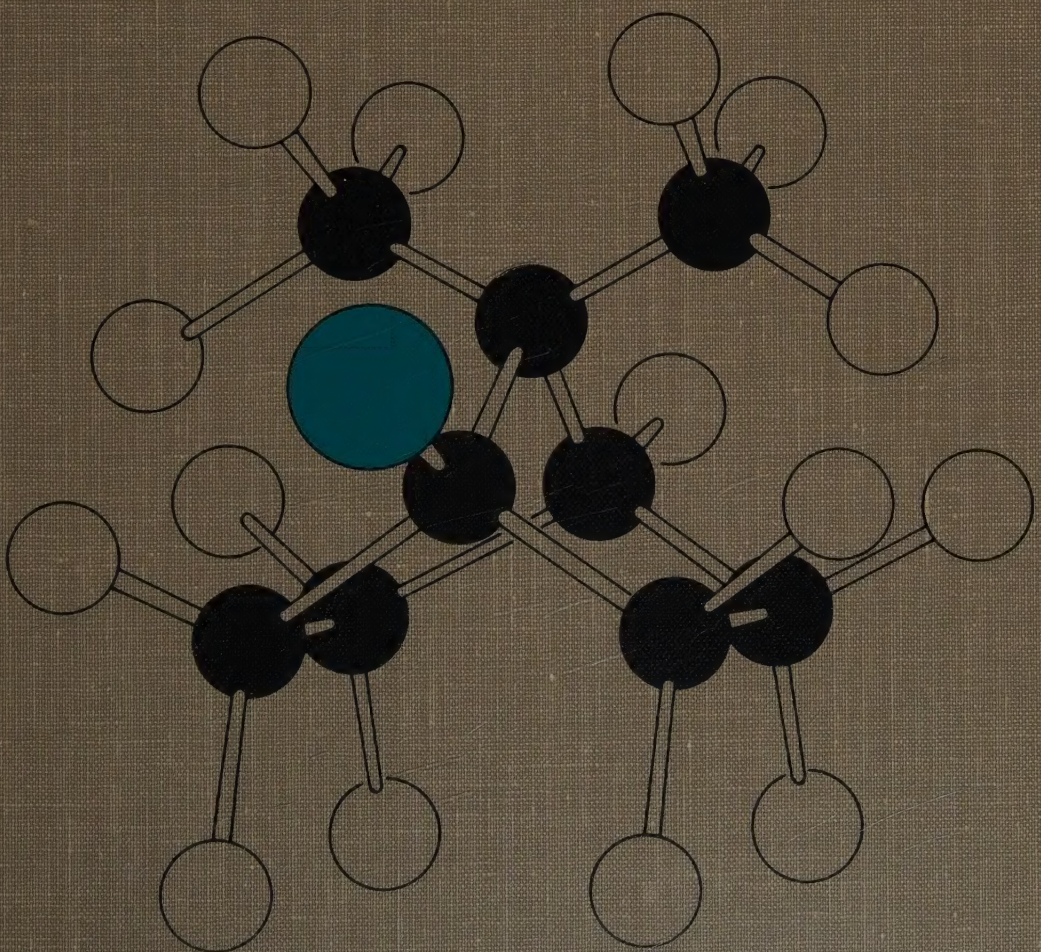
FOURTH EDITION

PRINCIPLES OF Organic Chemistry

T. A. Geissman



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Preface

This revision of *Principles of Organic Chemistry* is designed to meet what I believe are the changing needs of instruction in the modern one-year college or university course in organic chemistry. The last decade has seen some pronounced changes in the teaching of the subject. It was not long ago that many universities offered two kinds of courses: a rigorous two-semester or three-quarter course for students majoring in chemistry, and a less intensive and usually abbreviated course for students in the biological and medical sciences.

It is becoming increasingly apparent that the educational needs of students in the life sciences can no longer be met by the kind of organic chemistry courses that once fulfilled their curricular requirements. The growing sophistication of modern instruction in biology, with its emphasis upon the details of processes at the molecular level, requires a background in organic chemistry that consists of more than a descriptive presentation of the subject. A thorough understanding of the chemical events in biological systems now requires the student to pursue a course of study in organic chemistry that possesses much of the rigor of the traditional course for chemistry majors. That this is now recognized is shown by the increasing proportion of biology majors in regular one-year organic chemistry courses.

At the same time, students whose professional activities will lie within the area described as organic chemistry are faced with new developments and departures in the field. In recent years there have been many new and important developments in the chemistry of living organisms and of biologically active substances. Many of these are the products of the research of organic chemists, most of whom have been led by their work into realms that are as much biological chemistry as organic chemistry. Indeed, such terms as "bioorganic chemistry" and "molecular biology" are applied to fields of study in which expertise in both chemistry and biology is essential.

These considerations have led to this revision, in which the biological aspects of organic chemistry and the organic chemistry of biological transformations have been combined in a textbook that, it is hoped, will serve the educational needs of students of both biological and physical sciences. Although distinctions can be seen between the extremes of these, there can be no doubt that the middle ground is expanding, and that what was once a discrete interface between biological and organic chemistry is rapidly losing its definition.

This book is nevertheless a textbook of organic, not "bio-organic," chemistry. It presents the subject as a blend of theory and experimental observation, describing organic reactions as expressions of the properties and characteristic behavior of functional groups. But such general concepts as the making and breaking of chemical bonds, the theory of acid-base reactions, stereochemical relationships, the recognition of the reactive sites of organic compounds, and so on are as much within the province of biochemistry as of organic chemistry; and many of the principles of organic chemical reactivity can be illustrated by examples drawn from the realm of biological chemistry as well as—and often better than—by the more abstract examples drawn from classical organic chemistry.

The use and interpretation of physical data are again emphasized. The widespread use of modern spectroscopic instrumentation in undergraduate laboratories requires that the beginning student be instructed in the principles and practice of ultraviolet, infrared, nuclear magnetic resonance, and mass spectrometry. These techniques are discussed in their own chapters, but frequent references are made throughout the text to such physical data as they reflect and explain chemical properties and reactivity.

The application of chemical and physical evidence and degradative and synthetic procedures to the determination of the structures of organic compounds is presented in a separate chapter. This is the last chapter in the book because the structural study of even a simple compound usually requires the chemist to bring to bear knowledge of many aspects of physical and chemical properties. The instructor may wish to use this chapter by assigning for study those separate examples that are especially relevant to one or another of the earlier chapters. For example, the chemistry of the simple terpenes, ocimene and myrcene, could be studied in connection with the chemistry of olefinic compounds; of shikimic acid with carbohydrates; and of nicotine with amines or heterocyclic compounds. It did not seem advisable to make these associations

in the text, for no one of the compounds described represents solely one class of functionality.

This revision has not been greatly expanded in size, for it is not intended to be encyclopedic or even to cover everything that the graduate in chemistry is expected to know about organic chemistry. Certain theoretical topics are dealt with briefly or omitted, chiefly because the chemistry major will encounter them in further courses for which this one-year course serves as a foundation and prerequisite; the student of the life sciences will find more valuable those topics that have been added. Moreover, students should be encouraged to do additional reading, and there are available for this purpose reference works, excellent monographic paperbacks, and the limitless literature of the periodical journals.

Finally, a word about the content and organization of this book. Although it is generally agreed that the presentation of a subject should proceed in a progressive and cumulative manner, so that topics discussed early in the book provide a basis for a rational development, there are certain topics so essential to the understanding of organic chemistry that they must be introduced even before the student has the background to master them fully. Three such topics are stereochemistry, the concepts of which pervade the entire field; the energy relationships embodied in reaction rate and equilibrium; and "resonance," or charge delocalization. It will be obvious to the teacher of organic chemistry that to introduce these at an early point requires the use of specific examples of compound classes that the student may not find familiar. There is, however, no reason why these earlier chapters cannot be referred to when their content is again relevant. In the same way, it is seldom possible to discuss a compound class in isolation from others. For example, the preparation of olefins necessarily involves a discussion of alcohols; esters and saponification could be introduced either along with the chemistry of alcohols or later, with carboxylic acids. The choice of the sequence of topics is entirely by the preference of the author, but it is not ineluctable. If the user of the book prefers to present the chemistry of alcohols before that of olefins, there is no reason why chapter study assignments cannot be altered. A later chapter is not necessarily more complex or difficult of comprehension than an early one.

For these reasons there is necessarily—and advisedly—some duplication to be found throughout the text. The student studying a given chapter cannot be expected to recall everything contained in the chapters preceding it, and a recapitulation of a topic or the rewriting of a structural formula will be both an aid to the student's understanding and a concession to his natural reluctance to interrupt his thoughts to search the Index or an earlier chapter to refresh his memory.

On the other hand, in some of the textual material and in some of the Problems and Exercises compounds are given by name only. In certain cases the formulas for these compounds are not to be found in the chapter or section where the names appear, or even not in the book at all. This is done purposely: it is hoped that it will encourage the student to have frequent recourse to the library and to become familiar with the

reference books (and eventually with the monographic and periodical literature) that are there for him to use.

There are three reference works that are unexcelled for ready information about names, structures, and properties of organic compounds, and that will be found in most chemistry libraries:

Dictionary of Organic Compounds, 4th edition. Edited by I. Heilbron. Oxford University Press, New York. 1963.

Chemistry of Carbon Compounds, 2nd edition. Edited by E. H. Rodd and S. Coffey. Elsevier, New York. 1964, continuing.

Merck Index, 8th edition. Merck & Company, Rahway, New Jersey. 1968.

Answers to selected problems are provided in an appendix.

Los Angeles, California
1 March 1976 *T. A. Geissman*

PRINCIPLES OF

Organic Chemistry

1

Introduction. Characteristics of organic compounds

It is well for a student of any organized discipline of learning to become aware of its origins and its evolution into modern form, for this will enlarge his perspective and permit him to appreciate the facts and theories he encounters in his study as the end products of decades or even centuries of inquiry and debate.

Organic chemistry is an experimental science: its theories have grown out of experimental observations and have been tested and verified by experimental means. It is not an empirical science but it is in large measure a pragmatic one, and resorts finally to the observed behavior of discrete substances. For this reason, this chapter dwells at some length upon the general properties of organic compounds, upon the ways in which they are purified and analyzed, and upon the early stages of their experimental manipulation.

Sections 1-12 and following deal with the specific analytical procedures that are universally employed by organic chemists. These basic procedures have in recent times been augmented by sophisticated methods of physical measurement, but they have not been superseded by modern instrumentation. The student is urged to cultivate an attitude of recognition that he is always dealing with actual substances, and that their physical properties and elementary composition are not simply pieces of numerical data, but represent information that is fundamental to the development of his understanding of their chemical behavior.

1-1 What is organic chemistry?

With the rapid growth of the science of chemistry in the past half-century has come its separation into a number of special areas: physical chemistry, analytical chemistry, biological chemistry, organic chemistry, and others. These areas are not mutually exclusive, for each permeates the others; yet each is characterized by the emphasis that is placed upon it, by some special approach in the techniques utilized, or by the kinds of compounds that are dealt with. *Organic chemistry* deals with the chemical compounds of carbon, and principally with compounds in which carbon is combined with hydrogen, oxygen, nitrogen, sulfur, and the halogens. It is a special area of chemistry because of the enormous number of carbon compounds—over a million are known, and the number is increasing at the rate of about five percent per year. More than ninety percent of these are synthetic substances, the remainder having been isolated from living organisms (animals, plants, fungi, microorganisms) and their fossil remains (coal, petroleum).

The *naturally occurring* organic compounds are of concern to the biochemist as well as to the organic chemist, and indeed it is in dealing with such substances that biochemistry and organic chemistry come together and lose their individual identity. The naturally occurring compounds include the proteins, fats, carbohydrates, vitamins, and hormones that compose living cells; many of the drugs used to control disease and relieve suffering; the perfumes and colors of the plant world; and thousands of other substances that participate in the metabolic activities of living things.

The *synthetic* organic compounds are derived largely from natural sources of carbon—coal and petroleum—but are the products of man's voluntary ingenuity rather than of the involuntary activities of living organisms. There is no limit to the number of organic compounds that can be made, and indeed the known synthetic compounds include many naturally occurring compounds that have been prepared synthetically as final confirmation of their structures. The only *kinds* of compounds that have so far resisted the attack of the synthetic organic chemist are the complex carbohydrates, the nucleic acids, and the complex combinations of these that make up the essential stuff of the living cell. Although the complete synthesis of only a few substances identical in structure and function with these natural materials has been accomplished, further achievement will surely come in time. It is to the new generations of scientists who will pursue these goals that this book is addressed, in the hope that it will help to impart that basic understanding of the scientific principles of organic chemistry that must underlie future progress in both chemistry and biology.

1-2 The development of organic chemistry

The scientific revolution of the sixteenth and seventeenth centuries was characterized by the birth of a spirit of inquiry and skepticism that marked a new phase of the

intellectual development of mankind. The influence of this spirit upon chemistry was felt at a time when alchemy had given way to the application of chemistry to medicine, and the dominance of an earlier mysticism was crumbling. The new approach to chemistry was the experimental attack, and through its chief proponent, Robert Boyle (1627–1691), this new philosophy gave to chemistry the status of an independent science. The chemists of the seventeenth and eighteenth centuries soon began the task of systematizing the growing body of empirical facts that their experiments revealed, and began to create generalizations into which numbers of facts could be grouped. The early theories and much of the work devoted to their study did a great deal to define the area of intellectual activity that is the science of chemistry, and thus to attract to these new studies the attention of men of an inquiring turn of mind.

Toward the end of the eighteenth century chemists began to turn to the examination of living organisms, and a great many compounds were isolated from plant and animal sources. Plants had been used in medicine since ancient times, and enlargement of interest in chemistry led in the first years of the nineteenth century to the study of plants of medicinal importance and to the isolation in crystalline form of such complex substances as strychnine ($C_{21}H_{22}O_2N_2$), quinine ($C_{20}H_{24}O_2N_2$), and morphine ($C_{17}H_{19}O_3N$), the structures of which were to remain unknown for another hundred years.

A bar to progress during these early stages of what was known as "organic" chemistry was the persistent belief that compounds formed in living organisms had properties, and owed their formation to laws, that set them apart from compounds of inanimate origins. This doctrine of a *vital force* persisted through the first quarter of the nineteenth century. It can be readily understood how such a belief could prevent the development of a rational theory. It could not, however, prevent the progress of experimental studies, and important developments took place, starting with Lavoisier's (1743–1794) recognition of the fact that organic compounds could be burned, and that by weighing the products of the combustion accurately it was possible to determine the *composition* of a compound. Lavoisier had at his disposal only a limited number of compounds, most of them from vegetable sources, so his experiments led him to believe that organic compounds were composed of carbon, hydrogen, and oxygen. His contemporaries and followers soon discovered the presence of nitrogen, sulfur, and phosphorus in organic compounds of animal origin, yet before long it was realized that there is no sharp distinction between organic substances that is based upon their origin. The importance of Lavoisier's contribution was that it introduced the *quantitative* element into the study of chemistry, and it so influenced further development of the subject that his work marks a real chemical revolution and can be regarded as the beginning of the modern science.

An important early discovery was that of Wöhler (1800–1882), who in 1828 found that urea, an organic substance that derives its name from urine, in which it is found, could be prepared by heating the "inorganic" compound ammonium cyanate:

$$\underset{\text{Ammonium cyanate}}{NH_4NCO} \rightleftharpoons \underset{\text{Urea}}{NH_2CONH_2}$$

Wöhler's discovery did not immediately demolish vitalism, but the disintegration of that enervating doctrine continued from that time on, with the increasing number of syntheses of other organic compounds from inorganic materials.

1-3 The introduction of analytical methods

Developed chiefly by Gay-Lussac (1778–1850) and Liebig (1803–1873), quantitative analysis of organic compounds by combustion became a powerful tool for the discovery of many new facts. By 1830, improvements in the methods of determining the carbon and hydrogen content of organic compounds, as well as the analytical method for nitrogen (Dumas, 1800–1884), had made it possible to ascertain the composition of these substances with a high degree of accuracy. From then on, the development of organic chemistry proceeded with amazing rapidity. In less than fifty years thousands of new compounds were discovered and synthesized; an enormous chemical industry developed in Europe; and there evolved a valid structural theory, which survives to the present day.

Thus we have seen how the scientific revolution of the seventeenth century set mankind on the road of free inquiry; how Lavoisier's chemical revolution a century later established the importance of accurate quantitative observations; and how, another century later, chemistry was at last firmly based on experimental method and the beginnings of theory. The stage was now set for the twentieth-century discoveries on the nature of atoms and molecules and the forces that bind them together, and for the growth of the modern theories of organic chemistry around which this book is constructed.

1-4 Isomerism and the concept of structure

One of the most important discoveries that resulted from the development of accurate quantitative analysis of organic compounds was that it is possible for two or more compounds to have identical chemical *composition*, yet to be quite different in their chemical and physical properties. Liebig found that both silver cyanate and silver fulminate, two quite distinct substances, have the composition AgCNO. Wöhler observed that both ammonium cyanate and urea were represented by the formula CH_4N_2O, and in 1828 he discovered that ammonium cyanate could be converted into urea simply by heating it. Up to this time it had been regarded as self-evident that substances of the same compositon were identical. The observations of Liebig and Wöhler were soon followed by others, and the Swedish chemist Berzelius (1779–1848)

proposed the term *isomerism* for the relationship between two substances with different properties but identical composition. Since then these criteria have been refined by the concept of molecular weight, so that we now define isomers as *compounds having different properties but identical molecular formulas.*

The recognition of isomerism was the first step toward the solution of the problem of the molecular structure of organic compounds. Berzelius recognized that isomerism could be explained only by supposing that the relative positions of the atoms in isomeric compounds must be different. The *fact* of difference—the experimental observations of composition and chemical behavior—led to the question of the *reason* for the difference, and thus the concept of isomerism has within it the concept of structure.

1-5 Molecular and structural formulas

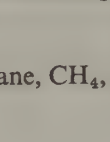
It will be seen that the molecular formula of a compound does not define either its chemical properties or the class to which it belongs. As simple a molecular formula as C_2H_6O represents two quite different compounds: ethyl alcohol (C_2H_5OH) and dimethyl ether (CH_3OCH_3). Three quite different compounds are represented by C_3H_8O, and $C_4H_{10}O$ is the molecular formula for seven compounds.

It is evident that even though carbon, hydrogen, and oxygen atoms possess definite and invariable combining powers, there can be more than one way in which a certain number of these atoms can be joined together; but there cannot be an unlimited number of ways. There exists, for example, only one compound CH_4O, only one C_2H_6, one CH_2O, one $C_2H_2O_2$, and one $C_2H_2O_4$. But as the number of carbon atoms increases, the number of isomers increases rapidly, as the examples in the preceding paragraph have shown.

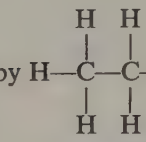
The problem that confronted the chemists of Liebig's time was to express the constitution of organic compounds in terms of their internal nature and to devise formulas that not only clearly distinguished isomers but suggested the chemical differences between them. One of the earliest observations contributing to the solution of this problem was made in 1832 by Liebig and Wöhler, who showed that there exist certain groups of atoms that behave as unchanging units when passing through a series of chemical transformations. The compound benzaldehyde, C_7H_6O, was converted to benzoic acid, $C_7H_6O_2$, and this in turn was transformed into benzoyl chloride, C_7H_5OCl, benzamide, C_7H_7ON, and methyl benzoate, $C_8H_8O_2$. All of these compounds can be regarded as consisting of the group of atoms C_7H_5O, called the benzoyl group, in combination with H, OH, Cl, NH_2, or CH_3O in the compounds mentioned. Gay-Lussac had observed earlier that the cyanogen group could appear in the compounds HCN, $(CN)_2$, BrCN, ClCN, and so on.

The discoveries and theories of the next twenty-five years culminated in 1858 with the publication by Kekulé (1829–1896), and independently by Couper (1831–1892), of

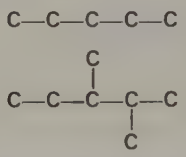
a structure theory that for the first time represented the individual atoms in organic compounds and showed how they were joined. Kekulé proposed that the "combining power" of the elements was fixed, and that carbon had four, nitrogen had three, oxygen had two, and hydrogen had one combining unit (or, as we would say, a *valence* of four, three, two, and one). Thus methane, CH_4, could be represented by



ethane by



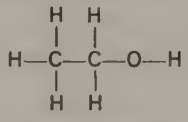
and carbon *chains* could be constructed by linking together carbon atoms and filling with other atoms or groups the remaining combining capacities of the carbon atoms.



"Straight" or unbranched chain

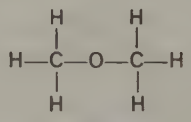
Branched chain

We can now represent ethyl alcohol and dimethyl ether, both C_2H_6O, in a way that clearly shows the difference between them:



CH_3CH_2OH

Ethanol
(ethyl alcohol)



CH_3OCH_3

Dimethyl ether

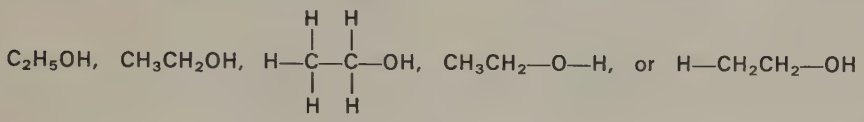
These formulas are *structural formulas*. Those in which all the bonds are shown are *graphic* structural formulas; the others (for example, CH_3CH_2OH) are *condensed* structural formulas. Note that in both of the above structural formulas the *group* of atoms CH_3— appears. This is called the *methyl group*. The word *group* denotes a structural entity only; it is not a substance, but a component part of a substance.

Exercise 1

Write graphic structural formulas for the three isomeric compounds C_3H_8O.

The short lines that join the atoms together in the graphic formulas are symbols for the *bonds* between the atoms. We speak of the carbon-carbon bond, the carbon-hydrogen bond, and the oxygen-hydrogen bond, and often abbreviate these by the terms C—C bond, C—H bond, and O—H bond.

It is important to recognize that structural formulas are only conventional symbols for molecules. Ethanol is one compound, whether it be written



Each way of writing the formula for a given compound may have particular advantages in describing one or more aspect of its behavior. For example, if we wished to depict the reaction of ethanol with sodium, we might write

$$C_2H_5OH + Na \longrightarrow C_2H_5ONa + \tfrac{1}{2}H_2$$

On the other hand its oxidation to acetic acid, in which the methyl group remains unchanged, could be written

$$CH_3CH_2OH \xrightarrow{oxid.} CH_3COOH$$

to show the kind of change that takes place. As we grow more familiar with ways of writing structural formulas we shall feel at ease even with symbols such as Me for CH_3— (*me*thyl), *n*-Pr for $CH_3CH_2CH_2$— (*n*ormal-*pr*opyl), and others.

1-6 The nature of organic compounds

Let us examine a list of 6,500 organic compounds that was compiled for a well-known chemical handbook. Of these, only about 70 (1%) contain no hydrogen, and most of these are derived from hydrogen-containing compounds by the replacement of hydrogen by halogen atoms. Of those compounds that contain six carbon atoms only, we find the distribution listed in Table 1-1. While this table represents an arbitrary sample that includes only a small percentage of all of the known six-carbon-atom compounds, it does show that the preponderance of organic compounds contain hydrogen, and that the bulk of these also contain oxygen or nitrogen.

Everyday experience has made us familiar with other characteristics of many organic compounds. The burning of wood, paper, coal, and petroleum is evidence of the susceptibility of organic substances to oxidation. The end products of such oxidations are carbon dioxide (the ultimate oxidation state of carbon), water, and other oxides or their corresponding elements. The charring of paper, the caramelization of sugar, and the roasting of foodstuffs show us that heat can change and decompose organic substances. Extreme temperatures cause *pyrolysis*, in which extensive decomposition

Table 1-1
Some compounds containing six carbon atoms

Elements in C_6 compounds	*Number listed*	*Percentage of total*
C and O, N, X*, or S only	8	1.5
C, H only	24	4.6
C, H, O only	185	35.2
C, H, O, N only	128	24.3
C, H, N, X only	58	11.0
C, H, X only	56	10.5
C, H, O, X only	55	10.4
C, H, O, S only	13	2.5

* Here X stands for halogen.

takes place, often to simple compounds that escape as vapors. The "coking" of coal, with the production of a distillate known as coal tar, and the now obsolete process of "destructive distillation" of wood, with the formation of a distillate containing methanol (wood alcohol), are examples of pyrolysis. While most organic materials, simple or complex, decompose at high temperature, most of them survive the moderate elevation of temperature required to melt them, if they are normally solids, or to distill them, if they are liquids.

Most *solid organic compounds* melt to liquids when heated to temperatures between about 30°C and 400°C. Let us have another look at the list of 6,500 compounds. In our handbook we find the data that are listed in Table 1-2; of our sample of 6,500 compounds, about 2,100 are liquids at ordinary temperature (those that are gases are relatively very few) and the others are crystalline solids.

Liquid organic compounds are those that are liquids at "ordinary" temperatures. It is obvious that this description imposes quite arbitrary limits, since a gas becomes liquid at a sufficiently low temperature and a solid becomes liquid if heated above its melting point. Liquid compounds may be mobile, nonviscous, colorless substances, such as ethyl alcohol, carbon tetrachloride, or gasoline; some, such as glycerol (glycerin), are viscous and nonvolatile. The boiling points of liquids may vary over quite as wide a range as the melting points of solids, but those with high boiling points (in the range of 300 to 400°C) often suffer decomposition when an attempt is made to distill them at ordinary (atmospheric) pressure. For these liquids, distillation at reduced pressure (1 to 10 mm of mercury, or about 0.01 atmosphere) is the usual practice.

The melting point (or boiling point) of an organic compound is a valuable and characteristic physical constant. It can usually be determined with ease, rapidity, and

Table 1-2
Melting points of some organic compounds

Ranges of melting points	*Number listed*
31–100°C	1580
101–150°C	1020
151–200°C	860
201–300°C	840
over 300°C	100
(over 360°C) *	(16)
Total	4400

* Beyond the range of conventional melting-point measuring devices.

accuracy, and it can be of considerable usefulness in identifying the compound or establishing its structure. Pure compounds usually melt abruptly, within a very narrow range of temperature; the presence of impurities usually causes a broadening of the melting point so that the impure compound may melt gradually, over a range of several degrees and at temperatures lower than that at which a pure specimen melts. Thus the melting point serves as an index of purity as well as an aid to identification.

1-7 The determination of structure

In this chapter we shall describe only the preliminary steps toward determining the structure of an organic compound. This problem is one to which organic chemists must apply all of their skill and knowledge. There is no single method or set of rules for establishing the structures of all organic compounds. There are, however, certain systematic ways of gathering the information that must be possessed before a structure can be learned.

First we must recognize that the chemist deals with *substances*, and uses theories and concepts of structure as a guide in his experiments and as a means of generalizing his results.

Let us suppose that we are confronted with an organic compound of unknown composition and structure; its appearance may give us no clue to its chemical nature. Our ultimate objective is to write a complete structural formula that will account for the compound's chemical and physical properties and enable us to predict how it will behave and how it might be used.

The first steps in the study of an organic compound are as follows:

1. Its purification by crystallization, distillation, chromatography, or other means, and determination of those physical properties that serve to characterize it (melting point, boiling point).
2. Determination of the kinds of elements it contains; if the compound is known to be organic, *qualitative analysis* is usually confined to tests for the presence of nitrogen, halogens, sulfur, and (if the compound is a salt) metals.
3. *Quantitative analysis* for the percentage of carbon, hydrogen, oxygen, and any other elements the compound has been found to contain.
4. Calculation of an empirical formula and, if necessary, determination of the molecular weight in order to obtain the molecular formula.

These four initial steps in the attack upon the problem of structure determination are discussed in the following sections.

1-8 Purification of organic compounds

It is usually unprofitable to attempt to determine the melting point, boiling point, or other physical property of a compound that is impure. It is particularly inadvisable to place confidence in analytical values unless the purity of the sample analyzed is assured. Purification may be the removal of small amounts of contaminating materials, or it may be the separation (or *isolation*) of a compound from a mixture in which the undesired substances are present in relatively large amounts.

Solid compounds may be effectively purified by a process of *recrystallization*. The compound is dissolved in a solvent in which it is more soluble hot than cold. The compound separates as crystals (*crystallizes*) when the solution is cooled, while impurities, if present in small amounts, usually remain in solution. The compound is collected on a filter, washed free of the solution with fresh solvent, dried, and its melting point taken. A second crystallization is carried out, and the melting point is again determined. When the melting point no longer changes upon further recrystallization, the substance may be regarded—at least provisionally—as pure and suitable for analysis.

Liquid compounds are usually purified by distillation. Impurities that are more volatile than the compound to be studied evaporate at a lower temperature and thus may be removed and discarded before the desired compound reaches its boiling point. Less volatile or nonvolatile impurities remain behind as a residue after the desired compound has been distilled. With refined apparatus, complete separations by distillation can be made with ease.

1-9 Chromatographic separations. Column chromatography

To separate a mixture of organic compounds into its several pure constituents, organic chemists widely use a technique known as *chromatography*. The term comes from the Greek word *chroma*, meaning color, because in its earliest applications the method was used to separate mixtures of colored compounds, so that separation could be observed visually. In the simplest form of chromatography, a solution of a mixture of compounds is passed through a cylindrical column packed with a suitable adsorbent. The constituents of the mixture pass through the column at different rates, with the result that a series of bands appear on the column and move downward in sequence. The solution, or *eluate*, flowing out of the column may be collected in a series of receivers; as each band moves down and out of the column it is collected separately and subsequently evaporated. Alternatively, the column packing may be extruded after

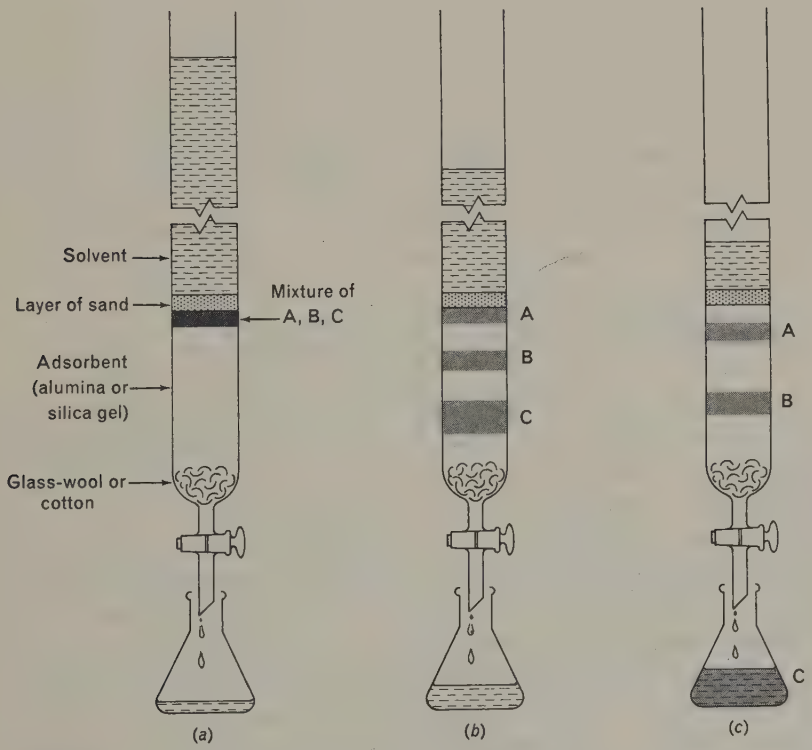


Figure 1-1
Separation of organic compounds by column chromatography. (*a*) Start: mixture has been adsorbed on top of column. (*b*) Development of column is proceeding. (*c*) Fastest-moving component has been eluted from column and collected in receiver.

the bands have developed, and each band then removed by cutting the cylinder of adsorbent into sections. Each section is then mixed separately with a suitable solvent to give separate solutions of each component of the original mixture.

When colorless compounds are separated by chromatography, the usual procedure is to collect numerous arbitrary fractions, identify which individual compound is present in each (for example, by a color reaction or by observation of some physical property), combine those fractions containing the same component of the mixture, and evaporate each group of fractions separately.

In Figure 1-1 is shown a diagram of a typical chromatographic column. Many kinds of packing materials are used, depending upon the kinds of compounds being separated. The commonest, for organic compounds, are alumina and silica gel. The choice of the solvents used for development of the column and for elution of the separate components depends upon the character of the compounds in the mixture. The following generalizations can be made: the lowest elution power is found in saturated petroleum fractions ("petroleum ether," pentane, hexane), followed by benzene, chloroform, ether, and methanol or ethanol; the ease of elution from the column increases from saturated hydrocarbons (alkanes), through unsaturated hydrocarbons, aromatic hydrocarbons, ethers, esters, ketones, alcohols, and phenols, to acids. The usual procedure is to allow the mixture to be separated to be adsorbed on the top of the column, and then to elute, with the collection of fractions, successively with hexane, hexane-benzene mixtures of gradually increasing benzene content, benzene, benzene-ether mixtures with increasing ether content, and finally ether and ether-methanol mixtures. Many variations of this routine are possible.

1-10 Establishment of purity by chromatography

The use of a thin layer of an absorbent permits the separation of the components of a mixture on a sheet or plate, upon which they form individual bands or spots. These can be examined visually under either ordinary or ultraviolet light (which causes many compounds to fluoresce), or they can be subjected to the action of suitable reagents, with the production of colored products that can be observed visually. There are two common techniques for performing this kind of chromatography.

Paper chromatography. A small spot of the compound or mixture is placed at the bottom of a strip of absorbent paper (filter paper). This end of the strip is dipped into a solvent, which is allowed to rise up the paper strip by the action of capillarity. If a single pure compound is applied to the paper, it moves from the origin, usually lagging behind the advancing solvent front, and forms a single spot at some point on the paper. If a mixture is applied to the paper, a series of spots usually results, corresponding to the components of the mixture. Separation is effected to some degree because each compound is differently partitioned between the developing solvent and the water

phase that is present in paper under ordinary laboratory conditions. This is called *paper-partition chromatography.*

Thin-layer chromatography. A thin (0.25-mm) layer of a specially prepared silica gel spread uniformly (as a slurry) on a glass plate serves, after drying, as the absorbent film. A small spot of the compound or mixture is applied at one end of the plate and the chromatogram is developed as in paper chromatography. The individual components may be seen as discrete spots by visual examination, either immediately or after the use of a reagent (applied as a fine spray) that produces a colored spot (Figure 1-2).

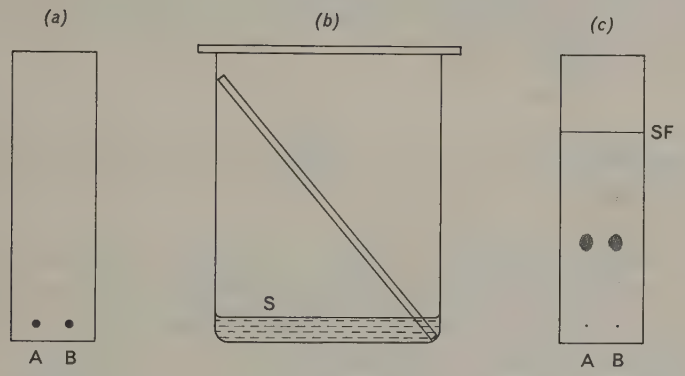


Figure 1-2
Thin-layer chromatography. (*a*) Specimens A (pure compound) and B (compound A with small amounts of impurities) at the bottom of a thin-layer plate. (*b*) Plate being developed by upward flow of solvent S in a tank with a close-fitting lid. (*c*) Plate after removal from tank, showing a single spot of pure A and minor contaminants in B (SF = solvent front), after development by a suitable sprayed reagent.

Both paper chromatography and thin-layer chromatography are ordinarily used as analytical procedures, because the amount of material needed is usually very small. Chromatographic separation procedures are extraordinarily sensitive; amounts of material as small as 1 microgram can often be detected with ease. However, both methods can be adapted to separations on a preparative scale by the use of thick paper or thicker (1- or 2-mm) layers of silica gel.

Compounds on chromatograms are usually identified by comparing the rate of travel of known and unknown compounds on the same paper sheet or thin-layer plate (Figure 1-2). Impurities in a compound whose purity may be suspect can usually be detected by the appearance of one or more spots in addition to that of the principal component.

1-11 Vapor-phase chromatography

Compounds that are gases, or that can be vaporized at temperatures below their decomposition points, can be separated by *vapor-phase chromatography* (VPC). In this method the mixture of compounds to be separated is passed in the vapor phase in a current of inert gas (nitrogen or helium) through a column containing a solid porous support that is impregnated with a nonvolatile liquid. The compounds are separated by differences in their partition between the stationary liquid phase and the moving gaseous phase; in many cases they move out of the column in successive discrete fractions of separate, pure components. Their presence in the exit gases may be detected and recorded (*analytical VPC*), or they may be collected in suitable traps (*preparative VPC*). VPC is a very efficient method of separating mixtures and is widely applied in organic chemical studies.

1-12 Qualitative analysis for the elements present in an organic compound

After a compound has been purified and before quantitative analysis is carried out, it is necessary to determine whether it contains any elements other than carbon, hydrogen, and oxygen. We may suppose that our observations of the compound during its purification have assured us that it is organic. If this is not certain, we can determine whether it is organic by a few simple operations. If a sample of an organic substance is heated on a piece of platinum foil in the flame of a burner, it will burn or char; if the latter occurs the charred mass will at length burn away. If the compound is a metallic salt (of an organic acid, for instance), the metal or its oxide will be left as a residue that can be identified by standard methods of inorganic analysis. Another way of testing for the presence of carbon and hydrogen is to mix the sample with dry, powdered copper oxide and heat the mixture to redness in a test tube. Water formed from hydrogen in the compound will condense as drops on the colder parts of the test tube; carbon dioxide formed from the carbon in the compound can be recognized by passing the gases formed into barium hydroxide solution.

Other elements can be detected by the *sodium fusion test*, in which a sample of the compound to be analyzed is dropped onto metallic sodium in a test tube that has been heated to redness in the direct flame of a burner.* In the vigorous reaction that ensues the compound is decomposed and the sodium combines with the halogens, sulfur, and

* Other methods of carrying out this decomposition are also used. For example, the compound to be tested can be allowed to react with a strongly heated mixture of powdered magnesium and potassium carbonate. The overall result is the same: the compound is decomposed with the formation of the inorganic ions noted.

nitrogen that are present to form sodium halides, sodium sulfide, and sodium cyanide. For example,

$$CH_3SO_2NHCH_2CH_2Br \xrightarrow[\text{heat}]{Na} NaBr, Na_2S, NaCN + \text{carbonaceous decomposition products}$$

The charred mass that results from the reaction is cooled and then boiled with water; the solution is filtered. The presence of *halogen* is recognized by the formation of the insoluble silver halide when silver nitrate solution is added to the acidified (with nitric acid) test solution. *Sulfur* is detected by the formation of black lead sulfide when lead acetate is added to another portion of the solution, which has been acidified with acetic acid. *Nitrogen* is detected by a test for cyanide ion: the reaction between cyanide ion and ferrous hydroxide yields ferrocyanide ion, and this, upon the addition of a ferric salt, is transformed into the deeply colored, characteristic "Prussian blue," ferric ferrocyanide.

1-13 Quantitative analysis for elements other than carbon and hydrogen

If qualitative analysis shows the presence of halogen, sulfur, or nitrogen, the amounts of these must be determined by separate quantitative analyses. Analysis for halogen can be carried out by decomposing a sample of the compound at a high temperature (200°C) with nitric acid and silver nitrate in a sealed tube (the Carius method), and collecting and weighing the silver halide that is formed. The amounts of sulfur and phosphorus can be determined by nitric acid oxidation in the same way, the quantity of resulting sulfate (or phosphate) being estimated by the usual methods.

An alternative procedure is to burn the sample in a Parr bomb with sodium peroxide, which oxidizes carbon and hydrogen to carbon dioxide and water and converts halogen, sulfur, and phosphorus into the sodium halide, sulfare, and phosphate.

Example

A 7.96-mg sample of an organic compound known to contain bromine was heated at 200°C in a sealed tube with 0.5 ml of fuming nitric acid and 1 g of silver nitrate. After cooling, the tube was opened, water was added, and the contents were filtered. The silver bromide was dried and weighed, and amounted to 7.55 mg.

The percentage of bromine in the sample can now be calculated:

$$7.55 \text{ mg AgBr} \times \frac{79.90}{187.77} = 3.21 \text{ mg Br}$$

$$\% \text{ Br} = \frac{\text{wt. of bromine in sample}}{\text{wt. of sample}} \times 100 = \frac{3.21}{7.96} \times 100 = 40.3$$

Nitrogen is usually determined by the *Dumas method.* The Dumas method depends upon the fact that when a nitrogen-containing organic compound is heated strongly with copper oxide it is decomposed into carbon dioxide, water, and nitrogen and its oxides. In this procedure a weighed sample of the compound to be analyzed is mixed with powdered copper oxide and heated in a tube through which pure carbon dioxide can be passed. The exit end of the tube is attached to a gas-measuring burette (a nitrometer) filled with a strong solution of potassium hydroxide. The body of the tube is packed with copper and is heated in an electrical furnace; the copper reduces oxides of nitrogen to pure nitrogen. The tube is then swept with a stream of carbon dioxide, and the issuing gases are conducted into the nitrometer, where the carbon dioxide is absorbed and the nitrogen collected. The amount of nitrogen in the sample is read directly on the calibrated burette, and is corrected to standard conditions of temperature and pressure in the usual way.

Example

A 3.36-mg sample of an organic compound gave by the Dumas method 0.45 ml of nitrogen (corrected to 0°C, 760 mm Hg).

This volume of nitrogen weighs

$$\frac{0.45}{22.4} \times 28 = 0.56 \text{ mg}$$

$$\% \text{ nitrogen} = \frac{0.56}{3.36} \times 100 = 16.67$$

1-14 Carbon-hydrogen analysis

The quantitative analysis of an organic compound is the most important of the initial stages in the determination of its structure. This analysis tells us what elements the compound contains and the proportions in which they are present. With this information we can calculate the simplest, or *empirical*, formula. The true, or *molecular*, formula can then be written when the molecular weight is known.

Since all organic compounds contain carbon and nearly all of them hydrogen, the analysis for these two elements is the most universally applicable to organic substances. Carbon-hydrogen analysis is carried out routinely on most organic compounds that have been prepared for the first time. Even if the compound has been synthesized by methods that leave no doubt about its structure, a carbon-hydrogen analysis is reported as confirmatory evidence of its constitution, and most of the chemical journals of the world require that such analytical data accompany a description of reported work.

This method of analysis of organic compounds was essentially developed by Liebig and Gay-Lussac from procedures first used by Lavoisier. Since then the principal refinement has been the reduction in the size of the sample, from the 0.5 to 1.0 g used in Liebig's day, to about 0.1 g used early in the twentieth century, to the present 3 to 5 mg. This was made possible by improvements in the balance utilized. The modern microbalance is capable of weighing samples of a few milligrams with a precision of 0.002 mg.

If a sample of ordinary sugar, sucrose, is burned in a stream of oxygen, the reaction that occurs is

$$C_{12}H_{22}O_{11} + \text{excess } O_2 \longrightarrow 12CO_2 + 11H_2O$$

Ethanol burns according to the equation

$$C_2H_5OH + \text{excess } O_2 \longrightarrow 2CO_2 + 3H_2O$$

In the quantitative analysis for carbon and hydrogen, the combustion is carried out in a quartz tube packed with granular copper oxide. The tube is heated over about 8 inches of its length in a furnace kept at 750 to 800°C. The sample, in a platinum boat in another part of the tube, is heated with a flame or an auxiliary electric heating coil. A slow stream of carefully dried oxygen passes first over the sample and then over the heated copper oxide in the main body of the tube, where the oxidation of the compound is completed. The products of the combustion are swept by the oxygen stream into accurately weighed absorption tubes, the first containing anhydrous magnesium perchlorate (Anhydrone), and the second a specially prepared material consisting of asbestos impregnated with sodium hydroxide (Ascarite). The absorption tubes are weighed on the microbalance, and thus the weights of water in the Anhydrone and carbon dioxide in the Ascarite are determined.

The *results* of a carbon-hydrogen analysis are expressed as percentages of carbon and hydrogen. For example, a 3.42-mg sample of a compound was found to yield 5.28 mg of CO_2 and 1.98 mg of water:

$$\text{wt. of carbon} = 5.28 \times \frac{12.01}{44.01} = 1.44 \text{ mg}$$

$$\% \text{ of carbon in sample} = \frac{1.44}{3.42} \times 100 = 42.11$$

$$\text{wt. of hydrogen} = 1.98 \times \frac{2.016}{18.016} = 0.221 \text{ mg}$$

$$\% \text{ in hydrogen in sample} = \frac{0.221}{3.42} \times 100 = 6.46$$

The unaccounted for 51.43% [100−(42.11+6.46)] is taken as the oxygen content if it has been found that no halogen, nitrogen, or other elements are present in the

compound. If one or more of these is present, separate analyses must be carried out by the methods already described.

1-15 Determination of the empirical formula

Let us carry out the combustion of a sample of 4.64 mg of an organic compound that we have shown by qualitative analyses to contain no elements other than C, H, and O. There is formed 11.70 mg of CO_2 and 1.46 mg of water:

$$\% \text{ C} = \frac{11.70 \times 12/44}{4.64} \times 100 = 68.77$$

$$\% \text{ H} = \frac{1.46 \times 2.016/18.016}{4.64} \times 100 = 3.52$$

$$\% \text{ O (by difference)} = 27.71$$

The relative *atomic* proportions of C, H, and O can be calculated by dividing each of the above values by the atomic weight of the element it represents (Table 1-3). The *atomic ratios* of C:H:O are thus 5.73:3.49:1.73, or 3.31:2.02:1.00. That is, we could express the relative numbers of atoms in the compound by the formulas $C_{5.73}H_{3.49}O_{1.73}$ or $C_{3.31}H_{2.02}O_{1.00}$. However, it is customary to express these proportions in terms of the smallest-possible *whole* numbers. Since the formula $C_{3.31}H_{2.02}O$ contains the atoms in the same proportions as the formula $C_{10}H_6O_3$, this is the *empirical formula* of our compound.

We can now confirm our result by calculating by simple arithmetic the percentage composition of a compound having the formula $C_{10}H_6O_3$:

carbon =	10 × 12*	= 120
hydrogen =	6 × 1.008	= 6
oxygen =	3 × 16	= 48
	Total	174

$$\% \text{ C} = 120/174 \times 100 = 68.97 \text{ calculated; } 68.77 \text{ found}$$
$$\% \text{ H} = 6/174 \times 100 = 3.45 \text{ calculated; } 3.52 \text{ found}$$
$$\% \text{ O} = 48/174 \times 100 = 27.59 \text{ calculated; } 27.71 \text{ found}$$

The agreement between the "calculated" and "found" values is within the usual limits of variation of the C-H analysis. For a compound having a content of carbon of, say, 70.40%, "found" values between 70.2% and 70.6% are generally regarded as acceptable.

* The atomic weights 12.01 for carbon and 1.008 for hydrogen are ordinarily used by analysts in calculating the results of carbon-hydrogen analyses. We shall use the approximation 12 for carbon in the remaining examples in this chapter.

Table 1-3
Relative atomic proportions of carbon, hydrogen, and oxygen

	Relative weights	*Relative atomic proportions*	*Number of atoms relative to* 0
C	68.77	68.77/12 = 5.73	5.79/1.73 = 3.31
H	3.52	3.52/1.008 = 3.49	3.49/1.73 = 2.02
O	27.71	27.71/16 = 1.73	1.73/1.73 = 1.00

The importance of knowing the molecular weight of the unknown compound can be appreciated when it is recognized that the same composition by weight is found for $C_{10}H_6O_3$, $C_{20}H_{12}O_6$, and $C_{30}H_{18}O_9$. However, with reliable carbon-hydrogen analyses a relatively less accurate determination of molecular weight is usually adequate. For instance, the above three formulas correspond to molecular weights of 174, 348, and 522. Thus, if the molecular weight were found by an experiment to be 185, this result, even though not an accurate one, would clearly rule out all but the first of these.

Here is another example. A substance is found to contain nitrogen, and an analysis by the Dumas method gives the value 11.40% for nitrogen. From 3.69 mg of the compound are obtained 9.26 mg of CO_2 and 2.36 mg of water:

$$\% \text{ C} = \frac{9.26 \times 12/44}{3.69} \times 100 = 68.44$$

$$\% \text{ H} = \frac{2.36 \times 2.016/18.016}{3.69} \times 100 = 7.16$$

$$\% \text{ N} = 11.40$$

$$\% \text{ O (difference)} = 13.00$$

Atoms C = 68.44/12 = 5.70		Atoms C/atom N = 5.70/0.814 = 7.0	
H = 7.16/ 1 = 7.16		H/N	= 8.8
N = 11.40/14 = 0.814		N/N	= 1.0
O = 13.00/16 = 0.813		O/N	= 1.0

Thus the empirical formula appears to be C_7H_9ON:

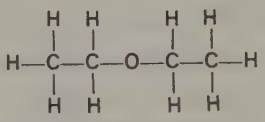
Calculated for C_7H_9ON: C, 68.28; H, 7.33; N, 11.38
Found: C, 68.44; H, 7.16; N, 11.40

This is acceptable agreement, so the C_7H_9ON formula may be taken as correct. A molecular-weight determination will show whether the molecular formula is C_7H_9ON, $C_{14}H_{18}O_2N_2$, etc.

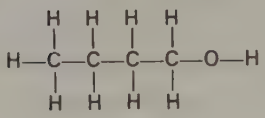
1-16 Preliminary deductions from the molecular formula

When we recall that the formula $C_4H_{10}O$ is that of seven different compounds, it becomes apparent that the molecular formula itself gives very little information about structure. In Chapter 2 we shall see that there are many ways in which carbon, hydrogen, oxygen, and other atoms can be joined together; and we shall now see how the molecular formula can often reveal that certain modes of combination may be found in our unknown compound, or show that they are absent. Two such modes of combination are *double bonds* between carbon and carbon, or between carbon and oxygen.

Let us suppose the formula $C_4H_{10}O$ has been determined by analysis. With the knowledge that carbon has a valence of four, oxygen two, and hydrogen one, we can write a number of structural formulas; it is apparent by inspection that the two following contain only *single bonds*:



$CH_3CH_2OCH_2CH_3$ $(C_4H_{10}O)$

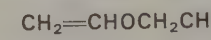


$CH_3CH_2CH_2CH_2OH$ $(C_4H_{10}O)$

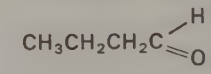
Exercise 2

Write both "graphic" and "condensed" structural formulas for the other five isomers of $C_4H_{10}O$.

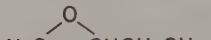
If a C_4 compound contains a carbon-carbon or carbon-oxygen double bond, or if the compound is cyclic (that is, contains a ring), the maximum number of hydrogen atoms it can contain is eight. This can be seen by inspection of the following structures:



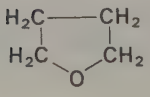
C_4H_8O One C=C bond



C_4H_8O One C=O bond



C_4H_8O One ring

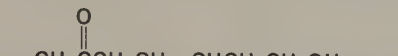


C_4H_8O One ring

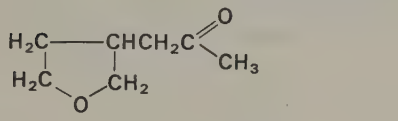
We can generalize these conclusions into the statement that a compound containing carbon, hydrogen, and oxygen and having no double bonds or rings has a ratio of carbon to hydrogen of $n:2n + 2$; if one double bond or ring is present, the ratio C:H is $n:2n$; for two double bonds or rings, or one of each, the ratio is $n:(2n - 2)$; and so on.

Let us suppose, for instance, that an unknown compound is found by analysis to have the formula $C_7H_{12}O_2$. A fully-saturated (no double bonds), acyclic (no rings) C_7 compound with two oxygen atoms would have to be $C_7H_{16}O_2$. Thus our unknown compound must have (*a*) two double bonds, (*b*) two rings, or (*c*) one ring and one double bond. The following structures confirm this:

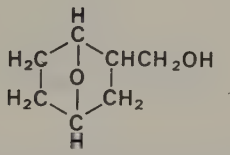
$C_7H_{12}O_2$



$C_7H_{12}O_2$



$C_7H_{12}O_2$



$C_7H_{12}O_2$

It should now be clear that to be able to write a number of structures that agree with a molecular formula is only a way of laying out the problem for inspection and attack. The four structures written above for a $C_7H_{12}O_2$ compound can now be distinguished only by further study by chemical and physical means.

Exercise 3

Nitrogen has a valence of three, and thus a saturated primary amine, for example $CH_3CH_2CH_2NH_2$, has the formula $C_nH_{2n+3}N$. What can be said about the possible structures for

(*a*) C_5H_5N (*b*) C_4H_9N (*c*) $C_8H_{19}N$

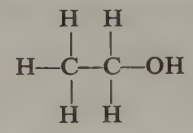
Problems

1. Devise and describe a method that could be used to determine the percentage of silver in an organic compound such as, for example, a silver salt of an organic acid.

2. It is possible to perform a direct analysis for *oxygen* in organic compounds. Why is it valuable to have an analytical figure for the percentage of oxygen in a compound?

3. When compounds containing nitrogen are tested for halogen by the sodium-fusion method, it is necessary to boil the solution after acidification with nitric acid before adding silver nitrate. Why must this be done?

4. Write the graphic (as in example *a* below) and the condensed (as in example *b*) formulas for all of the compounds of the composition $C_5H_{12}O$.



(*a*) ethanol,

(*b*) diethyl ether, $CH_3CH_2OCH_2CH_3$

5. Write graphic and condensed structural formulas for all the possible isomers of each of the following, remembering that carbon has a valence of four; oxygen, two; nitrogen, three; and halogens and hydrogen, one: (*a*) C_2H_5Br, (*b*) C_3H_7Cl, (*c*) $C_2H_4Cl_2$, (*d*) C_2H_7N, (*e*) C_3H_9N.

6. How much barium sulfate would be formed from 4.52 mg of $(CH_3)_2S$ after oxidation with nitric acid and precipitation with barium chloride?

7. How large a sample of each of the following must be burned to give 4.40 mg of carbon dioxide? (*a*) CBr_4, (*b*) C_3H_6, (*c*) CH_4O, (*d*) $C_2H_2O_4$, (*e*) $C_6H_{12}O_6$.

8. What is the percentage of bromine in each of the following? (*a*) AgBr, (*b*) C_2H_5Br, (*c*) $BrCH_2CH_2Br$, (*d*) $BrCH_2CONH_2$, (*e*) CH_2ClBr.

9. What is the minimum possible molecular weight of a compound that contains 31.56% bromine?

10. A sample of 6.23 mg of a liquid organic compound gave on combustion 9.17 mg of CO_2 and 3.78 mg of water. In a molecular-weight determination it was found that 357 ml of the vapor of the compound, measured at 27°C and 750 mm, weighted 0.890 g. Calculate the empirical and molecular formulas for the compound.

11. A compound contained 69.95% carbon and 11.60% hydrogen (by analysis). A qualitative test showed that nitrogen was present. Calculate a possible empirical formula. If the molecular weight of the compound is less than 170, is a formula containing both nitrogen and oxygen possible with the analytical figures given?

12. Silver lactate has the composition 18.3% C, 2.5% H, 24.4% O, and 54.8% Ag. Calculate the molecular formula, assuming one silver atom per mole.

13. Oxidation of lactic acid with potassium dichromate and sulfuric acid produces acetic acid, which has the molecular formula $C_2H_4O_2$ and contains a methyl group (CH_3—). Using this information and that from Problem 12, write a structural formula for lactic acid.

14. Calculate the percentage composition for each of the compounds $C_{27}H_{46}O$ and $C_{28}H_{48}O$. What can you say about the practical limitations of the carbon-hydrogen analysis?

15. A nitrogen-containing organic compound gave the following analytical figures: C, 75.45%; H, 6.61%; N, 8.40%. Calculate an empirical formula and check it by comparing the percentage composition calculated from that formula with the analytical result.

16. A compound was analyzed to contain 75.20% C and 10.75% H. The compound contains only carbon, hydrogen, and oxygen, and its molecular weight is found to be about 115. Chemical tests prove that the structural element $-\overset{|}{C}=O$ (a carbonyl group) is present. What else can be said about the structure?

17. Suppose that the compound whose analysis is given in the preceding problem is found not to contain a carbonyl group. Write a possible structure for the compound.

18. Write the molecular formula for each of the following:
(*a*) $CH_2{=}CHCH_2CH_2CH{=}NCH_3$ (*c*) $CH_3CH_2CH_2CH_2CH_2{\equiv}N$
(*b*) $CH_3C{\equiv}CCH_2CH_2CH_2NH_2$

19. Write two structural formulas that could represent a compound whose molecular formula is C_6H_9N.

2

Some important classes of organic compounds

This chapter introduces the student to some of the principal classes of organic compounds and to the structural features by which they may be recognized. Although all of these will be dealt with in later chapters, it will often be necessary to allude to compounds before their chemical behavior is taken up in detail. An early recognition of what is meant by the names ester, amine, alcohol, aldehyde, alkene, and so on will lay the groundwork for discussions of general properties that, in turn, will form the basis for detailed inquiry into chemical behavior. This chapter might be described as presenting the simple vocabulary needed to understand what will follow. It is intended only to present a broad perspective view, the details of which will be added as our study develops.

Chemists communicate with both words and chemical structures; the recognition of a structure from a name and the ability to give a name to a compound written in structural form can be important to understanding a discussion of chemical behavior. This ability cannot be acquired at once—certainly not by learning a simple set of rules—but it will develop as study proceeds and familiarity grows. This chapter is the starting point.

2-1 The common functional groups

Organic chemistry would be a bewildering study if it were necessary to deal with each one of more than a million compounds as an individual that bore no systematic relationship to any other. Fortunately, this is not necessary, for many organic compounds

can be grouped into distinct *classes*, the members of which behave in similar ways. Although each organic compound *is* a distinct substance, the members of a given class usually have many properties in common. Thus a knowledge of the chemical behavior of a class of compounds enables us to recognize and predict many of the properties of individual compounds of that class.

Organic compounds are classified by the presence in their molecules of certain characteristic groups of atoms known as the *functional groups*. As this term implies, the functional group is that part of a molecule that confers upon a compound a characteristic type of reactivity.

2-2 The use of the symbol "R"

Chemists find it convenient to represent the rest of the molecule, that is, the part other than the functional group, by the symbol R. Thus we can write RCH_2OH as a general form for primary alcohols, RCHO for aldehydes, RCOOH for carboxylic acids, and so on. Equations such as

$$RCH_2OH + HBr \longrightarrow RCH_2Br + H_2O$$

show that it is a *general property* of primary alcohols to react with HBr to give alkyl bromides. The use of this kind of symbolism affords great economy and comprehensibility of expression in formulating characteristic kinds of chemical behavior.

In most cases the symbol R stands for an *alkyl group*, such as CH_3—, CH_3CH_2—, $(CH_3)_2CH$—, and so on. When the formulation is broadened so that the R— groups are not necessarily the same, the symbols R, R′, and R″, or R^1, R^2, R^3, and so on, may be used. When the compounds to be represented contain aromatic groups, such as phenyl (C_6H_5—) in benzaldehyde, phenol, aniline, and so on, it is convenient to use the symbol Ar, as in ArOH for phenols, ArCOOH for aromatic acids, and so on.

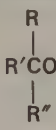
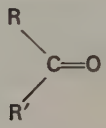
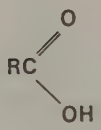
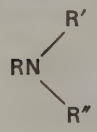
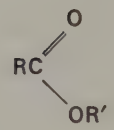
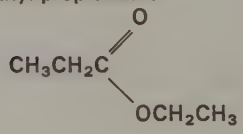
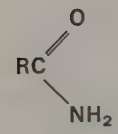
In Table 2-1 is given a summary of various structural classes, each of which is represented by a formula that combines the group R with a functional group.

2-3 Naming organic compounds

The naming of functional groups and of compounds that contain them is governed by rather simple and straightforward rules, which are discussed in Appendix A. This should be studied now and referred to as new classes of compounds are encountered in the chapters to follow. In some cases additional comment on nomenclature will be found in these chapters, but the general discussion in Appendix A will serve as a substantial basis for this important aspect of the study of organic compounds.

The student may ask why it is important to learn how to name organic compounds

Table 2-1
Some classes of organic compounds

Class	*General formula*	*Example*
paraffin hydrocarbons (alkanes)	RH	ethane (CH_3CH_2—H) or CH_3CH_3
olefins (alkenes)	RCH═CHR′	2-butene : $CH_3CH{=}CHCH_3$
alcohols:		
primary	RCH_2OH	ethanol: CH_3CH_2OH
secondary	RCHOHR′	2-butanol: $CH_3CHOHCH_2CH_3$
tertiary		*t*-butyl alcohol: $(CH_3)_3COH$
aldehydes	RCH═O	acetaldehyde: CH_3CHO
ketones		acetone: $(CH_3)_2CO$
carboxylic acids		propionic acid: CH_3CH_2COOH
amines:		
primary	RNH_2	methylamine: CH_3NH_2
secondary	RNHR′	methylethylamine: $CH_3NHCH_2CH_3$
tertiary		trimethylamine: $(CH_3)_3N$
ethers	ROR′	ethyl *n*-propyl ether: $CH_3CH_2OCH_2CH_2CH_3$
esters		ethyl propionate: 
amides		acetamide: CH_3CONH_2

when structural formulas can be written. The answer is twofold: (1) a name is often quite sufficient and more convenient to use in a discussion; and (2) names are *used* by organic chemists, so that oral and written accounts of chemical behavior cannot be understood by the reader who does not know what a name means.

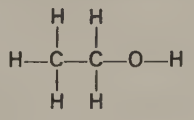
It is not recommended that the student attempt to learn by rote a vast array of individual names. He should learn the basic rules and relatively few widely used common names. As his study progresses he will learn a great deal about nomenclature, not by conscious effort, but by a process of accretion.

In the following paragraphs the names of compounds are given with their structures. In later chapters will be found brief discussions of individual nomenclature. Most of these are elaborations of the basic systems described in Appendix A, which should be referred to frequently until the student finds it easy to recognize compounds by name and to name compounds whose formula is given.

2-4 The principal functional classes

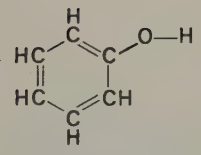
Table 2-1 is elaborated by the following discussion of the commonest functional groups that are responsible for the characteristic behavior of classes of organic compounds.

The hydroxyl group. The hydroxyl group, —OH, is present in two large classes of compounds, *alcohols* and *phenols*. A typical alcohol is ethanol; a typical phenol is the compound that bears the name of the class, phenol itself. In alcohols, the —OH group is bonded to a carbon atom, which in turn is attached to three other carbon or hydrogen atoms. In phenols, the —OH group is bonded to a carbon atom of an aromatic ring (for example, a benzene ring):

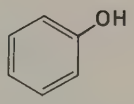


or CH_3CH_2OH

Ethanol

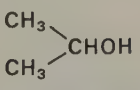


usually written



Phenol

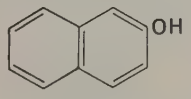
Other examples are



2-propanol
(a secondary alcohol)

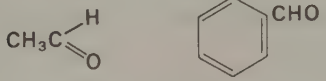
$(CH_3)_3COH$

t-butyl alcohol
(a tertiary alcohol)



2-naphthol

The carbonyl group. The carbonyl group, $-\overset{|}{C}=O$, is the characteristic functional group of *aldehydes* and *ketones*. In aldehydes, one of the remaining bonds is to a hydrogen atom; in ketones, the carbonyl group is attached to two other carbon atoms:

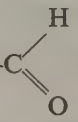


Acetaldehyde Benzaldehyde

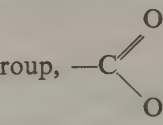
(aldehydes)

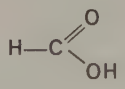
Acetone Cyclohexanone

(ketones)

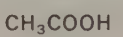
In aldehydes, the complete grouping  can be regarded as the functional group.

It is called the *formyl group*. Nevertheless, it is the carbonyl group of both aldehydes and ketones that determines their characteristic, and in many ways similar, behavior.

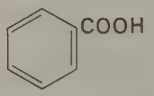
The carboxyl group. The carboxyl group,  (usually written —COOH or —CO_2H), in which the carbonyl and hydroxyl groups (hence the name) are combined in a single unit, is the functional group of the *carboxylic acids*. Although the carboxyl group contains both the carbonyl and the hydroxyl group, the presence of these on the same atom lends to each of them characters that distinguish carboxylic acids from alcohols and from aldehydes and ketones. A few examples of this large and important class of compounds are the following:



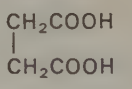
Formic acid



Acetic acid

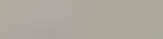


Benzoic acid



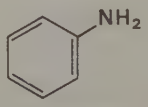
Succinic acid

The amino group. The amino group, —NH_2, is present in primary amines. These compounds, derivatives of ammonia, are the organic bases. Like ammonia, they form stable salts with strong acids. Many of them have ammoniacal odors. Some typical primary amines are:



Methylamine

t-butylamine



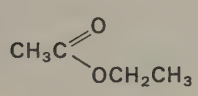
Aniline

Derivatives of alcohols, amines, and carboxylic acids. Substitution of another atom or group for one or more of the hydrogen atoms of —OH or $—NH_2$ provides, respectively, *ethers* and *secondary* and *tertiary amines*:

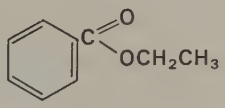
$CH_3CH_2OCH_2CH_3$	$(CH_3)_2NH$	$(CH_3CH_2)_3N$
Diethyl ether	Dimethylamine	Triethylamine

Substitution for the hydrogen atom or the hydroxyl group in —COOH yields acid derivatives, which include *esters*, *acid halides*, *acid anhydrides*, and *amides*. It will be noted that in all of these the *acyl group*, $RC(=O)—$, is not attached to a carbon atom; thus, acid derivatives are clearly distinguished from ketones.

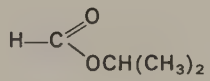
Esters



Ethyl acetate

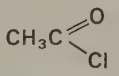


Ethyl benzoate

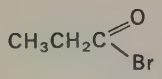


Isopropyl formate

Acid halides

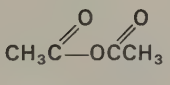


Acetyl chloride

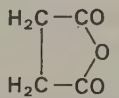


Propionyl bromide

Acid anhydrides

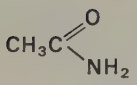


Acetic anhydride

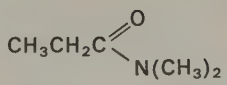


Succinic anhydride

Amides



Acetamide



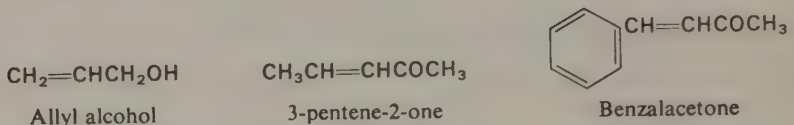
N,*N*-dimethylpropionamide

Salts of carboxylic acids are not usually regarded as acid derivatives because their relationship to carboxylic acids depends simply upon a difference in pH. Nevertheless, they are a distinct class of compounds with definite composition and properties. Sodium acetate, $CH_3COO^-Na^+$ (usually written simply as CH_3COONa), for example, is a crystalline compound of definite melting point.

The carbon-carbon double bond. The structural unit $—C=C—$ is found in many organic compounds. Hydrocarbons containing the carbon-carbon double bond are

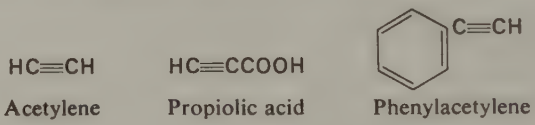
called *olefins*, or by the systematic name *alkenes*. Some common olefins are the following:

The carbon-carbon double bond is a center of *unsaturation* in the molecule, and compounds containing it are known collectively as *unsaturated* compounds. There exist unsaturated alcohols, unsaturated ketones, unsaturated carboxylic acids, and so on. It should be noted that unsaturated alcohols, ketones, and carboxylic acids are



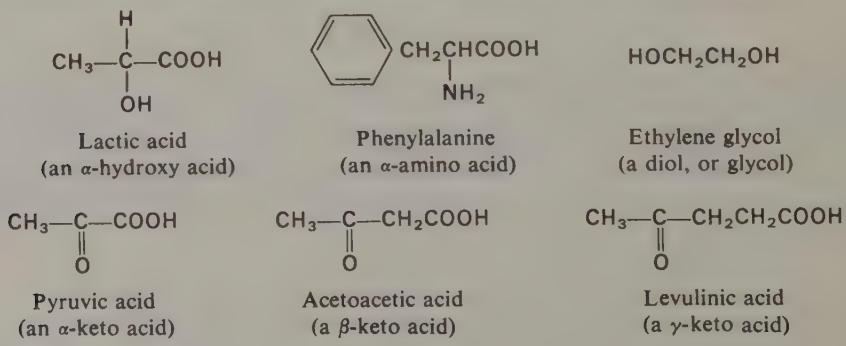
not called alkenes or olefins; these names are confined to hydrocarbons that contain the double bond but no other functional groups.

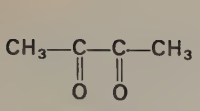
The carbon-carbon triple bond. The functional unit in *acetylenic* compounds is —C≡C—. Acetylenic hydrocarbons are called *alkynes*; as in the case of the double bond, acetylenic alcohols, ketones, and so on are also known.



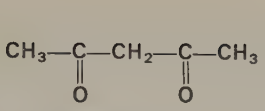
2-5 Polyfunctional compounds

Many organic compounds contain more than one of the typical functional groups that have just been described, and often the presence of one functional group in a molecule will alter the behavior of another from what might have been anticipated.

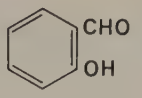




Biacetyl
(an α-diketone)



Acetylacetone
(2,4-pentanedione or
pentane-2,4-dione, a β-diketone)



Salicylaldehyde
(a phenolic aldehyde)

Exercise 1

Write structural formulas for all of the isomers of the carboxylic acids of (*a*) the composition $C_6H_{10}O_3$ and (*b*) the composition $C_6H_{12}O_3$.

The best way to approach the problem of understanding, explaining, and predicting the properties of polyfunctional molecules is to study the characteristic properties of the simple functional groups. After reaching an understanding of these it is possible to extend the simpler principles to combinations of groups.

2-6 The paraffin hydrocarbons

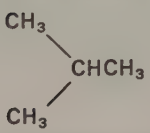
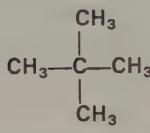
A large and industrially important class of organic compounds is characterized by the absence of functional groups of any kind and by a remarkable chemical inertness. These are the saturated, or *paraffin*, hydrocarbons (paraffin, from Latin, means "little affinity"). They contain carbon and hydrogen only, and all of the carbon valences are utilized; that is, there are no unshared bonding electrons, so that none of the atoms possesses unsatisfied valence bonds. All of the carbon bonds are single bonds. The chemical inertness of the saturated hydrocarbons can be ascribed to this "saturation" of the carbon valences. In order for these compounds to react with other molecules, energy must be supplied sufficient to break one or more of the C—H or C—C bonds. This bond rupture exposes the carbon atom at which the break occurs to attack by reagents, which can thus form a new bond to replace the old.

Typical saturated hydrocarbons are the *homologous series* whose simplest member is methane. Succeeding members differ by increments of CH_2, up to quite large and complex molecules. The paraffin hydrocarbons may possess either unbranched (that is, "straight") or branched chains of carbon atoms, as shown in Table 2-2.

Exercise 2

Write the structures of all of the possible isomeric compounds of the composition (*a*) C_5H_{12} and (*b*) C_7H_{16}.

Table 2-2
Paraffin hydrocarbons (alkanes)

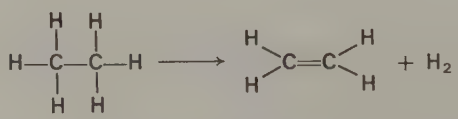
Structural formula	*Molecular formula*	*Name*
CH_4	CH_4	methane
CH_3CH_3	C_2H_6	ethane
$CH_3CH_2CH_3$	C_3H_8	propane
$CH_3CH_2CH_2CH_3$	C_4H_{10}	butane
	C_4H_{10}	isobutane
$CH_3CH_2CH_2CH_2CH_3$	C_5H_{12}	pentane
	C_5H_{12}	neopentane
$CH_3(CH_2)_{10}CH_3$	$C_{12}H_{26}$	dodecane
$CH_3(CH_2)_{28}CH_3$	$C_{30}H_{62}$	triacontane

Although paraffin hydrocarbons are reluctant to engage in reactions, they can be induced to do so under proper conditions. Chemical transformations of the paraffin hydrocarbons are the basis for the many industrial processes that utilize the enormous natural sources of them, the most important being petroleum and natural gas.

Thermal cracking, or pyrolysis in the absence of air, is a process that uses heat energy to bring about extensive rupture of hydrocarbon molecules. At sufficiently high temperatures methane is decomposed into elementary carbon and molecular hydrogen:

$$CH_4 \longrightarrow C + 2H_2$$

Ethane can be "cracked" in a more useful manner to lose one molecule of hydrogen, yielding ethylene:



When higher paraffin hydrocarbons are subjected to cracking, a number of processes can ensue because of the greater number of points at which bond breaking can occur. More than one carbon-carbon bond may be broken and hydrogen may be lost from

the fragments, producing a mixture of saturated and unsaturated hydrocarbons with various numbers of carbon atoms.

Cracking thus has two important results: (1) large molecules are fragmented into smaller ones; (2) unsaturated hydrocarbons are produced. As we shall see, unsaturated hydrocarbons are reactive substances well fitted for use in synthetic processes from which a large number of useful products are obtained.

In modern petroleum technology, cracking is carried out in the presence of catalysts. The petroleum vapors are passed over a bed of catalyst consisting of granules of an acid-treated clay or a synthetic aluminum-oxide/silicon-oxide complex, at temperatures of over 300°C. Catalytic cracking produces, in addition to low-molecular-weight paraffins and olefins, secondary products that arise from isomerization and aromatization, so that high-quality motor fuels can be prepared at lower cost than by purely thermal processes.

The fragmentation of large hydrocarbons into smaller ones plays an important part in petroleum refining. Petroleum is a naturally occurring mixture of carbon compounds, a large proportion of which consists of paraffin hydrocarbons. The low-molecular-weight members of this group constitute the mixture known as gasoline. Gasolines differ in composition, but a typical automotive gasoline consists largely of a mixture of hydrocarbons ranging from about C_5H_{12} to $C_{10}H_{22}$,* with boiling points ranging from about 30° to 200°C. Higher-boiling fractions comprise kerosene, fuel oils, and, finally, viscous and oily high-molecular-weight fractions that are used as lubricating oils. The chemical inertness of the paraffin hydrocarbons is of obvious value in preserving a lubricant that in use is exposed to oxygen at elevated temperatures.

Natural gas is usually composed largely of methane (a typical natural gas may be 80% methane), along with smaller amounts of ethane and propane. Natural gas is used chiefly as a domestic and industrial fuel, but large quantities are also consumed by the chemical industry as the starting material for the synthesis of numerous organic chemicals.

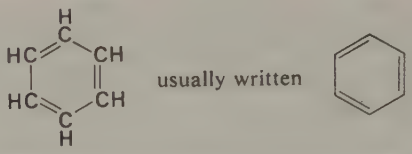
2-7 Aromatic hydrocarbons

The earth, which yields petroleum and natural gas, also provides coal, another major source of energy and of organic compounds. The carbon compounds derived from coal are obtained chiefly from the production of coke by destructive distillation. As coal is converted into coke (which is largely a mixture of amorphous carbon and the mineral constituents of coal) there is produced a gas (coal gas) and a viscous black distillate known as *coal tar*. The redistillation of coal tar yields a number of fractions of which

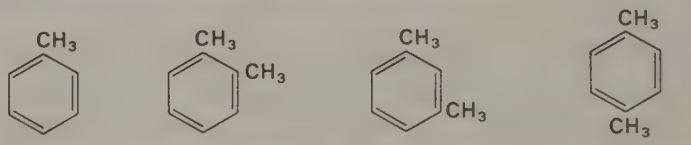
* Present-day high-antiknock gasolines are prepared by more complex processes than those described, and contain aromatic and unsaturated hydrocarbons as well as certain special additives in addition to their chief content of saturated hydrocarbons.

the lowest-boiling contains a mixture of hydrocarbons. Additional amounts of these compounds can be obtained by cooling and scrubbing the coal gas.

The most important constituent of coal tar, both industrially and scientifically, is benzene, a cyclic hydrocarbon of the composition C_6H_6. We shall have more to say about its structure in a later chapter, but for the present we can represent it as



Accompanying benzene in the more volatile fractions of coal tar are the simple homologous hydrocarbons toluene and the three xylenes:



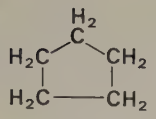
Toluene *ortho*-xylene *meta*-xylene *para*-xylene

These compounds, which are characterized by the "benzenoid" six-membered ring have unique properties, distinct from those of olefins, and are called *aromatic* compounds. By successive substitution on the ring or on previous substituents, it is possible to derive a group of compounds as large and various as the group of derivatives of the paraffin hydrocarbons. Several other aromatic compounds have already been mentioned in this chapter (phenol, benzoic acid, aniline, salicylaldehyde).

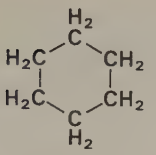
Benzene and its homologues are produced in enormous quantities as raw materials for the synthesis of organic chemicals, dyes, drugs, insecticides, perfumes, flavoring materials, fibers, and a host of other useful products. The historical fact that benzene was first derived solely from coal tar has led to the widespread use of such terms as "coal-tar derivatives" to designate compounds prepared from benzene. At the present time, aromatic compounds are produced largely from raw materials derived from petroleum, and coal is no longer the principal source of benzene and its homologues.

2-8 Cyclic compounds other than aromatic compounds. Alicyclic compounds

The angles between carbon-carbon bonds permit carbon atoms to be joined in rings to form cyclic structures. In five- and six-membered rings the angles between the carbon-carbon bonds are close to the "normal" tetrahedral bond angle of 109.5°; such rings are thus essentially without strain and show extraordinary stability. For example, cyclopentane and cyclohexane exhibit a chemical inertness comparable to that of the noncyclic paraffin hydrocarbons. It is possible to form rings of as few as three carbon

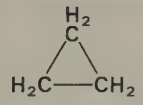


Cyclopentane

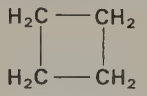


Cyclohexane

atoms, as well as rings containing many more than six carbon atoms. The smaller rings (cyclopropane and cyclobutane) are under strain, owing to the considerable distortion of the carbon-carbon bond angles from the normal 109.5°. For this reason



Cyclopropane
(C—C—C angle 60°)



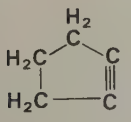
Cyclobutane
(C—C—C angle 90°)

compounds containing 3- and 4-membered rings show a considerably greater reactivity than their open-chain counterparts. Their reactions commonly involve an opening of the ring to give compounds that are less highly strained.

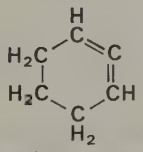
Rings of greater than six members are not strained by the distortion of bond angles, but some of them are difficult to prepare for other reasons. Further discussion of this will be found in Chapter 27.

2-9 Limitations on structural possibilities

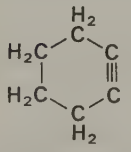
The requirements imposed by the normal bond lengths and bond angles of covalently bound carbon limit the number of permissible structures that can be drawn by simply obeying the usual valence rules. For example, in the compound allene, $CH_2{=}C{=}CH_2$, the three carbon atoms are known from experimental measurements to be arranged linearly; the same is true of the four carbon atoms of dimethylacetylene, $CH_3{-}C{\equiv}C{-}CH_3$. For this reason no such compounds as cyclopentyne or 1,2-cyclohexadiene have yet been prepared, owing to the great distortion that would be required to form them.



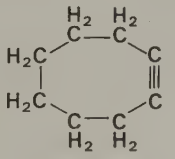
Cyclopentyne
(unknown)



1,2-cyclohexadiene
(unknown)



Cyclohexyne
(unknown?)



Cyclo-octyne
(known)

How large must a ring be to accommodate the linear C—C≡C—C or the linear C=C=C unit? No final answer to this can yet be given; at the present time, cyclohexyne is not known, but it has been suggested that it is formed as a transitory and extremely

reactive intermediate in certain reactions. Cyclo-octyne, however, is a known compound. Here, the joining of the ends of the linear $—CH_2C{\equiv}CCH_2—$ unit by four $—CH_2—$ groups can be accomplished, not *without* strain, but with energetically permissible strain.

2-10 Sources and uses of organic compounds

The importance of organic chemistry and the products of the organic-chemical industry in the day-to-day life of modern man are too well recognized to need emphasis. We rely upon the organic chemist to provide plastics and synthetic textiles, drugs and pharmaceutical preparations, coatings and finishes, dyes, perfumes, flavoring substances, explosives, and fuels. Our crops are protected by organic insecticides; our soils are treated with organic soil conditioners and fertilizers; and our fields are kept free of weeds by synthetic herbicides. There is no aspect of life that is not touched by the hand of the organic chemist.

But organic chemists are not committed solely to the discovery and production of compounds for our material comfort and convenience. The chemist is curious about the nature of the physical world; he may, for example, have a very esoteric interest in a minute detail of a chemical reaction or the way in which a living organism transforms one substance into another. Whatever his interests are, he develops and pursues them by experimental attack; to perform experiments he requires the apparatus in which to carry out chemical reactions, instruments with which to measure and study the properties of the substances he prepares, and, above all, chemical compounds to work with.

The research laboratories and the manufacturing facilities of the organic-chemical industry provide a great number of pure organic compounds, some of which are products that can be put to immediate practical use, but most of which are materials used by the research chemist for the preparation of new compounds. Carbon itself, which the chemical industry needs for the preparation of its products, seldom occurs in nature in pure elemental form; even coal—a complex mixture of carbon compounds—contains, besides carbon, small proportions of hydrogen, oxygen, nitrogen, and sulfur.

The utilization of elemental carbon for the preparation of organic compounds depends first of all upon its transformation into a reduced form. There are two important ways in which this is done: (1) through the conversion of coke into calcium carbide by the high-temperature reaction of lime and carbon, followed by the generation of acetylene by the reaction of calcium carbide and water,

$$CaO + 3C \longrightarrow CaC_2 + CO$$
$$CaC_2 + 2H_2O \longrightarrow Ca(OH)_2 + HC{\equiv}CH$$

and (2) through the high-temperature reaction of coke with steam to form a mixture

of carbon monoxide and hydrogen, and the subsequent reduction of the carbon monoxide by the hydrogen to produce methanol or (depending upon how the process is conducted) compounds of higher molecular weight:

$$C + H_2O \longrightarrow CO + H_2$$
$$CO + 2H_2 \longrightarrow CH_3OH$$

Acetylene and methanol are simple, abundant, inexpensive, and valuable materials, from which many organic compounds can be prepared.

Some of the uses of natural gas and petroleum as organic raw materials have already been described. These materials, along with coal, constitute the bulk of the world's supply of carbon that is readily available for transformations into organic compounds. The supplies of alcohols, ethers, aldehydes, ketones, acids, esters, and other organic chemicals on the market are for the most part derived from these raw materials. A "fine chemical" industry also exists; its role is to transform the simple compounds available cheaply and in large quantities into more complex substances.

Thus, the organic chemist has at his service a market in which a great many compounds can be obtained for his research. From this research come new ways of transforming carbon into useful substances, new compounds useful to man, and further understanding of nature.

2-11 Natural sources of carbon compounds

Nature provides additional sources of carbon compounds, many of them in large amounts. The forests and the cotton plant provide cellulose, a complex compound of carbon, hydrogen, and oxygen; sugar cane and sugar beets provide enormous tonnages of a pure compound, sucrose; the fragrant exudates and essences of trees and flowers provide oils and perfumes; and, until the rise of the synthetic-dye industry, plants were important sources of dyestuffs. Most of these compounds are used without being subjected to extensive transformation: cellulose is used in the form of paper, textiles, and films; fragrant oils as flavoring materials and perfumes; sugar as a food; drugs (such as morphine and cocaine) as medicinals. The organic chemist discovers and isolates such compounds, determines their structure, synthesizes them from simpler compounds, and often inquires into the physiological processes by which they are formed in the living cell, or asks how they are transformed in the body when used as food or as drugs.

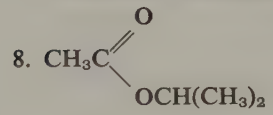
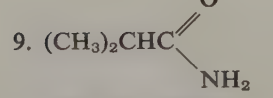
In order to achieve these ends the organic chemist must be able to bring about and interpret the chemical transformation that takes place when one organic compound is changed into another. The study of organic chemistry provides him with the understanding that he needs to manipulate organic compounds in predictable and understandable ways, and that he needs to apply the knowledge he gains in this research to the recognition and solution of new problems.

Problems

1. Write an acceptable structural formula for each of the following:
   (*a*) an ester of the composition $C_8H_{14}O_2$
   (*b*) a cyclic ketone of the composition C_5H_6O
   (*c*) a phenolic carboxylic acid
   (*d*) a carboxylic acid of the composition $C_5H_6O_2$
   (*e*) a cycloheptenone
   (*f*) a β-diketone of the composition $C_5H_6O_2$
   (*g*) the amide of (*d*)
   (*h*) 1,2-cyclo-octadiene

2. What is the origin of the following words: (*a*) petroleum, (*b*) allyl, (*c*) formic, (*d*) oxalic, (*e*) methyl, (*f*) olefin, (*g*) sebacic, (*h*) suberic? (NOTE: Refer to a good standard dictionary.)

3. Select from column B the kind (class) of each compound whose structural formula is given in column A.

A	B
1. $CH_3CH_2CH_2OH$	(*a*) a carboxylic acid
2. $CH_3COCH(CH_3)_2$	(*b*) an unsaturated ether
3. $CH_3CH{=}CHCOOH$	(c) a tertiary amine
4. $CH_3CH_2N(CH_3)_2$	(*d*) a secondary alcohol
5. $(CH_3CH_2)_2CHOH$	(*e*) a saturated primary alcohol
6. $(CH_3)_3CCH_2NH_2$	(*f*) an unsaturated primary alcohol
7. $CH_2{=}CHCH_2CH_2OH$	(*g*) an ester
8. 	(*h*) an acid anhydride
	(*i*) a saturated ketone
	(*j*) an amide
9. 	(*k*) an unsaturated ketone
	(*l*) an amino ketone
	(*m*) an unsaturated acid
	(*n*) a secondary amine
	(*o*) a saturated primary amine
10. $(CH_3CH_2CO)_2O$	
11. $CH_2{=}CHOCH_2CH_3$	
12. $CH_2{=}CHCOCH_3$	
13. $(CH_3)_2CHCH_2COOH$	
14. $CH_3CH_2COCH_2CH_2NH_2$	
15. $CH_3NHCH_2CH_2CH_3$	

3

Atomic and molecular structure. Chemical bonds

This chapter describes two of the fundamental aspects of organic chemistry: (1) the manner in which atoms are joined together by chemical bonds; and (2) the extension of bonds in space—that is, the size and shape of organic compounds.

The study of the arrangement in space of the atoms composing a molecule is called *stereochemistry*, whose concepts are found, explicitly or implicitly, throughout organic chemistry. A central fact of organic stereochemistry is the tetrahedral form of the tetracovalent carbon atom and the molecular dissymmetry that is often the consequence. Since a large proportion of organic compounds contain one or more such centers of dissymmetry, it is important for the student to encounter stereochemical ideas at an early point in his study.

The student will learn that the chemical formulas on the printed page represent material, three-dimensional objects. He will learn some of the conventional ways of representing chemical structures, which include the use of dotted, bold, and light lines to represent the three-dimensional extension of bonds; perspective drawings; and, in some cases, scale models. When spatial concepts have become familiar, it will become apparent that simpler expressions, in which the spatial relationships are implicit, can be used.

Stereochemical relationships will be discussed further in a later chapter, but stereochemistry should not be looked upon as a special topic.

3-1 Regularity of structure. Molecular architecture

In order for organic compounds to exist as unique substances having characteristic properties and showing definite behavior, the atoms of carbon, hydrogen, and oxygen (and other elements) that compose them must be held together in definite, stable arrangements. For example, the fifteen atoms of carbon, hydrogen, and oxygen that constitute a molecule of *n*-butyl alcohol form a constellation of atoms in a certain arrangement, joined by bonds of definite lengths with fixed angular relationships. The fifteen atoms of the isomeric compound diethyl ether are fixed in quite a different arrangement; yet both of these compounds are represented by the formula $C_4H_{10}O$. The reasons for the differences between these isomers are to be found in the manner in which their constituent atoms are joined together; that is, in the *structures* of the molecules.

3-2 Valence, or combining power

From general chemistry and from the preceding chapters we are familiar with the concept of valence, or the combining power of an element. Hydrogen is typically monovalent, and the valence of another element may be determined by noting the number of hydrogen atoms with which it combines. Thus in methane, CH_4, carbon is tetravalent; in ammonia, NH_3, nitrogen is trivalent; in water, H_2O, oxygen is divalent; in sodium hydride, NaH, sodium is monovalent. Although the concept of valence is an important one, it cannot alone account for the differences between isomers. For example, there are six compounds with the composition C_4H_8; in all of them carbon is tetravalent and hydrogen is monovalent. We must look beyond the idea of valence to discover the differences between the molecules of these six compounds; we can do this best by examining the nature of the bonds by which their atoms are joined: their length, direction, and relative disposition in space.

3-3 The structure of the atom

An atom of any element is composed of a dense, compact nucleus and one or more negatively charged electrons. The nucleus, which contains at least one proton and a number (possibly none) of neutrons, bears a positive charge that is equal to the number of protons it contains. This number, the *atomic number*, ranges from 1 for hydrogen, the lightest element, to 103 for lawrencium, the heaviest of the known elements. When an atom is electrically neutral, the number of electrons that surround the nucleus is equal to the number of protons, or positive charges it contains.

The mass of an atom is concentrated in the nucleus, and the *mass number* of an atom is equal to the total number of protons and neutrons in the nucleus. Hydrogen, with atomic number 1, consists of a nucleus of one proton, with one extranuclear

electron. The mass number of hydrogen is thus 1. In deuterium, the nucleus contains a proton and a neutron, and thus the mass number is 2; but since the neutron carries no charge, the atomic number is still 1. Tritium, with mass number 3 and atomic number 1, is a third *isotope* of hydrogen.

As more protons are added to the nucleus, with a corresponding increase in the number of extranuclear electrons, the elements that make up the periodic table are formed. Our chief concern will be with those of the *first short period*, or row, since in this group are found carbon, nitrogen, and oxygen. We can discuss the nature of most organic compounds quite adequately in terms of hydrogen, carbon, nitrogen, oxygen, and the halogens (of which fluorine will serve as the type for our initial discussions). Organic compounds containing elements of the *second short period* (sodium, magnesium, aluminum, silicon, phosphorus, sulfur, and chlorine) are also well known and important both practically and theoretically, and will be dealt with when discussion of them is appropriate.

3-4 Electronic structure and symbolism

The electrons in an atom do not move around the nucleus in a random way, but are grouped according to their energy and distance from the nucleus into structures called *shells*, which are given numbers, beginning with 1 for the innermost. Each of these is composed of one or more *subshells*, which are distinguished by the letters *s*, *p*, *d*, *f*, ... These in turn are composed of one or more *orbitals*, each of which can contain up to two electrons. Usually only the electrons in the outermost shell participate in chemical bonding; they are referred to as *valence electrons*.

Figure 3-1 summarizes the electron structure of the lighter elements of the periodic table in terms of the disposition of the extranuclear electrons in atomic orbitals. Note that pairs of electrons occupying a given orbital are distinguished by opposite spins, indicated by the vertical arrows. Note, too, that the 2*p* subshell includes three orbitals (see Section 3-12).

It is convenient to adopt a symbolism for the electronic structures of atoms that is less awkward than writing each orbital individually. A satisfactory device for the first-period elements is to consider the nucleus and the 1*s* electrons as a unit, called the *kernel*, and to show the valence electrons as dots surrounding the usual symbol of the atom. Thus, we write

Similarly, sodium is conveniently written as Na·, since only the single 3*s* electron is involved in the usual reactions of sodium:

$$\mathrm{Na}\cdot \longrightarrow \mathrm{Na}^{+} + e$$

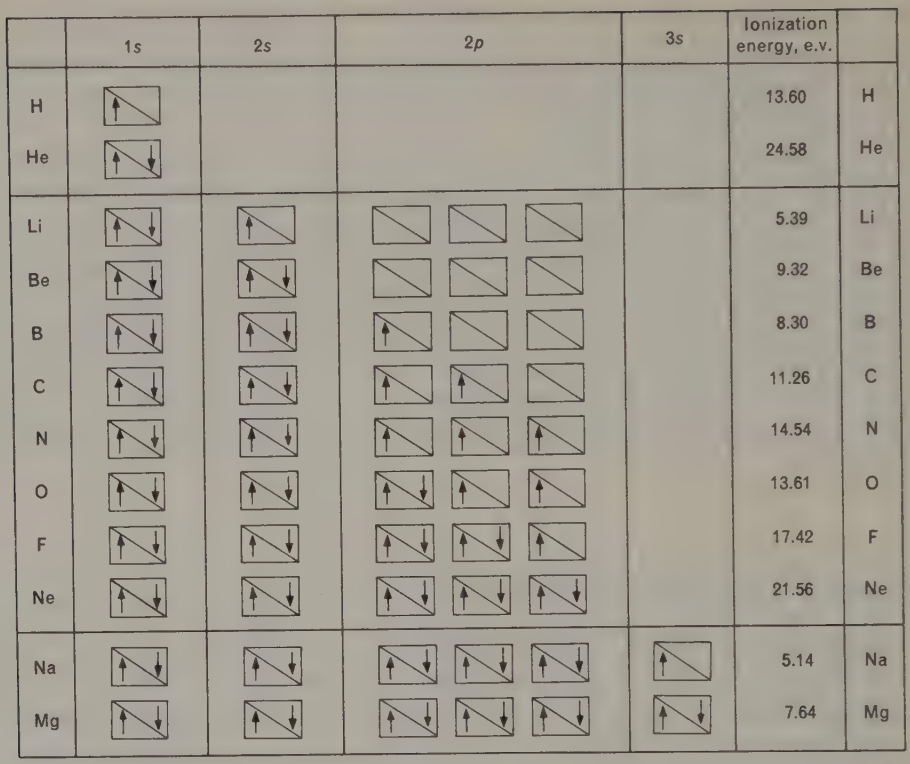


Figure 3-1
The electronic atomic structures of the first twelve elements of the periodic table.

The unspecified ten electrons of the filled $1s$, $2s$, and $2p$ shells of sodium are not involved in reactions that will concern us, and they are understood to make up the electronic complement of the sodium ion when it is written Na^+. Chlorine and bromine will be encountered later in the text as the molecule, the atom, the cation, and the anion:

$$:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}: \qquad :\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}\cdot \qquad :\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}^{+} \qquad :\ddot{\underset{\cdot\cdot}{\mathrm{Cl}}}:^{-}$$

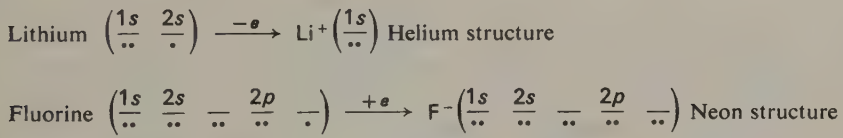
In chlorine, the external shell, or *valence shell*, is composed of the seven electrons of the $3s$ (two) and $3p$ (five) subshells. The bromine atom is similarly represented as $:\ddot{\underset{\cdot\cdot}{\mathrm{Br}}}\cdot$, in which the seven valence-shell electrons are those of the external shell ($4s^2$ and $4p^5$). The complete electronic complement of the bromine atom can be shown by the symbol $1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2 4p^5$.

Exercise 1

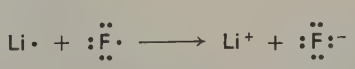
Using the notation just described for bromine, write the symbols for the electronic structures of (*a*) nitrogen, (*b*) aluminum, (*c*) carbon, (*d*) silicon, (*e*) phosphorus, (*f*) boron, (*g*) oxygen, and (*h*) sulphur. Compare (*a*) with (*e*), (*b*) with (*f*), (*g*) with (*h*) and (*c*) with (*d*). What similarities do you find?

3-5 The noble-gas structure. The "octet"

An electronic interpretation of chemical bond formation was proposed in 1916 by G. N. Lewis (1875–1946). Lewis pointed out that the chemical inertness of the noble gases indicated a high degree of stability of the electronic complement of these elements: helium, with a shell of two electrons, neon with shells of two and eight, and argon with shells of two, eight, and eight. The first consequence to be noted is that elements near the ends of a period tend to lose or gain electrons in such a way as to acquire a noble-gas structure. For instance,



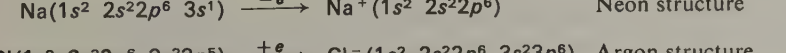
Since a chemical reaction in which lithium is converted to lithium ion involves a transfer of the electron to some other atom, the two changes shown in these equations can be written as a single reaction:



Lithium has now attained the helium structure, and fluorine has attained the neon structure.

The complete eight-electron grouping of four completely filled (one *s*, three *p*) orbitals was called by Lewis the *octet*. Helium is of course the unique exception, since it possesses only the 1*s* shell. The completion of a pair of electrons in the 1*s* shell by gain (hydrogen) or loss (lithium, beryllium) is the counterpart of the completion of the octet by atoms of higher atomic number.

Sodium, like lithium, is an alkali metal that readily loses an electron and is transformed into a positive ion. Chlorine, like fluorine, is a halogen, and readily gains an electron to become chloride ion.



3-6 The ionic bond. Electrovalence and organic salts

The bond that holds sodium ions and chloride ions in the definite arrangement that we recognize in sodium chloride is an electrostatic attraction between the oppositely charged ions. A crystal of sodium chloride consists of a closely packed array of these two ions, in which we cannot discern any pairs that might be called sodium chloride molecules. The attractive forces between these ions have no fixed direction in space, and each ion is surrounded by ions of the opposite kind. When a salt such as sodium chloride is dissolved in water its ions become largely independent; each exerts its electrostatic attraction upon the surrounding water molecules to become a *hydrated ion.*

In organic chemistry the ionic bond is found chiefly in salts of organic acids and bases; in this respect it needs no special discussion. Organic salts are usually water-soluble for the same reasons that the more familiar inorganic salts are soluble; the ions, bound in a regular lattice in the crystal, dissociate and solvate when put into water to yield a solution of the separate ions. The organic portion retains its structural integrity; for example, sodium acetate dissolves in water to give a solution of sodium ions and *acetate* ions:

$$CH_3COO^-Na^+ + H_2O \longrightarrow CH_3COO^- + Na^+ \quad \text{(Both solvated)}$$

NH_4^+	Cl^-	$CH_3NH_3^+$	Br^-
Ammonium	chloride	Methylammonium	bromide
$CH_3CH_2NH_3^+$	CH_3COO^-	$((CH_3)_3NH^+)_2$	$SO_4^=$
Ethylammonium	acetate	Trimethylammonium	sulfate

Salts of amines consist of equal numbers of substituted ammonium cations and organic or inorganic anions, which in the solid state form a crystal lattice by virtue of the electrostatic attraction of the oppositely charged ions.

Most salts are solids, often with high melting points because the ionic interactions are so strong that vigorous thermal agitation, brought about by elevation of the temperature, is necessary to destroy the ordered arrangement of the ions. In this respect, ionic organic compounds (usually salts of the kind described) are not much different from salts consisting wholly of inorganic ions. They differ chiefly in melting points, those of many organic salts being much lower than those of the familiar inorganic salts.

3-7 The covalent bond

The tendency for the elements near the ends of a period to gain or lose electrons and thus attain the electronic structures of the rare gases is not found in the elements near the center of a period. The energy required to add successive electrons to nitrogen or carbon to form N^{3-} or C^{4-}, or the energy required to remove successive electrons from boron or carbon to form B^{3+} or C^{4+}, is prohibitive for simple electrostatic reasons. These atoms may, however, acquire a complete octet of electrons by *sharing* electrons with other atoms. This sharing of electrons joins the atoms together by a *covalent bond.*

The electrons are not transferred from an orbital of one atom to that of another; rather, they spend some time in the orbitals of both atoms so that each atom has a filled outer shell.

3-8 The hydrogen molecule

The simplest and purest example of the covalent bond is found in the hydrogen molecule. When two atoms of hydrogen collide, the single electron of each can be accommodated into the 1*s* orbital of the other (for an orbital can contain a pair of electrons). The great gain in stability brought about by this combination is evidenced by the large quantity of energy liberated (for example, as heat) when the hydrogen molecule is formed:

$$H\cdot + H\cdot \longrightarrow H_2 + 104 \text{ kcal}$$

The covalent bond is thus a strong bond, for it would require 104 kcal to dissociate a mole of hydrogen into its constituent atoms.

What is the reason for the great stability of the covalent bond? The two positively charged nuclei are held together by the attractive force of two electrons, which are now to be found largely in the region between the nuclei.

In order for two hydrogen atoms to form a hydrogen molecule, the two atoms must clearly approach one another close enough to permit their 1*s* orbitals to *overlap*, permitting both electrons to occupy either orbital and to find their way from one to the other without leaving the attractive influence of a nucleus (Figure 3-2).

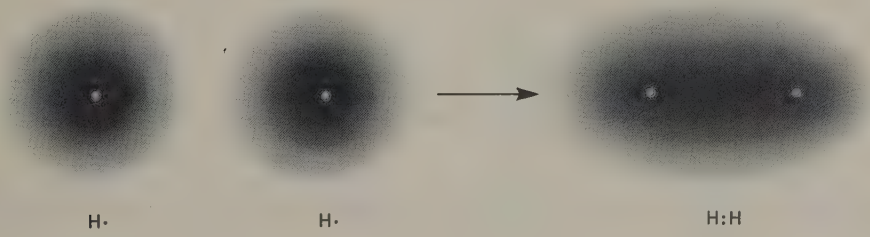


Figure 3-2
The formation of the hydrogen molecule by combination of hydrogen atoms.

But the atoms cannot approach closer than a certain distance, because the repulsive force of the two positively charged nuclei will then increase sharply as the distance between them diminishes. In the normal hydrogen molecule, then, the atoms are separated by a fixed distance, known as the *bond length*. Figure 3-3 is a graphical representation of the energy of the H—H system as a function of the internuclear distance.

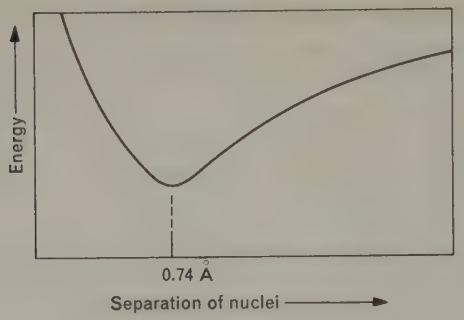


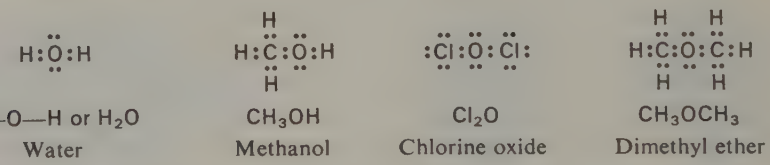
Figure 3-3
Energy diagram for the hydrogen molecule. The distance 0.74 Å is the H—H bond length.

3-9 The covalent bond between unlike atoms

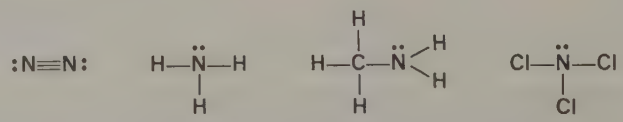
Only a few elements form simple diatomic molecules. The halogens, by sharing the single unpaired electron in the outer (2*p* in fluorine, 3*p* in chlorine) valence orbital, can form a covalent bond to form, for example, F_2, Cl_2, Br_2, and I_2. As in hydrogen, the paired electrons occupy a *molecular orbital* that includes the two atomic nuclei. The formation of the molecular orbital, with the completion of the electronic complement of all four of the outer *s* and *p* orbitals of each atom (the octet), results in an arrangement more stable than the separate atoms.

The majority of known covalent compounds are constructed of bonds between unlike atoms. The same process of electron sharing is involved in such bonds, but for elements near the center of a period, two, three, or four electrons are needed to complete the octet, with the result that more than one covalent bond can be formed.

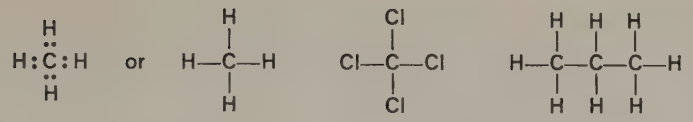
Oxygen, with six electrons in its valence shell, can complete its octet by forming two covalent bonds with other atoms, as in the compounds water, methanol, chlorine oxide, and dimethyl ether:



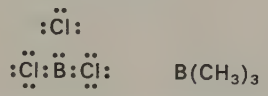
Nitrogen, with five valence electrons, can acquire a complete octet by forming three covalent bonds:



The ability of carbon to form covalent bonds not only with atoms of other kinds, but also with other carbon atoms, gives rise to the enormous number of organic compounds. The pairing of its four outer electrons in bond formation gives carbon its characteristic valence:



Boron, however, can form only three bonds by the simple process of electron-pair formation with single electrons of other atoms:

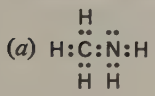


Note, however, that in BCl_3 and $B(CH_3)_3$ the boron atom has not completed its octet, and thus has the capacity for accepting another pair of electrons. This property of boron (and its second-row counterpart, aluminum) has important chemical consequences, which will be dealt with later in this chapter.

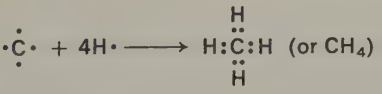
Exercise 2

Write complete electronic structures for the following compounds: (*a*) CH_3NH_2, (*b*) CH_2Cl_2, (*c*) CH_3CH_2Br, (*d*) CH_3OCH_3, (*e*) $(CH_3)_2CHOH$, (*f*) HOCl, and (*g*) H_2NOH.

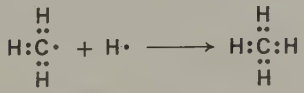
Show all covalent bonds and all unshared pairs of electrons. As an example,



The nature of the covalent bond is independent of the way in which it is formed. For example, methane is the same compound whether it is formed by the combination of carbon and hydrogens atoms,



by the combination of a methyl radical and a hydrogen atom,



or by the loss of carbon dioxide from acetic acid,

$$CH_3COOH \xrightarrow[\text{soda lime}]{\text{heat with}} CH_4 + CO_2$$

3-10 Unequal sharing of electrons in the covalent bond

In the H—H bond of the hydrogen molecule the electrons are equally shared between the two atoms; that is, the molecular orbital is symmetrical with respect to the two nuclei. In diatomic molecules consisting of two different atoms joined by a covalent bond, a greater share of the pair of electrons is held by one of the atoms; the molecular orbital is unsymmetrical, and one end of the covalent bond is negative with respect to the other. This dissymmetry is reflected in the physical and chemical properties of the compounds in which such covalent bonds are present.

A conspicuous property of diatomic compounds containing dissymmetric covalent bonds is their tendency to orient themselves in an electrostatic field. The measure of this tendency is expressed numerically as the *dipole moment* of the molecule; it is the product of the difference in charge and the distance between the positive and negative centers. In Table 3-1 are given the dipole moments of a few simple dipolar molecules.

Table 3-1
Dipole moments of some simple molecules

Compound	*Dipole moment (D)* *
HF	1.9
HCl	1.1
HBr	0.8
HI	0.4
FCl	0.9
HCN	3.0
NH_3	1.5

* Dipole moments are recorded in *Debye units*, named after Peter Debye, who made the first experimental studies of this property. One Debye unit is equal to 10^{-18} e.s.u. × cm.

The presence of a dipole moment in a molecule confers upon it certain properties that are the result of the electrical dissymmetry. Dipolar molecules tend to orient themselves toward each other so that opposite charges attract and like charges repel. The result is that while a nonpolar substance is a randomly oriented population of molecules, a dipolar substance has a degree of structural organization in the liquid and solid state. The additional energy required to overcome these intermolecular attractions is reflected in high boiling points for dipolar liquids and high melting points for dipolar solids—that is, higher than the boiling points and melting points of nonpolar substances of comparable molecular size and weight.

Dipolar character in a bond results in greater bond strength than would be expected were it not a factor. The reason for this is that the energy required to break

the bond (to separate the two atoms) must be sufficient to overcome the electrostatic attraction of the two oppositely charged atoms joined by the bond. For example, the experimentally determined values of the H—H, Cl—Cl, and H—Cl bond energies are:

$$\text{H—H} \longrightarrow \text{H}\cdot + \text{H}\cdot \quad -104 \text{ kcal/mole}$$
$$\text{Cl—Cl} \longrightarrow \text{Cl}\cdot + \text{Cl}\cdot \quad -58 \text{ kcal/mole}$$
$$\text{H—Cl} \longrightarrow \text{Cl}\cdot + \text{H}\cdot \quad -102 \text{ kcal/mole}$$

If the H—Cl bond energy were simply the sum of the contributions of one-half each of the H—H and Cl—Cl bond energies, it would be $104/2+58/2 = 81$ kcal/mole. This bond is in fact much stronger than this (by 21 kcal/mole), because of the unequal sharing of the valence electrons between H and Cl. The dipole moment of HCl (1.10 D) can be represented as

$$\overset{+\longrightarrow}{\text{H—Cl}}$$

The direction of the arrow indicates the greater share of the valence electrons on chlorine; thus, chlorine is more *electronegative* than hydrogen.

3-11 Electronegativity

The ionization energy of an element is a measure of the attraction of the positively charged nucleus for the peripheral electron that is removed in the process $X \rightarrow X^+ + e$. The actual value of the energy is modified by the character and position of the orbital in which the electron is found, but the ionization energy, and thus the nuclear attraction of the valence electrons, rises from left to right in a row of the periodic table. By calculations that will not be given here, Linus Pauling has assigned numerical values to this electron-attracting power and called this set of values an electronegativity scale. A portion of the scale is given in Table 3-2.

Our chief concern in what follows will be with the charge distribution in single bonds between carbon and other elements of the first long row (Li to F). The nature of C—X (X = halogen), C—N, and C—O bonds will be of primary importance. It is easy to see that in each of these examples the *carbon atom is positive with respect to the other atom*, and thus will be the center of attack by reagents that provide electrons to form new bonds.

The decreasing electronegativity of the halogens as the atomic number increases is the result of the greater distance of the electrons in the outer shell from the positively charged nucleus.

The greatest value of the concept of electronegativity to the organic chemist is in its qualitative applications. Only rarely are the numbers given in the table used in calculations. These values do, however, permit us to recognize the nature of a chemical bond and, roughly, the degree of its polarization. For example, in the molecule of

Table 3-2
Electronegativity values for some of the elements commonly found in organic compounds (H = 2.1)

Groups						
I	*II*	*III*	*IV*	*V*	*VI*	*VII*
Li 1.0	Be 1.5	B 2.0	C 2.5	N 3.0	O 3.5	F 4.0
Na 0.9	Mg 1.2	Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0
						Br 2.8
						I 2.5

methyl chloride, CH_3Cl, whose dipole moment is 1.9 D, chlorine, which is the more electronegative, is the negative end of the dipole.

3-12 The extension of covalent bonds in space. The geometry of organic molecules

Atomic orbitals. The atomic orbitals (in the first-row elements, the 1*s*, 2*s*, and the three 2*p* orbitals) occupy definite regions in space. The extranuclear electrons are distributed around the nucleus in certain well-defined ways.

The 1*s* orbital is spherically symmetrical about the nucleus; this is true also of the 2*s* orbital, which surrounds and is concentric with the 1*s* orbital (Figure 3-4).

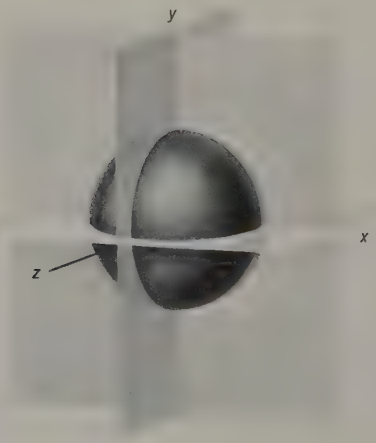


Figure 3-4
Spatial disposition of the *s* atomic orbital.

The electrons in these orbitals are found somewhere in a diffuse spherical volume, and their locations can be defined only as probabilities. In the hydrogen atom, the most probable distance of the 1*s* electron from the nucleus is 0.53 Å; in heavier atoms with greater nuclear charge, the 1-shell becomes smaller. The most probable distance for the electrons in the 2*s* orbital also depends upon the magnitude of the nuclear charge, but again we find that the distribution is spherically symmetrical.

The three 2*p* atomic orbitals are not spherically symmetrical, but extend at right angles to each other along what may be considered the *x*, *y*, and *z* axes (Figure 3-5).

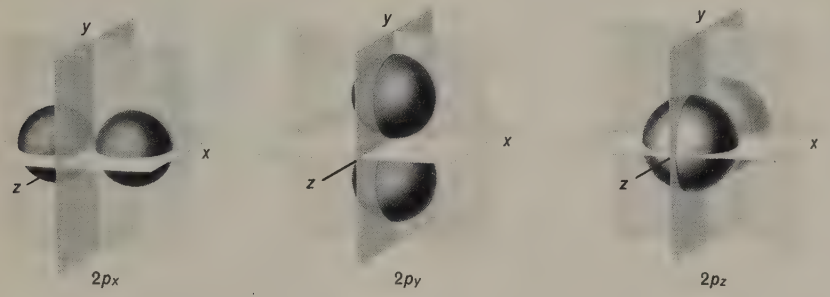


Figure 3-5
Spatial disposition of the *p* atomic orbitals.

Molecular orbitals. When two hydrogen atoms combine to form a hydrogen molecule, the 1*s* orbitals overlap so that the resulting molecular orbital, containing the two electrons, can encompass both nuclei (Section 3-8). It is clear that overlap is a necessary condition for the formation of the molecular orbital; since electron density drops off sharply with increasing distance from the nucleus, the two hydrogen atoms must approach each other closely to permit both electrons to come under the attractive influence of both nuclei.

Although the atomic *s* orbitals are spherical, and thus can engage in molecular orbital formation from any direction, the atomic *p* orbitals extend along three axes at right angles to each other. Thus if two atomic *p* orbitals of an atom were to be used to form bonds with two other atoms, the two bonds (molecular orbitals) so formed might be expected to be at right angles to each other.

This can be seen in the combination of two hydrogen atoms and an oxygen atom to form a molecule of water. Oxygen, with six electrons in the 2-shell, can complete a full complement of eight electrons (four filled orbitals) by forming two covalent bonds with two hydrogen atoms:

$$\mathrm{O}\left(\frac{1s}{\cdot\cdot}\ \frac{2s}{\cdot\cdot}\ \frac{\quad}{\cdot\cdot}\ \frac{2p}{\cdot}\ \frac{\quad}{\cdot}\right) + 2\mathrm{H}\left(\frac{1s}{\cdot}\right) \longrightarrow \mathrm{H_2O}\left(\frac{1s}{\cdot\cdot}\ \frac{2s}{\cdot\cdot}\ \frac{\quad}{\cdot\cdot}\ \frac{2p}{\cdot\cdot\ \mathrm{H}}\ \frac{\quad}{\cdot\cdot\ \mathrm{H}}\right)$$

What is the shape of the water molecule? Our first assumption might be that since two *p* orbitals of the oxygen atom have been used, and these are at right angles to each other, the H—O—H bond angle would be 90°. The experimentally determined bond angle is in fact 104.5°. Figure 3-6 is a representation of the molecule: (*a*) is a schematic drawing in which the molecular orbitals are indicated; (*b*) is a molecular model.

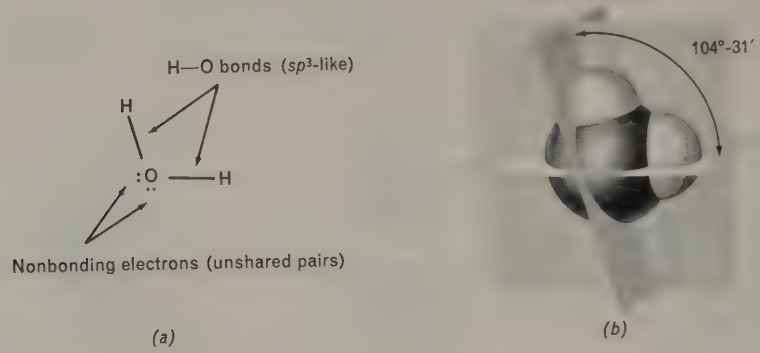


Figure 3-6
(*a*) Disposition of the bonding and nonbonding electrons in the water molecule. (*b*) A model of the water molecule.

It must be recognized, however, that when oxygen combines with hydrogen to form the water molecule, the H—O bonds found in the completed water molecule constitute *molecular orbitals*, and thus need not have the geometry of the atomic *p* orbitals of the lone oxygen atom. The eight electrons around oxygen in the water molecule, found in the two H—O bonds and in the two unshared pairs of electrons, can be expected to be disposed in such a way as to compose an arrangement of minimum energy. They can no longer be described in the same way as the atomic 2*s* and 2*p* orbitals. For one thing, the two molecular orbitals of the H—O bonds extend from the oxygen atom toward the hydrogen atoms; atomic orbitals, on the other hand, are symmetrical with respect to the nucleus and possess a node or nodal plane of zero probability density at their centers. If these two molecular orbitals are altered in character, it is to be expected that the remaining two orbitals on oxygen, each of which contains an unshared ("lone") pair of electrons, are also different from the atomic 2*s* and 2*p* orbitals.

A useful guiding principle for assessing the probability distribution of electrons (or bonds) about an atomic nucleus is the simple rule that the electrostatic repulsion between the electrons will cause them to be arranged in such a way as to minimize these repulsive forces. Imagine the electrons as situated on the surface of a sphere. Two like charges or electron pairs on the spherical surface would tend to move to opposite sides and to arrive at a position 180° from each other. Three pairs of electrons would

arrange themselves 120° apart on a plane; four pairs at the corners of a regular tetrahedron. Similar considerations for penta-, hexa-, and octacovalent molecules lead to the distributions shown in Figure 3-7.*

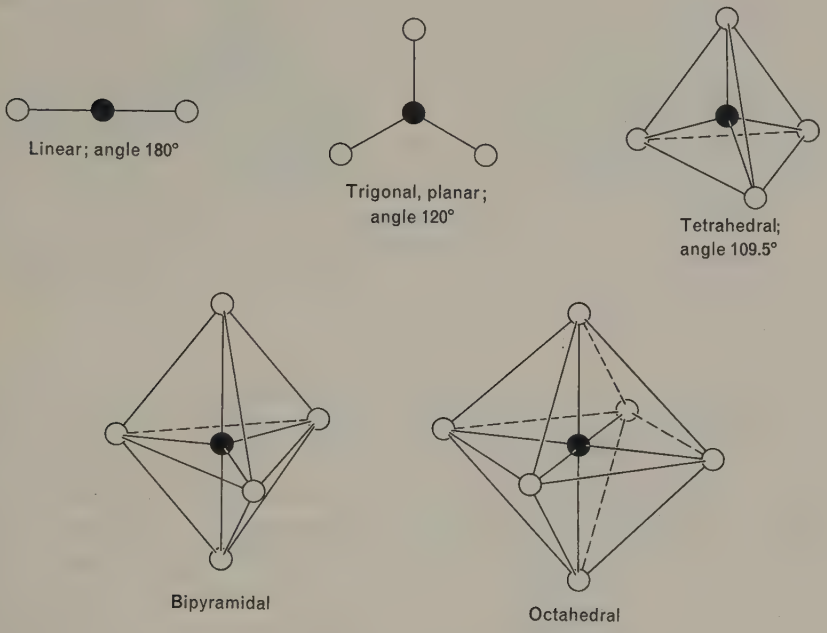


Figure 3-7
Angular distribution of bonds.

The geometry of the water molecule can now be pictured as resulting from the distribution of four electron pairs about the oxygen kernel: two pairs constitute the two H—O bonds, two pairs are lone. Were the tetrahedron formed by these four orbitals a regular one, the bond angles would be 109.5°. But the unshared pairs are closer to the oxygen nucleus than are those shared with the hydrogen atoms, and thus would be expected to exert greater repulsive force upon each other than upon the shared pairs. The result is that the angle between the lone-pair orbitals is slightly greater than 109.5°, and that between the H—O bonds slightly less. This qualitative approach to the problem gives us a picture of molecular geometry that is close to reality, although the precise values for the bond angles can be found only by experiment.

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* An excellent classroom demonstration of the distribution of bonds by mutual repulsion can be performed with cylindrical (sausage-shaped) balloons. A description of this demonstration is given by H. R. Jones and B. R. Bentley, *Proceedings of the Chemical Society* (London), November, 1961, p. 438. The elongated balloons required are readily obtained in model or toy shops.

The simplest description of ammonia, in which nitrogen is bonded to three hydrogen atoms by three atomic *p* orbitals, would be three *s-p* bonds at right angles to each other, and a 2*s* orbital occupied by an unshared electron pair.

The experimental facts are that the angles between N—H bonds in ammonia are 107°, and that the fourth pair of (unshared) electrons has its major extension from the nucleus in a direction opposite to the three N—H bonds. The molecule thus has N—H bonds extending to three corners of a distorted tetrahedron and the lone electron pair extending toward the fourth corner.

The larger atoms in group VI of the periodic table—sulfur, selenium, and tellurium —form hydrides in which the bond angles between hydrogen and the central atoms are nearly 90°. However, since these large atoms make use of orbitals above the 2*p* shell, the electronic distribution in their hydrides is complex, and a simple qualitative analysis is not adequate.

3-13 The tetrahedral carbon atom. The sp^3 bond and orbital hybridization

The formation of four bonds by carbon is one of the central facts of organic chemistry.

The disposition of the four C—H bonds in methane and in other compounds of the type CX_4 is *tetrahedral*. The bonds are all alike; no one can be distinguished from the other three. Were the 2*s* and 2*p* orbitals used in bond formation with retention of their atomic configuration, we might expect to find three C—H bonds 90° apart and a fourth, involving the spherical 2*s* orbital, with no fixed direction. This is contrary to the facts.

That the configuration of the carbon atom carrying four substituents, Cabde, is tetrahedral was postulated on quite empirical grounds by van't Hoff and Le Bel in 1874, and is the central postulate of the stereochemistry of organic compounds. The calculations of quantum mechanics lead to the same conclusion: the most stable configuration for the four orbitals in a tetracovalently bound carbon atom is that in which the bonds are tetrahedrally arranged (Figure 3-8).

Indeed, we could have arrived at the same conclusion from simple considerations of electrostatic repulsion. How can we distribute four bonds (pairs of electrons) around a central atom so that they are positioned as far as possible from one another, making repulsive forces between the electrons minimal? There is a simple geometrical answer: four bonds are uniformly disposed at the greatest separation when they are arranged tetrahedrally.

Four equivalent, symmetrically disposed bonds (as in a molecule like methane, CH_4, or carbon tetrachloride, CCl_4) are, of course, indistinguishable. To identify one as formed from an atomic 2*s* orbital and the other three from atomic 2*p* orbitals would be meaningless. They are all alike.

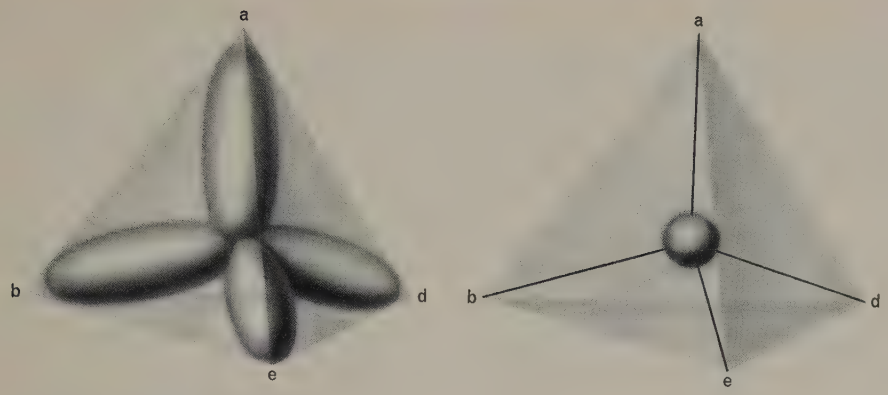
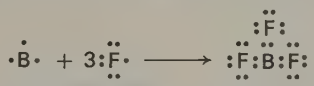


Figure 3-8
The tetrahedral disposition of the four sp^3 bonds of the saturated carbon atom.

The formation of four *equivalent* orbitals from one 2*s* and three 2*p* orbitals is called *hybridization* of the four orbitals, since the new molecular orbitals have neither the same angular relationship nor the same kind of symmetry with respect to the *x*, *y*, and *z* axes as the four original atomic orbitals. The new orbitals are called sp^3 orbitals, and the four bonds of a tetracovalent carbon atom like the one in methane are called sp^3 *bonds* ("*sp*-three" bonds).

3-14 Orbital hybridization in other first-period elements

Boron (atomic number 5; $1s^2 2s^2 2p^1$) typically forms compounds BX_3; for example, BF_3, BCl_3, and $B(CH_3)_3$. Thus it utilizes the three 2*s* and 2*p* electrons to form three covalent bonds by pairing these in two-electron molecular orbitals:



Boron trifluoride is a gas at ordinary temperatures, which is not characteristic of ionic compounds; the three B—F bonds are covalent bonds and BF_3 is a covalent molecule. Moreover, it has been found by physical measurements that the three B—F bonds are identical, and lie 120° apart in the same plane. Now since *s* and *p* orbitals are quite different in both energy and geometry, it is apparent that the three B—F bonds, which are all alike, cannot have been formed from *s* and *p* orbitals of boron in their atomic configuration; and since the three BF_3 bonds are in a single plane and 120° apart, it is equally clear that they have not been formed from the three *p* orbitals of boron. Thus the three B—F bonds represent a new kind of molecular orbital. This

is called a hybrid orbital, and, in the terminology already used for carbon, the bonds are called sp^2 ("*sp*-two") bonds.

Again, the electrostatic analogy gives a picture in agreement with the experimental facts: three pairs of electrons will occupy positions of minimum energy—that is, they will show minimum repulsive interactions—when they are arranged in a plane about the nucleus at mutual angles of 120° (a "trigonal" arrangement).

From the above discussion we can draw some general conclusions about the geometry of a number of simple molecules and ions. For example, the carbonate ion, in which three oxygen atoms are attached to a central carbon atom, can be expected to be planar and trigonal; similarly the methyl cation, CH_3^+, and the sulfur trioxide molecule can also be expected to be planar and trigonal.

The tetrahedral configuration is possessed by such tetracovalent compounds as the ammonium ion, NH_4^+, the perchlorate ion, ClO_4^-, the fluoborate ion, BF_4^-, and the silicon tetrachloride molecule, $SiCl_4$. Despite the wide range in the character of the central atoms and the peripheral atoms, all these substances have a common structure: each of them consists of a central atom surrounded by four bonds to identical substituents, and each bond consists of a shared pair of electrons; each bond is formed with the use of sp^3 hybrid orbitals of the central atom.

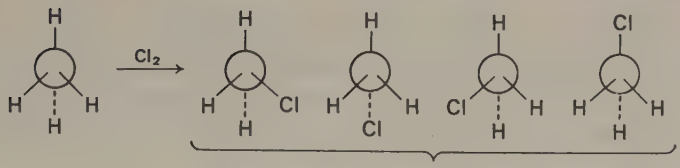
Since very few organic compounds consist only of a carbon atom surrounded by four identical substituents, the regular tetrahedron, with all four bond angles equal to exactly 109.5°, is seldom found. Nevertheless, a carbon atom carrying four substituents is tetrahedral in form, but when the four substituents are not the same there are small deviations from the regular 109.5° bond angle.

3-15 The stereochemistry of the tetracovalent carbon atom

Stereochemistry (*stereo*, from the Greek word for "solid," has the connotation of three-dimensional, or spatial) is the study of the arrangement of atoms within a molecule. Most of the chemical properties of organic compounds bear a definite relationship to the shape of the molecule and the relative positions of its constituent atoms. Nearly all considerations of the nature of organic substances must include explicit reference to the stereochemical aspects of their structures, and the establishment of the stereochemistry (that is, the configuration) of an organic compound is an integral part of the description of its structure.

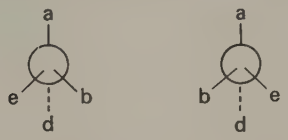
There are a number of simple consequences of the tetrahedral arrangement of the four bonds to the carbon atom. For one thing, certain stereochemical effects are at once apparent.

The four hydrogen atoms in methane are equivalent, and the replacement of any one of them by another atom or group gives but one compound. There is only one compound CH_3Cl, one CH_3Br, one CH_3OH, and so forth:

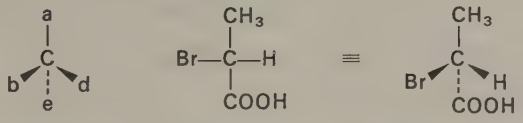


Four different drawings of one compound

A compound Cabde can exist in *two* forms. With a tetrahedral arrangement of the bonds to carbon, these two isomers of such a compound can be represented by



A moment's study of these structures (best of all, of actual models) will disclose that they are indeed different; they are not simply two ways of representing the same compound. The spatial relationships in this kind of carbon compound (for example, $(CH_3)CHBrCOOH$), represented in the most general terms as Cabde, are customarily represented as follows:



This molecule is asymmetric; it has no plane of symmetry.*

Exercise 3

Examine a three-dimensional model (or drawing) of each of the following compounds, and find the plane about which it is symmetrical:

(*a*) CH_3Cl (*b*) CH_2Cl_2 (*c*) CH_2ClBr (*d*) $CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

(*e*) $CH_3—O—CH_3$ (*f*) $CH_3CH_2—O—CH_3$ (*g*) H_2O

(*h*) cyclopropane (*i*) ammonia (*j*) NH_2OH

Note that a plane of symmetry of a molecule may cut through an atom or group, if that atom or group is itself symmetrical.

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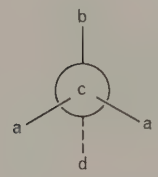
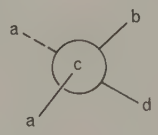
* Symmetry is an exact correspondence in shape, size, and relative position between the halves of a figure or object on opposite sides of an axis or plane; each half is the mirror image of the other half.

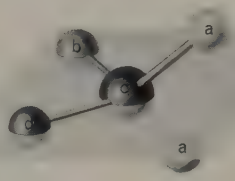
On the other hand, a molecule Ca_2bd is symmetrical—if b and d are themselves symmetrical—with a plane of symmetry represented in Figure 3-9(*c*). Note that if one of the a substituents is replaced by c, the top half is not a reflection of the bottom, and the plane that is shown is no longer a plane of symmetry.



(*a*) Plane of symmetry vertical, at right angle to page



(*b*) Plane of symmetry vertical, *in* the plane of the page



(*c*)

Figure 3-9
The molecule Ca_2bd, showing the plane of symmetry.

The ordinary printed or handwritten representations of carbon compounds such as $CH_3CH_2CH_2CH_3$ are conventional expressions of nonlinear molecules. Butane, for example, has the configuration shown in Figure 3-10.

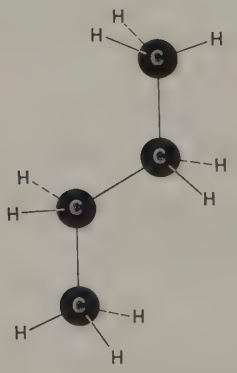


Figure 3-10
Three-dimensional structure of butane, $CH_3CH_2CH_2CH_3$.

Carbon chains may exist in other conformations than the regular zig-zag shown in Figure 3-10; moreover, thermal agitation may bring about molecular motions that cause the chain to alter its shape by twisting or, in the case of long chains, coiling. One of the various possible conformations of an organic molecule is usually more stable than others and is the most probable shape of the molecule. What we wish to emphasize here is that organic compounds, though represented in two-dimensional ways on paper, are structures with extension in three dimensions, and many of them do not possess rigid, fixed conformations.

The tetrahedral configuration of the four bonds to carbon can lead to the formation of stable cyclic structures, in which the ends of a chain of carbon atoms are joined to form a ring. Several cyclic compounds were illustrated in Chapter 2. The three-dimensional structure of a representative cyclic compound, cyclohexane, is shown in Figure 3-11.

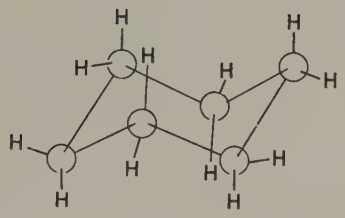


Figure 3-11
Three-dimensional representation of cyclohexane.

It should be noted that in both butane (Figure 3-10) and cyclohexane (Figure 3-11) *the arrangement of the four bonds around each carbon atom is tetrahedral.*

3-16 Elemental carbon. Diamond and graphite

Carbon occurs in nature in pure form as diamond and graphite, and in impure form—contaminated with inorganic materials and miscellaneous other organic compounds—as coal, coke, charcoal, and so on.

Diamond and graphite have definite structures: diamond consists of a repeating pattern of tetrahedrally bound carbon atoms, and the graphite "molecule" is a planar array of carbon atoms joined by trigonal bonds in a repeating pattern of hexagons (Figures 3-12 and 3-13). The symmetrical and compact network of fully saturated carbon atoms in diamond has a rigidity that accounts for its hardness and chemical

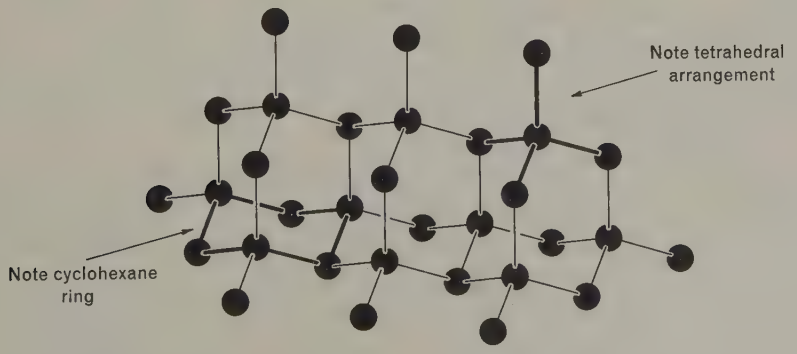


Figure 3-12
A portion of the diamond structure. The crystal lattice is a three-dimensional network of tetrahedrally bound carbon atoms.

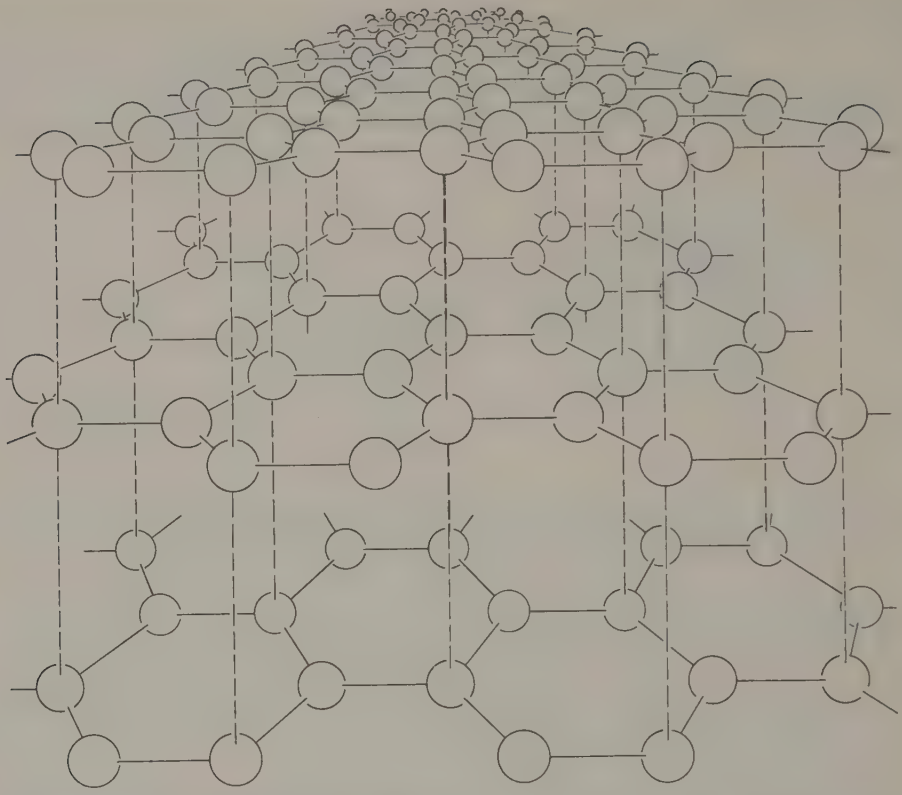


Figure 3-13
A portion of the graphite structure. The crystal lattice is composed of parallel sheets of carbon atoms in a repeating pattern of planar six-membered rings.

inertness. Since each of the orbitals of every carbon atom is fully occupied by an electron pair that is confined to an axis joining carbon nuclei, no capacity exists for reaction with an external reagent. The only way in which diamond can undergo chemical reaction (for example, by burning in oxygen) is by an initial rupture of a carbon-carbon bond followed by reaction at the carbon atoms so exposed to attack. Thus diamond can be burned but cannot be easily ignited.

Graphite consists of flat planar "sheets" of hexagonally bonded carbon atoms. The graphite crystal consists of a stack of these planar arrays (Figure 3-13). The C—C bond distance between the carbon atoms in the plane is 1.42 Å, and the distance between layers is 3.4 Å. Thus, there are no covalent or other strong bonds between the layers, and these can move with respect to each other. The usefulness of graphite as a lubricant depends upon this ability of the layers to slide over each other.

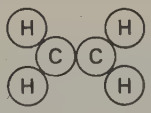
Since only three of the four valence electrons are used in forming the C—C single bonds between the carbon atoms in graphite, there is one electron for each

carbon atom still to be accounted for. These extra electrons confer some double-bond character upon each of the C—C single bonds (making them shorter than the 1.54 Å C—C bond length found in diamond); but perhaps the most useful description of the graphite molecule places a nonlocalized electron cloud above and below the plane. The electrical conductivity of graphite can be accounted for by this description, because the flow of electrons through this non-localized electron atmosphere can transfer charge from one point in the polyhexagonal plane to another.

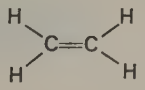
These two forms of carbon are excellent examples of some of the principles of carbon-carbon bond formation, and may be considered prototypes of the carbon-carbon bonds present in compounds to be discussed as we proceed.

3-17 Carbon-carbon multiple bonds

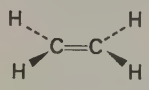
The carbon-carbon double bond. In ethylene, C_2H_4, two carbon atoms are joined together and two hydrogen atoms are attached to each carbon atom:



These facts are known from chemical evidence: we know that ethylene can be converted to ethane (CH_3CH_3), and it can be oxidized to two molecules of $H_2C{=}O$. We may write the structural formula of ethylene in conventional valence-bond notation, assigning a valence of four to carbon, as $CH_2{=}CH_2$, or in a graphic formula,



or in a perspective formula



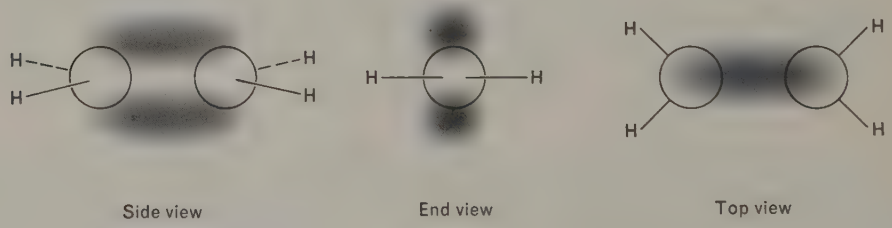
What kinds of bonds are involved in the structure of ethylene? Three physical facts must first be mentioned: (1) the carbon-carbon bond distance in ethylene is 1.34 Å, which is considerably less than that in ethane (1.54 Å); (2) the angle between the H atoms (that is, the H—C—H angle) is nearer to 120° than to the tetrahedral angle of 109°28′; (3) the carbon and hydrogen atoms are in one plane.

From these physical and chemical data, we can construct a reasonable picture of the ethylene molecule (Figure 3-14). We see first of all that the C—H bonds of each carbon atom and the carbon-carbon bond can most reasonably be arranged so that in each  the three bonds are symmetrical and planar. In this way the electron pairs are disposed for maximum stability by separation from each other, just as they are known to be in BCl_3, which is a symmetrical, planar, trigonal molecule.

Figure 3-14
Several views of a molecular model of ethylene.

The planar trigonal disposition of the three bonds to the carbon atoms in ethylene indicates that the bonds are formed with the use of sp^2 hybrid orbitals of carbon. We shall see that there are other consequences of this structure: for one, the C—H bond length in ethylene is 1.085 Å, compared with 1.10 Å for the C—H bond length in ethane. This is in accord with the view that sp^2 hybrid orbitals are used in bond formation, for the greater degree of s character implies that such an orbital lies closer to the nucleus than does an sp^3 orbital, with a consequent shortening of the bond to the hydrogen atom.

But what can be done with the extra electron pair in the C=C bond? We can expect to find that the total of four electrons of this double bond will be disposed for minimum mutual interaction; this can best be done if the two electron pairs are located between the carbon atoms, but in two regions of space that are separated from one another, as shown in Figure 3-15.



Side view End view Top view

Figure 3-15
Several views of the electron disposition in the ethylene double bond.

The summary of these considerations is this: in ethylene each carbon is approximately trigonal, and since there must be minimal mutual interaction between the C—H bonding electrons and the C—C bonding electrons, the molecule as a whole is planar, with regions of electron density extending above and below the plane. It can be seen from Figure 3-15 that all of the electron pairs are arranged in such a way as to produce minimal mutual interaction. The two carbon nuclei are under the mutual attraction of two pairs of electrons. The carbon atoms are drawn closer together than are those in the C—C single bond. The electrons between the carbon atoms are

distributed in such a way as to extend above and below the plane of the molecule and, furthermore, to extend into regions outside the carbon-carbon bond axis. Thus, these electrons are readily accessible to attack by electron-seeking reagents, and the carbon-carbon double bond is a center at which chemical reactions can occur readily.

The above description of the ethylene molecule accounts for the bond lengths, the bond angles, and the over-all shape of the molecule. A more refined description, in terms of molecular orbitals, will be given in Chapter 10.

The carbon-carbon triple bond. The carbon-carbon triple bond, found in acetylene, C_2H_2, can be described in terms comparable to those used in the foregoing discussion of the double bond. Acetylene is a linear molecule, with a carbon-carbon bond distance of 1.20 Å and a C—H bond distance of 1.06 Å. The electrons that form the triple bond are disposed between the carbon atoms in such a way as to form a cylindrically symmetrical shell of electron density about the carbon-carbon bond axis. The increased *s* character of the *sp* carbon orbitals is reflected not only in shorter bond lengths but in the increased acidity of acetylene. This will be discussed in Chapter 22: acetylene is a stronger acid than ethylene, which in turn is more acidic than ethane; that is, $HC{\equiv}C{:}^-$ is a weaker base than $CH_2{=}CH{:}^-$, which is a weaker base than $CH_3CH_2{:}^-$. In Figure 3-16 are shown the structures of ethane, ethylene, and acetylene. The conventional representation of double and triple bonds is shown by the following examples. The multiple bonds are shown as short lines and in this form no indication is given of the shapes of the molecules. A discussion of the stereochemistry of multiple bonds will be found elsewhere (see Chapters 6 and 7).

$CH_2{=}CH_2$	$CH_3CH{=}CH_2$	$CH_2CH{=}CH{-}CH{=}CH_2$
Ethylene	Propylene	1,3-pentadiene
$HC{\equiv}CH$	$CH_3C{\equiv}CCH_3$	$CH_3CH_2C{\equiv}CCH_2CH_3$
Acetylene	Dimethylacetylene or 2-butyne	3-hexyne

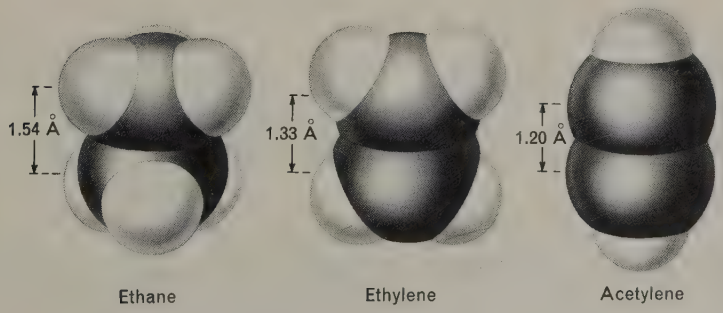
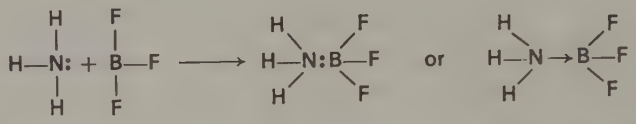


Figure 3-16
Molecular models of ethane, ethylene, and acetylene.

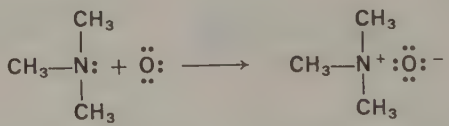
3-18 The semipolar bond

Another sort of covalent bond formation occurs when *both* electrons of the binding pair are donated by one atom to fill a vacant orbital of another. For example, boron, in its trivalent compounds such as boron trifluoride and trimethyl boron, has but six electrons in its valence orbitals and thus possesses a vacant orbital that is capable of forming a fourth covalence. Ammonia, on the other hand, is a compound in which the nitrogen atom possesses an unshared pair of electrons, and is thus also capable of forming a fourth bond. It is found that ammonia reacts with boron trifluoride in the following way:

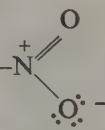


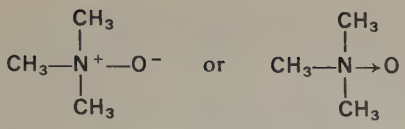
The product, $H_3N{:}BF_3$, is a neutral molecule, but an inspection of the electronic complements of the nitrogen and boron atoms discloses that the boron atom shares four electron pairs and thus possesses half of these, giving it a *formal* negative charge of one; and the nitrogen, which possesses half of the eight electrons it shares, has one electron less than the normal complement of five (in the neutral nitrogen atom), and thus has a *formal* positive charge of one. The ammonia/boron-trifluoride complex should thus be written $H_3\overset{+}{N}{:}\overset{-}{B}F_3$ (see Section 3-20).

Similarly, the unshared electron pair on the nitrogen atom of a tertiary amine such as $(CH_3)_3N{:}$ can be donated to complete the octet of an oxygen atom, forming a compound known as an amine oxide:

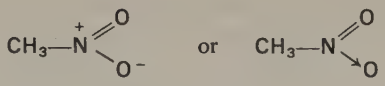


Trimethylamine Trimethylamine oxide

Dipolar covalent bonds such as the N—B and N—O bonds described above are found in many organic compounds. The common grouping  , called the *nitro group*, possesses a nitrogen-oxygen bond of this kind. It is customary for organic chemists to refer to this kind of covalent bond as the *semipolar bond*, and to designate it by the convenient symbols shown in the following examples. It is a matter of individual preference whether the formal charges are written or the arrow-headed bond is used; both mean the same thing.



Trimethylamine oxide



Nitromethane

The formation of the complex fluoborate ion, BF_4^-, by the reaction of boron trifluoride with fluoride ion would appear to be an example of the formation of a

---

Exercise 4

Inspect the electron distribution in the isomeric compounds *N,N,O*-trimethylhydroxylamine, $(CH_3)_2NOCH_3$, and trimethylamine oxide, $(CH_3)_3\overset{+}{N}—\overset{-}{O}$, and explain why no formal charges are written in the former.

---

semipolar bond. The process by which the B—F bond is formed is indeed the same as that in which the N—B bond is formed in the example described above; but there is no semipolar bond in the BF_4^- ion, since, although the ion carries a negative charge of one, the four fluorine atoms are completely equivalent and no one of them carries a formal charge. In the combination of ammonia with a proton (H^+), also, the bond is formed by the donation of the unshared pair of nitrogen to be shared by the proton. But NH_4^+ does not have a semipolar bond: all four hydrogen atoms are equivalent and the positive charge is symmetrically disposed about the ion as a whole.

The presence of a semipolar bond in a compound confers upon the compound physical properties that are often quite different from those of its isomers that do not possess semipolar bonds. The electrical forces induced by the formal charges on the atoms joined by one bond are molecular orienting influences that often result in an abnormally high melting point and boiling point.

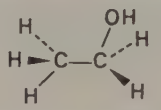
Exercise 5

Look up the following compounds in a good handbook, and compare their physical properties: methyl nitrite, CH_3ONO; nitromethane, CH_3NO_2. Write the electronic structures of these compounds.

3-19 The representation of organic structures by written formulas

The structures of organic compounds may be represented by written formulas in a number of ways. The selection of a representation depends upon the purpose for

which it is intended, and often one or more features of the complete structure may be omitted. For example, ethanol may be written as C_2H_5OH or CH_3CH_2OH if all that is desired is to show its constitution and that it contains a hydroxyl group. To write it as C_2H_6O would be less useful, because methyl ether, CH_3OCH_3, also has this composition. If the possession of unshared electrons on the oxygen atom is relevant to the discussion, ethanol may be writtten $CH_3CH_2\ddot{O}H$. If the arrangement of the atoms in space needs to be represented, one can use a conventional figure such as

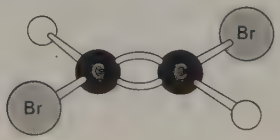


in which the heavy bonds (►) project toward the reader, the dashed bonds (---) are behind the plane of the page, projecting away from the reader, and the light single bonds (—) are in the plane of the page.

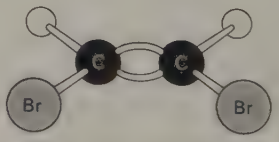
The purpose of writing a chemical formula is to provide a visual aid to a discussion or a description of the molecule's properties, and to point out molecular features that are pertinent to what is being said. Many simplifying conventions are employed, partly for economy and partly to focus attention upon the particular structural feature that is being examined and to clarify it. For example, there are three compounds of the composition $C_2H_2Br_2$. These can first of all be written in a form that distinguishes one of them clearly from the other two:

$$Br_2C{=}CH_2 \qquad \text{and} \qquad BrCH{=}CHBr$$

The second of these formulas represents two compounds, distinguished by the stereochemical disposition of the hydrogen and bromine atoms. The following are ball-and-stick drawings of these:

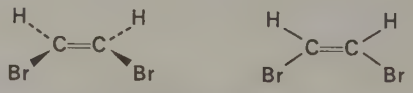


trans-1,2-dibromoethylene



cis-1,2-dibromoethylene

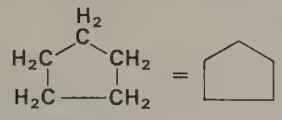
Because it would be awkward to have to make such drawings whenever one wrote about these compounds, various simple conventional substitutes for the drawings are commonly used, such as the following representations for the *cis* isomer:



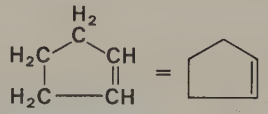
cis-1,2-dibromoethylene

Certain other conventions that simplify the representation of organic structures will be introduced from time to time as the reader gains facility and familiarity with the subject. One that will be useful from the start is the method usually adopted for

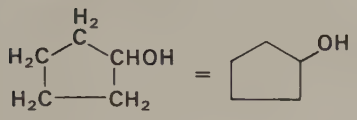
writing cyclic structures. Cyclopentane, cyclopentene, cyclopentanol, and cyclohexanone can be written in a simple fashion that is adequate for most purposes:



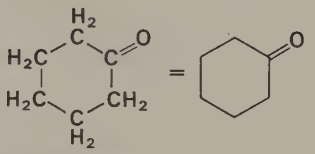
Cyclopentane



Cyclopentene



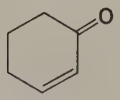
Cyclopentanol



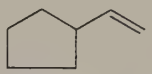
Cyclohexanone

Similarly:

Cyclopropane

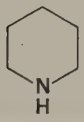


2-cyclohexen-1-one

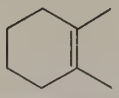


Vinylcyclopentane

Ethylene oxide



Piperidine



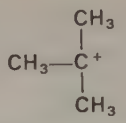
1,2-dimethylcyclohexene

3-20 Formal charges

Compounds in which carbon contains four covalent bonds, nitrogen three, oxygen two, and hydrogen one are the ones most frequently encountered in organic chemistry. If we examine these we see that electrons form covalent bonds in such a way that a maximum of eight electrons (four pairs) occupies the valence shell of each atom (except hydrogen).

For carbon this means that four single bonds, one double and two single bonds, one triple and one single bond, or two double bonds represent possible covalent states. Carbon cannot form stable compounds with more than four covalent bonds, because only four stable orbitals (the 2*s* and 2*p* orbitals) are available for bond formation.

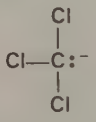
However, unusual valence states of carbon are known to exist in which less than four covalencies are present. The methyl "radical," $\cdot CH_3$, can be produced experimentally. It is, however, very unstable, and seeks to complete its complement of eight 2-shell electrons by reacting with other molecules. The "carbonium" ions, for example



are also recognized as intermediates in many chemical reactions.

As we shall see, the ability of the carbon atom to exist in the radical or ionic conditions depends very greatly upon the kinds of groups or atoms to which it is attached. For the present we shall note, for the purposes of inventory only, that carbon "possesses" one of the electrons in the pair that forms each covalent bond. Thus we see that in a radical such as the methyl radical

the carbon kernel possesses its normal complement of four electrons, and the radical $\cdot CH_3$ is neutral in charge. In the $(CH_3)_3C^+$ ion, on the other hand, the central carbon atom possesses but three electrons (one from each of the three carbon-carbon bonds); since this is one less than carbon's normal four, it may be considered to have a *formal charge* of $+1$. In fact, the charge is distributed over the entire ion, giving it a positive charge. In a carbon *anion*, such as

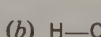


carbon (although it has eight electrons in its valence shell) "possesses" five (one in each of the three covalent C—Cl bonds and two in the unshared pair). The ion is therefore negatively charged, because the normal complement of the carbon atom is four electrons.

Exercise 6

Assign the proper charge (if any) to the carbon atom in each of the following:

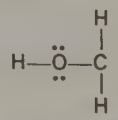
(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*) 

(*f*) 

NOTE: Here, as in the discussion in the text, the symbol for an element represents the atomic kernel; electrons and bonds that are shown involve external (valence) orbitals only.

A neutral nitrogen atom has five valence electrons in its outer shell. If three of its electrons engage in covalent-bond formation, an unshared pair remains. For example, in the uncharged ammonia molecule

nitrogen possesses a total of two (in the unshared pair) plus three (in the three covalent bonds) valence electrons, which is its normal complement of five.

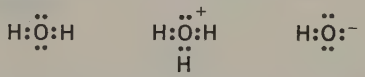
In the ammonium ion

the pair of electrons that was unshared in ammonia is now shared with hydrogen. Nitrogen now possesses only *one* of the electrons of this pair and thus owns a total of four. This is one less than the *five* possessed by the neutral nitrogen atom; the ammonium ion thus has a positive charge.

In the amide ion

nitrogen possesses two unshared pairs of electrons plus one in each of two covalent bonds, or a total of six. The amide ion therefore has a negative charge.

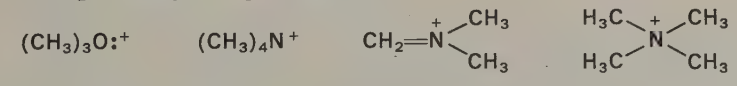
The three well-known combinations of oxygen with hydrogen are water, the hydronium ion, and the hydroxide ion. These are respectively neutral, positively charged, and negatively charged:

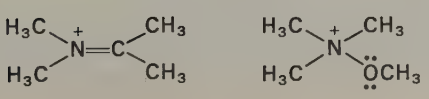


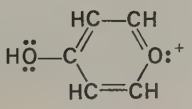
The explanations of these charge states can easily be worked out from the knowledge that the normal electronic complement of the valence shell (that is, the electrons external to the 1*s* orbital) of the neutral oxygen atom is six.

In summary, when carbon has four, nitrogen three, and oxygen two covalent bonds, no excess or deficit of electrons is involved.

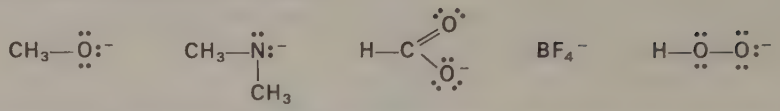
Tetracovalent nitrogen, however, is positively charged; *tricovalent oxygen* is also positively charged. We can see at once, then, without counting electrons, that the following are all positively charged ions:







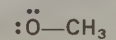
The following are negatively charged:



These should be worked out in detail by counting the electrons on the relevant atoms and noting how the charge types are arrived at. It can be pointed out here that the methyl group, $—CH_3$, as a substituent in a formula, can be dealt with as a unit and can be taken as a monovalent group, equivalent to a hydrogen or a halogen atom.

Exercise 7

Assign the proper charges to the following:

(*a*)  (*b*) $:NCl_3$ (*c*) $H_3C—NH_3$

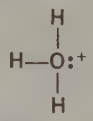
(*d*) BCl_4 (*e*) $BeCl_4$ (*f*) $CH_2{=}NH_2$

3-21 Maximum covalency

Experience has shown that *none of the atoms of the first period forms more than four covalent bonds.* In other words, there are no such stable compounds as NH_5, in which the five electrons of nitrogen form electron-pair bonds with five hydrogen atoms.

An equivalent statement regarding the covalency maximum of the first-period elements is that these atoms cannot have more than eight electrons in their valence shell.

The utilization of all four of the nitrogen orbitals in bond formation is observed in the ammonium ion, NH_4^+. Why, then, cannot oxygen form H_4O^{++}, and fluorine H_2F^+ and H_3F^{++}? The answer to this question is that although in H_3O^+ (which is known) there remains a fourth unshared pair of electrons on oxygen



it is so firmly bound to the oxygen by reason of the positive charge on the nucleus that the orbital lacks sufficient extension from the nucleus to form a stable bond. In HF, the high electronegativity of fluorine exerts a comparable restraint on its unshared electrons, and thus effective sharing of these electrons with other atoms does not occur.

In the hypothetical ion $:CH_3^-$, isoelectronic with H_3O^+, the unshared pair would be so readily accessible for bond formation, because of the smaller nuclear charge on

carbon, that the ion would be exceedingly avid for another atom's vacant orbital. Thus, carbon nearly always displays its maximum covalency.

Elements of the second period (sodium to argon) and of higher periods utilize higher orbitals, of which nine (in all) are available. Thus covalencies greater than four are not prohibited. Some examples are PCl_5, SF_6, IF_5, and $Fe(CN)_6^{3-}$.

Problems

1. What is the atomic number of (*a*) carbon, (*b*) nitrogen, (*c*) sodium, (*d*) aluminum, and (*e*) chlorine? Write electronic structures for these atoms, as in the example of fluorine, $1s^2 2s^2 2p^5$.
2. How might dimethylberyllium, $(CH_3)_2Be$, react with ammonia?
3. The ion C^{4+}, in which the helium structure is found, would be formed by the loss of four electrons from the neutral carbon atom. This ion is unknown. Why?
4. Suggest a plausible reason for the fact that while the hydride ion, $H:^-$, is well known, the sodium ion, $Na:^-$, is not.
5. Write electronic structures (using the $1s2s2p$ notation) for (*a*) beryllium; (*b*) the beryllium ion, Be^{++}; (*c*) the fluoride ion, F^-; (*d*) the sodium ion, Na^+; (*e*) the aluminum ion, Al^{3+}; and (*f*) argon.
6. The electron representation of carbon tetrachloride is

   Using this notation, write electronic structures for (*a*) methanol, (*b*) methyl chloride (chloromethane), (*c*) ammonia, (*d*) magnesium chloride, (*e*) nitrogen trichloride, (*f*) hydrogen peroxide, (*g*) ozone, (*h*) ammonium chloride, (*i*) diethyl ether, and (*j*) boron trifluoride.
7. Write the equation for the reaction of boron trichloride with diethyl ether.
8. Trimethylamine, $(CH_3)_3N$, can be oxidized to trimethylamine oxide, $(CH_3)_3\overset{+}{N}—\overset{-}{O}$. Why does not trimethylboron, $(CH_3)_3B$, form a corresponding oxide?
9. The H—S—H bond angle in H_2S is nearer 90° than is the H—O—H angle in water. What would you predict for the H—Se—H angle in hydrogen selenide?
10. Calculate the formal charge on the nitrogen atom in each of the following compounds: (*a*) CH_3NH_2, (*b*) CH_3NH_3Br, (*c*) HN_3, (*d*) $(CH_3CH_2)_3NO$, (*e*) $(CH_3)_2NOCH_3$, (*f*) NH_2NH_2 (both nitrogen atoms), and (*g*) KNH_2.

11. What change should take place in the carbon-boron bond angles when trimethylboron reacts with trimethylamine to form $(CH_3)_3N—B(CH_3)_3$? What C—C bond angles would you expect to find in the trimethylcarbonium ion, $(CH_3)_3C^+$?

12. What would you expect the configuration of the bonds to be around the following:
    (*a*) nitrogen in the NH_4^+ ion
    (*b*) boron in the BF_4^- ion
    (*c*) boron in the $NH_3 \cdot BF_3$ complex
    (*d*) tellurium in dimethyl telluride, $(CH_3)_2Te$
    (*e*) oxygen in OF_2
    (*f*) beryllium in dimethylberyllium, $(CH_3)_2Be$
    (*g*) oxygen in the hydronium ion H_3O^+

13. What can you suggest as two of the factors that would operate against the formation of a complex (of the $B^-—N^+$ type) between trimethylboron and tri-*tertiary*-butylamine $[(CH_3)_3C]_3N$? SUGGESTION: Make sketches of the configuration of the amine and of the amine-trimethylboron complex. What are the respective C—N bond dispositions? What influence could the large and bulky *tert*-butyl groups have?

14. The protons of methane, CH_4, have no demonstrable acidic character. Can you suggest a reason why H—C bond in chloroform, $CHCl_3$, has a small but demonstrable degree of acidic character?

15. Why does nitrogen not form electron-pair bonds with all five of its 2-shell electrons in such compounds as NH_5 or NCl_5?

4

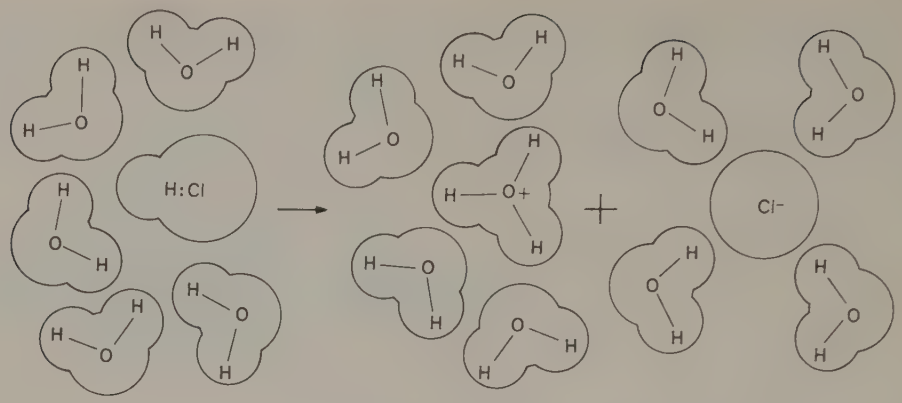
Acids and bases. Proton-transfer reactions

By far the greater number of the reactions of organic compounds take place in solution, in many cases under the catalytic influence of inorganic acids and bases. The transfer of protons (protonation) to organic molecules, and the removal of protons from organic molecules by strong bases, are prominent features of organic reactions of many kinds. This chapter reviews briefly the theories of acids and bases that the student has become familiar with in other courses, and applies them to organic compounds.

The concepts of protonation, removal of protons by bases, and solvation and solubility are indispensable to the interpretation of how and why organic reactions proceed as they do. Because the participation of acids and bases in organic reactions is so pervasive, the student is urged not to treat this as a discrete "topic" but to keep it constantly in mind.

4-1 Dissociation in solution. The role of the solvent

The early concept of Arrhenius that an acid is a compound that dissociates in solution to yield an anion and a hydrogen ion, H^+, has been displaced by the recognition that



$$HCl + H_2O \rightarrow H_2O^+(aq) + Cl^-(aq)$$

Figure 4-1
Dissociation of HCl in water; solvation of ions is a factor in the reaction.

the free, uncombined proton is unlikely to have an independent existence in solution. Thus, the equilibrium

$$HCl \rightleftharpoons H^+ + Cl^- \tag{1}$$

is for practical purposes nonexistent. In water solution, however, dissociation does occur, but the proton does not simply separate from the chloride ion. Instead it transfers from the chloride ion to water:

$$H_2O + HCl \rightleftharpoons H_3O^+ + Cl^- \tag{2}$$

Evidence for these conclusions is found in the observations that (*a*) acids such as HCl and HBr are not ionized in the pure liquid state or in the vapor state; (*b*) hydrogen acids in the crystalline state do not form crystal lattices containing H^+; and (*c*) HCl and HBr are only slightly soluble, and do not dissociate, in solvents such as paraffin hydrocarbons, benzene, and concentrated sulfuric acid, which do not combine with protons.

The combination of a proton with water may be regarded either as protonation of the water molecule or as the hydration (solvation) of the proton. Indeed, it is probable that an aqueous solution of an acid such as HCl contains hydrogen ions solvated further to form, besides the *hydronium ion*, H_3O^+, such species as $(H_5O_2)^+$, $(H_7O_3)^+$, and so on. Solvation of the anion is also to be expected, and a proper

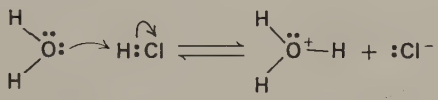
expression for the dissociation of HCl in water is

$$HCl + n\,H_2O \rightleftharpoons H_3O^+(aq) + Cl^-(aq) \qquad (3)$$

where "aq" means hydration of the ions (Figure 4-1).

4-2 Dissociation as a displacement reaction

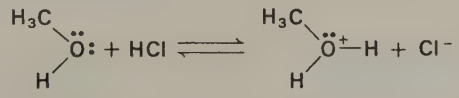
The formation of hydronium and chloride ions in a water solution of HCl is thus a transfer of the proton from :Cl to H_2O:, a process that may be regarded as an attack of the water molecule upon HCl, with expulsion, or *displacement*, of the chloride ion:*



(4)

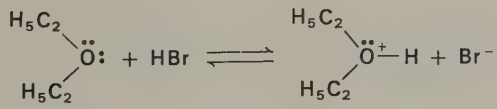
It is apparent that this represents a competition of H_2O and Cl^- for the proton. Since we know that in dilute aqueous solution HCl is almost completely ionized, we can conclude that water has a greater tendency to be protonated than the chloride ion.

Since the displacement of the chloride ion with its bonding electron pair is coupled with the formation of a new bond between the hydrogen atom and the attacking molecule—in the above case, water—it is clear that an essential requirement for the dissociation of the HCl molecule is the ability of the attacking molecule to provide the electron pair needed for the formation of the new bond. It may further be expected that a similar dissociation will occur in solvents other than water, provided the solvent molecule possesses an unshared electron pair. *Alcohols, ethers, amines, and numerous other organic compounds containing atoms with unshared electron pairs* can be protonated in the same way:



(5)

Methanol



(6)

Ethyl ether

$$CH_3\ddot{N}H_2 + H_2SO_4 \rightleftharpoons CH_3NH_3^+ + HSO_4^- \qquad (7)$$

Methylamine

---

* Although the complete expression for the electronic structure of HCl, showing the external electrons, is $H:\ddot{\underset{\cdot\cdot}{Cl}}:$, it is usual to show explicitly only the electrons involved in the bond-breaking and bond-making process. When electronic structures have become sufficiently familiar, the dots may be omitted altogether.

$$(CH_3)_2C{=}\ddot{O}: + H_2SO_4 \rightleftharpoons (CH_3)_2C{=}\ddot{O}H^+ + HSO_4^- \qquad (8)$$

Acetone

Protonation is the term generally used to describe the reactions shown in these examples. Thus, $CH_3OH_2^+$ can be called *protonated* methanol, $(CH_3)_2C{=}OH^+$ protonated acetone, and so on. We shall see that proton transfer from one molecule to another is a feature of a great many organic reactions. Since the reaction is seldom uniquely dependent upon the specific acid that provides the proton, the term protonation has the added advantage that it focuses attention upon the compound that accepts the proton rather than upon the proton-donating agent.

4-3 Conjugate acids and bases

Proton-transfer reactions are reversible. The equilibrium constant of the reaction may be such that the dissociation is for practical purposes complete, but even in the reaction

$$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^- \qquad (9)$$

in which the equilibrium lies far to the right, the transfer of protons from H_3O^+ to Cl^- is real. Thus, H_2O may be considered a base that is protonated by HCl, and Cl^- a base that is protonated by H_3O^+. The relationship between HCl and Cl^- and between H_3O^+ and H_2O is expressed by the statement that each pair is a *conjugate pair* of an acid and a base. HCl is the conjugate acid of the base Cl^-; H_3O^+ is the conjugate acid of the base H_2O. Other conjugate-acid/conjugate-base pairs are the following:

Conjugate acid	*Conjugate base*
H_2SO_4	HSO_4^-
HSO_4^-	$SO_4^{=}$
HNO_3	NO_3^-
$CH_3OH_2^+$	CH_3OH
H_2O	OH^-
NH_4^+	NH_3
$(CH_3)_2C{=}OH^+$	$(CH_3)_2C{=}O$
CH_3OH	CH_3O^-
CH_3COOH	CH_3COO^-

These examples permit two further observations: (1) a given molecule or ion may act as both an acid and a base (HSO_4^- is the conjugate base of the acid H_2SO_4

and the conjugate acid of the base $SO_4^{=}$); and (2) the conjugate acid of a base is the *protonated base.*

4-4 The Brønsted-Lowry concept of acids and bases

The view of proton transfer described in the foregoing section is embodied in a concept of acids and bases put forward in 1923 by J. M. Brønsted (Copenhagen) and T. M. Lowry (Cambridge), who proposed that:

An *acid* is a substance that can donate a proton to another substance; and

A *base* is a substance that can accept a proton from an acid.

The characteristic of a base is its possession of an unshared (non-bonding) electron pair. The conjugate acid-base pairs mentioned in Section 4-3 can be related by the general expression

$$\underset{\text{Acid}_1}{\text{H:A}} + \underset{\text{Base}_2}{\text{:B}} \rightleftharpoons \underset{\text{Acid}_2}{\text{H:B}} + \underset{\text{Base}_1}{\text{:A}} \qquad (10)$$

in which the bases :B and :A possess unshared electron pairs to which the proton can be bound. It can be seen, therefore, that any substance that possesses an unshared electron pair in its valence shell can, in principle, act as a base and by protonation be converted into its conjugate acid. Many organic compounds, especially those containing oxygen, nitrogen, or sulfur, fit this requirement and can be protonated to a degree that depends upon their strength as bases and the strength of the protonating acid.

A *strong acid* in the Brønsted-Lowry view is a substance that has a strong tendency to give up its proton. Its conjugate base, then, is a very weak base.

A *strong base* is a substance that has a strong tendency to accept a proton. It can be protonated by a weak acid. Conversely, a weak base requires a strong acid for effective protonation.

The Brønsted-Lowry view of acids and bases is a very general one; it accommodates within a single concept the diverse behavior of many compounds. For example, both water and nitric acid are acids, yet both can also act as bases:

$$H_2O + NH_3 \rightleftharpoons HO^- + NH_4^+ \qquad \text{Water as an acid} \qquad (11)$$

$$HNO_3 + H_2O \rightleftharpoons NO_3^- + H_3O^+ \qquad \text{Nitric acid as an acid} \qquad (12)$$

$$HNO_3 + H_2SO_4 \rightleftharpoons H_2NO_3^+ + HSO_4^- \qquad \text{Nitric acid as a base} \qquad (13)$$

$$H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- \qquad \text{Water as a base} \qquad (14)$$

The degree to which proton transfer occurs in reactions of this kind—that is,

the position of equilibrium in the reaction—depends upon the strengths of the competing bases. For instance, since HCl is nearly completely dissociated in dilute aqueous solution we can conclude that chloride ion is a much weaker base than water. Acetic acid, on the other hand, is dissociated only to a small extent in aqueous solution,

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+ \qquad (15)$$

an indication that acetate ion is a stronger base than water. If acetic acid reacts with the strong bases OH^- or NH_3, dissociation (proton transfer) is essentially complete:

$$CH_3COOH + OH^- \rightleftharpoons CH_3COO^- + H_2O \qquad (16)$$

$$CH_3COOH + NH_3 \rightleftharpoons CH_3COO^- + NH_4^+ \qquad (17)$$

4-5 Strong and weak acids and bases

The common terms "strong" and "weak" for acids and bases describe their behavior in water solution. A strong acid, then, is one that is largely or nearly completely dissociated into H_3O^+ and its anion in water. It should be borne in mind, however, that this usage is vernacular. An acid that is "weak" with respect to the base water can be "strong" (that is, completely dissociated) with respect to a strong base, as the above equations indicate.

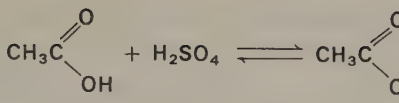
Exercise 1

An aqueous solution of sodium acetate has a pH above 7 as a result of the appearance of OH^- ions in the equilibrium

$$CH_3COO^- + H_2O \rightleftharpoons CH_3COOH + OH^-$$

Given the pK_a of acetic acid as 4.8, calculate an approximate value for the pH of a 0.1 *N* aqueous solution of sodium acetate.

Many organic compounds, of which only the amines are bases in the usual meaning of the term, and most of which are very weak bases in the Brønsted-Lowry sense, can be protonated. In particular, strong acids such as $HClO_4$, H_2SO_4, HCl, and H_3PO_4 can effect protonation of most oxygen-, nitrogen-, or sulfur-containing organic compounds:



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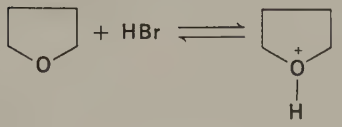

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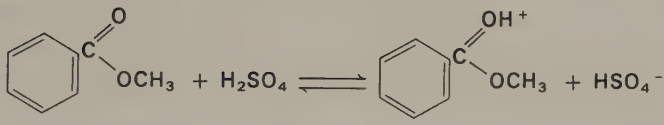

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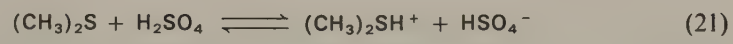
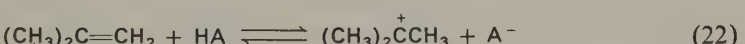


(21)

It will be shown in the discussion of the chemistry of the carbon-carbon double bond (alkenes, see Chapter 10) that unsaturated compounds, although they lack unshared electrons, can also react with strong acids, with protonation of the double bond:



(22)

Organic esters, ketones, alcohols, and ethers are very weak bases and are spoken of as "neutral" compounds. In most cases their protonation can be accomplished only by strong acids, and their aqueous or alcoholic solutions are not basic in the ordinary meaning of this term.

4-6 Nucleophilic reagents

The proton is the bare nucleus of the hydrogen atom. Compounds possessing the unshared electron pair to which a proton becomes attached in the protonation reaction are thus termed *nucleophilic* reagents. A *nucleophile* may be a strong (for example, OH^-) or a weak (for example, CH_3OCH_3) base, but in any case it possesses a free or available (for example, an alkene) electron pair. Although in this discussion the nucleophilic character of compounds has been dealt with in terms of protons, we shall later be most concerned with nucleophiles that can attack electron-seeking centers of many other kinds to form an electron-pair bond (Chapter 7).

4-7 Lewis acids. Electrophilic reagents

The acidic character of many substances that are not proton donors was recognized by G. N. Lewis, who extended the concepts of the Brønsted-Lowry theory. It has

long been known that many compounds, among them BF_3, $AlCl_3$, $FeCl_3$, $ZnCl_2$, and $SnCl_4$, have certain properties of Brønsted-Lowry acids. They combine with bases like ammonia and amines to form salt-like products; they affect indicators as acids; and, most important to the organic chemist, they catalyze many reactions that are also catalyzed by strong hydrogen acids.

Lewis' extension of the Brønsted-Lowry concept was to regard as acids those substances, *one of whose constituent atoms can receive into its valence shell an electron pair belonging to another atom*, with the formation of a covalent bond. Bases, in both the Lewis and the Brønsted-Lowry concepts, are substances possessing electron pairs that can be donated to form a (shared) covalent bond with a proton or a Lewis acid.

The Lewis theory is neither a substitute for nor a modification of the Brønsted-Lowry theory, but an extension that brings into consideration compounds *that possess a property also possessed by the proton*, namely, the ability to complete its valence shell by accepting a pair of electrons provided by another atom, forming a covalent bond with that atom. The free proton may be regarded as the simplest Lewis acid.

Let us examine a typical Lewis acid, boron trifluoride, BF_3. In this compound the three $2p$ electrons of boron have been utilized to form three covalent sp^2 bonds with fluorine. There remains a fourth orbital, unoccupied* in BF_3, but available for occupancy by a pair of electrons and therefore capable of forming a fourth covalent bond with a "donor" atom, one that can provide an unshared electron pair. Trivalent boron compounds are thus Lewis acids and are capable of reacting with bases (nucleophiles) to form compounds in which the boron atom possesses a complete octet of electrons in its external valence shell. Some examples of this are the following:

$$F^- + BF_3 \longrightarrow BF_4^- \tag{23}$$

$$(CH_3)_2O + BF_3 \longrightarrow (CH_3)_2\overset{+}{O}—\bar{B}F_3 \tag{24}$$

$$(CH_3)_3N + BF_3 \longrightarrow (CH_3)_3\overset{+}{N}—\bar{B}F_3 \tag{25}$$

$$(CH_3)_2C{=}O + BF_3 \longrightarrow (CH_3)_2C{=}\overset{+}{O}—\bar{B}F_3 \tag{26}$$

(27)

$$(CH_3)_2C{=}CH_2 + BF_3 \longrightarrow (CH_3)_2\overset{+}{C}—CH_2—\bar{B}F_3 \tag{28}$$

---

* The tetracovalency of boron in BF_3 is actually satisfied by delocalization of electron pairs of fluorine to form the hybrid structure, $F{=}\overset{+}{\underset{|}{\overset{F}{B}}}{-}\bar{F}$; but a good nucleophile X: can displace two of the electrons in the F=B bond to give the product XBF_3. It is therefore convenient and permissible to regard BF_3 as having three covalent B—F bonds and one vacant orbital.

Exercise 2

(*a*) Complete the above equations by showing the complete (relevant) electronic complements of the nucleophilic reagents (as in $CH_3—\ddot{O}—CH_3$) and the products. (*b*) Explain why the (+) and (−) charges shown in these equations are disposed as they are. (*c*) Write equations for the reactions of aluminum chloride with (*i*) diethyl ether; (*ii*) triethylamine; (*iii*) hydrogen chloride. (*d*) The product shown as the result of the addition of isobutylene to boron trifluoride is also a Lewis acid. Explain.

In everyday usage, the term "acid" is ordinarily used for proton donors, that is, such Brønsted-Lowry acids as HCl, CH_3COOH, and H_2SO_4. Acids of the Lewis type are usually explicitly referred to as *Lewis acids*. The reaction of a Lewis acid with an electron-pair donor is called *coordination*, and compounds such as $(CH_3)_3\overset{+}{N}—\overset{-}{B}F_3$ are called *coordination compounds* or *coordination complexes*.

It should now be apparent that many familiar reactions are Lewis-acid reactions. The hydration and ammoniation of many metallic ions, the formation of coordination compounds of many kinds, and many organic reactions with highly reactive electron-deficient intermediates are examples:

$$Al^{+++} + 6H_2O \longrightarrow Al(H_2O)_6^{+++} \tag{29}$$

$$Ag^{+} + 2NH_3 \longrightarrow Ag(NH_3)_2^{+} \tag{30}$$

$$Fe^{+++} + 6CN^{-} \longrightarrow Fe(CN)_6^{---} \tag{31}$$

$$Ag^{+} + CH_2{=}CH_2 \longrightarrow AgCH_2CH_2^{+} \tag{32}$$

$$AlCl_3 + (CH_3)_3CCl \longrightarrow (CH_3)_3C^{+}AlCl_4^{-} \tag{33}$$

Lewis acids, chiefly the familiar and readily accessible BF_3, $AlCl_3$, $SnCl_4$, and $ZnCl_2$, are important reagents in organic chemistry and are widely used, particularly in carrying out reactions of the acid-catalyzed type. Lewis acids of this kind are "strong" acids and are often more effective as catalysts than strong hydrogen (Brønsted) acids.

4-8 Hydrogen bonding and association

When we examine a homologous series of compounds, such as the alcohols, the amines, or the hydrocarbons, we note that the boiling points of the individual compounds increase as their molecular weights increase (Table 4-1).

Table 4-1
The boiling points of some alcohols, amines, and carboxylic acids

Alcohols	*B.p.*	*Amines*	*B.p.*	*Carboxylic acids*	*B.p.*
CH_3OH	56°C	CH_3NH_2	−6.7°C	CH_3COOH	118°C
CH_3CH_2OH	78	$CH_3CH_2NH_2$	16.6	EtCOOH	141
$CH_3CH_2CH_2OH$	98	$CH_3CH_2CH_2NH_2$	50	PrCOOH	164
$CH_3CH_2CH_2CH_2OH$	117	$CH_3CH_2CH_2CH_2NH_2$	78	BuCOOH	186
$CH_3(CH_2)_4OH$	138	$CH_3(CH_2)_4NH_2$	104	AmCOOH	205

It can be seen that the increase in the molecular weight of 14 (addition of —CH_2—) within a given class causes the boiling point to rise about 20 or 30°C. It should also be noticed that boiling point and molecular size bear no regular relationship if we compare alcohols with amines or acids (Table 4-2).

In compounds such as water, alcohols, amines, carboxylic acids, and others that possess both (1) a hydrogen attached to oxygen or nitrogen and (2) a donor atom, such as oxygen or nitrogen, intermolecular proton exchange can occur. The hydrogen atom possesses a certain positive character, relative to the other atom, which may be described by the symbol

$$R—\overset{\delta-}{O}—\overset{\delta+}{H}$$

The result of this is that a certain degree of organization exists in a medium consisting of such molecules, brought about by a weak binding, largely electrostatic in nature, caused by the attraction of positive and negative ends of the dipoles. The lining up of the molecules in such liquids creates loose polymolecular aggregates, with the result that the *effective* molecular weight, *compared with what it would be in the absence of such intermolecular forces*, is on the average greater than that calculated for the simple molecules. It should be pointed out that seldom can a definite polymolecular species

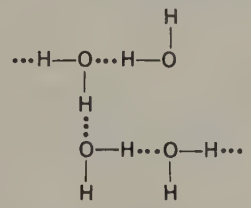
Table 4-2

Compounds	*Formula*	*Mol. wt.*	*B.p.*
n-butyric acid	$CH_3CH_2CH_2COOH$	88	164°C
n-amylamine	$CH_3CH_2CH_2CH_2CH_2NH_2$	87	104
n-amyl alcohol	$CH_3CH_2CH_2CH_2CH_2OH$	88	138
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	86	69

be identified in such a liquid, but the relationship between boiling point and chemical nature can be accounted for in qualitative terms on the basis of this concept.

It is probable that *hydrogen bonds* involve a certain degree of orbital overlap between the hydrogen atom and the donor atom, and are not to be attributed solely to dipolar interactions; were dipolar interactions the predominant factor, certain compounds with greater dipole moments, but without O—H or N—H bonds, would be associated to a greater degree than in fact they are.

In water we can picture a "water substance," which is impossible to define explicitly but can be represented by a picture such as the following,

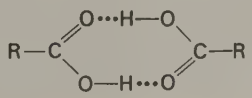


in which the dotted bonds indicate the dipolar attractions we have described. These hydrogen bonds are very weak, and are broken with rising temperature, until at the boiling point individual water molecules escape as vapor. But the temperature at which vaporization occurs is higher than it would be were no such organization present.

Exercise 3

Alcohols are capable of forming hydrogen-bonded complexes similar to that shown for water. Draw a portion of such an aggregate for methanol. Would you expect methanol to be more highly organized in such an aggregate than is water, or less so? Why? Would you expect the boiling point of methanol to be more than or less than 100°C?

In certain cases, aggregates of definite size are known. Measurements of the molecular weight of benzoic acid in benzene solution show that the acid exists as a *dimer*; it appears that two molecules of a carboxylic acid can associate to form a definable aggregate through the formation of hydrogen bonds in the following way:



In most cases, however, the association of the molecules in a liquid or solution is more random and less clearly defined than this.

It can be seen that these properties are consonant with the acidic and basic properties of the compounds we are discussing. The greater base strength of amines—or, what is equivalent, their lower degree of acidity as hydrogen acids—indicates that the electron pair between N— and H— is less strongly attracted to the N— than it is to the O— in the alcohols. Consequently, the proton is more strongly bonded to nitrogen and is less able to engage in intermolecular association with electron-donor atoms. That *some* such association occurs, however, is shown by the boiling points of amines, compared with those of ethers and hydrocarbons of the same molecular weight.

An appreciation of the influence of structural type upon boiling point can be gained by an inspection of Table 4-3, in which compounds of various classes with molecular weights in the range 58–62 are compared.

When a semipolar bond is present, the effect of this very strong dipole upon the boiling point is marked. In a molecule such as trimethylamine oxide, $(CH_3)_3\overset{+}{N}—\overset{-}{O}$, strong orienting forces result from the dipolar bond, with the result that the molecules in the aggregate have a high degree of organization. Trimethylamine oxide is quite involatile, compared with substances of comparable molecular weight but with no semipolar bonds, and sublimes from the solid state at about 180°C. It appears to be almost salt-like in nature, the strongly dipolar character of the molecule causing it to form a crystal lattice resembling that composed of the positive and negative ions of a salt like NaCl.

Table 4-3
The effect of structural type on boiling point

Class	*Compound*	*Formula*	*Mol. wt.*	*B.p.*
hydrocarbon	*n*-butane	$CH_3CH_2CH_2CH_3$	58	0°C
tertiary amine	trimethylamine	$(CH_3)_3N$	59	4
ether	methyl ether ether	$CH_3OC_2H_5$	60	6
ester	methyl formate	$HCOOCH_3$	60	32
secondary amine	methylethylamine	$CH_3NHC_2H_5$	59	36
primary amine	*n*-propylamine	$CH_3CH_2CH_2NH_2$	59	50
aldehyde	propionaldehyde	CH_3CH_2CHO	58	60
alcohol	*n*-propyl alcohol	$CH_3CH_2CH_2OH$	60	98
acid	acetic acid	CH_3COOH	60	118
amino alcohol	ethanolamine	$HOCH_2CH_2NH_2$	61	171
glycol	ethylene glycol	$HOCH_2CH_2OH$	62	197

Exercise 4

With the aid of a handbook, find the boiling points of all of the isomers of $C_4H_{10}O$. Can you suggest how the boiling points of these compounds can be reconciled with their structures?

4-9 Solubilities of organic compounds

A solid or liquid substance is an aggregate of individual molecules. If intermolecular forces are weak, so that the positions of the molecules are not fixed in definite orientations relative to one another, the physical state of the substance is that of a liquid; if the intermolecular forces are very weak, the substance is a gas, with the molecules in motion over appreciable distances. With increasing intermolecular associating forces—which may be weak chemical bonds or electrostatic attractive forces—the degree of organization increases until at length the *crystalline* state is reached. In the crystalline state the molecules are packed into definite arrangements (lattices) in which random molecular movements do not occur (except for vibrational motion about an average position). When molecular motion increases to the point at which intermolecular forces are overcome, the regular lattice breaks down, the structure becomes randomized, and the substance changes from a crystalline solid into a liquid. This process is called *melting*. The heat that is needed to raise a crystal to its melting point represents energy that is required to disrupt the intermolecular forces that hold the molecules in the regular arrangement of the crystal lattice.

The solution of an organic compound in a solvent is a process in which the intermolecular forces in the pure substance are replaced by forces that act between the molecules of the solute and those of the solvent. It is to be expected, therefore, that unless the balance between the solute-solute molecular forces and the solute-solvent molecular forces is in favor of the latter, the compound will be insoluble.

Some organic compounds are readily soluble in water, but the great majority are not. Most organic compounds are soluble in other organic compounds—the so-called organic solvents. Typical organic solvents are the simple alcohols (methanol, ethanol), ethers (diethyl ether), halogenated hydrocarbons (chloroform), ketones (acetone), esters (ethyl acetate), and hydrocarbons (benzene, light petroleum fractions).

What structural features determine whether an organic compound will be soluble or insoluble in water? Water solubility may be expected to involve binding forces between the molecules of water and those of the organic solute. Since the association of water molecules with each other in liquid water involves hydrogen bonding between the hydroxyl groups of the associated molecules, we may expect that for an organic compound to be soluble in water, it would have to possess structural features that permitted it to fit into the "water structure" and to play a role similar to that played

by the water molecules. For this reason, organic compounds that contain several hydroxyl groups (such as the sugars) or several carboxylic acid (—COOH) groups, or combinations of these, tend to be water-soluble. On the other hand, compounds of these kinds are usually insoluble in hydrocarbon solvents such as benzene or hexane. These solvents are lacking in functional groups that would permit the formation of associative bonds with hydroxyl or carboxylic acid groups. To put it in another way, the *intermolecular* forces within the crystal lattice of a hydroxyl-containing organic compound, such as a sugar, can be overcome only if forces between the sugar molecules and the solvent molecules can take their place. In a solvent such as benzene or hexane this cannot happen, so the sugar is insoluble; in water this can happen, and the sugar is soluble.

We are familiar with the solubility of inorganic salts in water. The *solvation* of the individual ions and the high dielectric constant of water contribute to disrupting the electrostatic forces in the ionic crystal lattice and dispersing the ions throughout the solvent, each within a shell of solvent molecules.

In the same way, organic compounds that can be ionized by aqueous solvents are soluble in such solvents. Aqueous acids (for example, dilute HCl) dissolve most amines by protonating the amine molecules and dispersing the resulting ammonium ions as solvates. Aqueous bases (for example, dilute NaOH) dissolve organic acids, converting them into the corresponding anions by removal of the protons.

Very weak bases, such as alcohols, ethers, and many nitrogen-containing compounds other than amines, are insoluble in dilute aqueous acids but are usually soluble in more concentrated acids. For this reason, concentrated sulfuric acid dissolves most organic compounds that contain oxygen, nitrogen, or sulfur; the ability of the concentrated acid to protonate even a very weak base permits the formation of the cation, which can then be dispersed (that is, dissolved) in the solvent acid.

Finally, it should be noted that low-molecular-weight organic compounds (containing less than five carbon atoms) that contain oxygen or nitrogen in any combination are usually water-soluble. The small size of these organic molecules does not allow for strong binding forces between them; thus, even weak binding forces between the solvent water molecules and the oxygen or nitrogen atoms of the solute molecules are sufficient to bring the organic compound into solution. Low-molecular-weight hydrocarbons, such as pentane, hexane, and so forth, are insoluble in water for reasons described in an earlier paragraph.

The solubility behavior of an organic compound provides valuable structural information. The examination of the solubility behavior of an unknown organic compound (by testing its solubility in water, dilute HCl, dilute NaOH, concentrated sulfuric acid, and in an organic solvent such as ether) is another stage in the step-by-step accumulation of information that eventually enables the chemist to establish its structure.

Table 4-4
Some simple solubility characteristics

Solvent	*Class of compound*	*Examples*
water and most organic solvents	low-molecular-weight alcohols, ketones, esters, acids, amines	ethanol, acetic acid, acetone
water, but not most organic solvents	polyhydroxy compounds, salts of organic acids and bases	sugars, sodium acetate, amine hydrochlorides
most organic solvents	most organic compounds of many classes	—
dilute acid (1 *N* HCl)	organic bases (amines)	aniline, triethylamine
dilute alkali (1 *N* NaOH)	organic acids (carboxylic acids and phenols)	benzoic acid, phenol
concentrated sulfuric acid	most oxygen- and nitrogen-containing organic compounds	—
organic solvents, but not sulfuric acid	paraffin hydrocarbons, halogenated hydrocarbons	*n*-hexane, chloroform, dichlorobenzene

Table 4-4 is a summary of a few generalizations concerning solubility relationships. This information is presented only as a guide to the solubility concepts discussed in this section. It must be recognized that solubility is not an all-or-none phenomenon. Chemists usually distinguish solubility from insolubility by some arbitrary ratio of solute to solvent. These details will not be discussed here; they are chiefly of importance in cases of "borderline" solubility behavior.

Problems

1. Write the equations for the proton-transfer reactions of HCl with (*a*) water, (*b*) hydroxide ion, (*c*) hydrazine, (*d*) dimethyl ether, (*e*) bicarbonate ion, (*f*) chloroamine ($ClNH_2$), (*g*) hydroxylamine ($HONH_2$), (*h*) sodium hydride, (*i*) guanidine, and (*j*) 1-butanol.

2. Perchloric acid monohydrate is $H_3O^+ClO_4^-$. What would be a more appropriate name for this compound?

3. What are the acids in (*a*) dilute aqueous HBr, (*b*) dilute aqueous phosphoric acid, (*c*) a solution of acetic acid in hexane, (*d*) a solution of ammonium chloride in water, and (*e*) a solution of acetic acid in 100% sulfuric acid?

4. Write equations for the reaction of acetate ion with (*a*) H_3O^+, (*b*) $CH_3OH_2^+$, (*c*) HSO_4^-, (*d*) ethanol, (*e*) water, (*f*) phosphoric acid, and (*g*) HCl.

5. Write the formula for the protonated form of each of the following; show all relevant nonbonding (unshared) electron pairs: (*a*) OH^-, (*b*) CH_3OCH_3, (*c*) CH_3SH, (*d*) CH_3OH, (*e*) $(CH_3)_3N$, (*f*) formic acid.

6. Arrange the following in the order of decreasing "strength" as acids: (*a*) H_2O, (*b*) HBr, (*c*) NH_4^+, (*d*) NH_3, (*e*) CH_3COOH, (*f*) Cl_3CCOOH, (*g*) $HClO_4$, (*h*) $H_2ONO_2^+$, (*i*) $CH_3COOH_2^+$, (*j*) NH_2^-.

7. Why is HOCl a stronger acid than water?

8. Write the equation for the reaction of dimethyl ether with each of the following: (*a*) BF_3, (*b*) $AlBr_3$, (*c*) $ZnCl_2$, (*d*) $MgBr_2$, (*e*) $SnCl_4$, (*f*) $HClO_4$, (*g*) CH_3^+, (*h*) phenol.

9. What is the approximate pH of a 0.1 *M* solution of benzoic acid in water? The pK_a of benzoic acid is 4.2.

10. Water is nearly insoluble in liquid SO_2. HBr is soluble in liquid SO_2 but the solution is not a conductor of electricity. When water is added to a solution of HBr in SO_2, an amount of water dissolves equivalent to the amount of HBr, and the resulting solution is a conductor of electricity. Explain.

5

Equilibrium and reaction rate

Most of the reactions of organic compounds do not occur instantaneously, but proceed at measurable rates. Precise measurement of the rate of a reaction at various temperatures and concentrations of the reacting compounds provides valuable information that permits the chemist to describe the step-by-step progress of the reaction in specific terms. Such a description of the course of the reaction is termed the "mechanism" of the reaction.

Given time, all reactions proceed to a state of equilibrium, depending on conditions that the chemist can often manipulate to favor the formation of a desired product or to shorten the time required to reach the equilibrium state.

This chapter introduces the basic concepts of the rate and equilibrium of organic reactions, concepts that will enter into much of the material to follow.

5-1 Reaction types

Chemical reactions most often encountered are those that may occur between (*a*) two ions:

$$\underset{\text{(In solution)}}{Ag^+ + Cl^-} \rightleftharpoons \underset{\text{(Insoluble salt)}}{AgCl} \qquad (1)$$

(*b*) an ion and a neutral molecule:

$$NH_4^+ + H_2O \rightleftharpoons NH_3 + H_3O^+ \quad (2)$$

$$OH^- + HCl \rightleftharpoons H_2O + Cl^- \quad (3)$$

$$OH^- + CH_3Br \rightleftharpoons HOCH_3 + Br^- \quad (4)$$

(*c*) two neutral molecules:

$$NH_3 + CH_3Br \rightleftharpoons CH_3NH_3^+ + Br^- \quad (5)$$

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+ \quad (6)$$

(*d*) a free radical and a neutral molecule:

$$Cl\cdot + CH_4 \rightleftharpoons HCl + CH_3\cdot \quad (7)$$

(*e*) two free radicals:

$$\cdot H + \cdot H \rightleftharpoons H_2 \quad (8)$$

$$CH_3\cdot + \cdot Cl \rightleftharpoons CH_3Cl \quad (9)$$

These reactions are written as equilibrium reactions, although in some of them the position of equilibrium is such that they are essentially complete in one direction. For instance, the association of two hydrogen atoms to give a molecule of hydrogen is accompanied by the liberation of a large amount of energy (104 kcal/mole), so that at ordinary temperatures the reverse reaction, dissociation of hydrogen into atoms, which would require this amount of energy, is unobservable. Similarly, the reaction of an acid such as HCl with a strong base such as OH^- is essentially complete.

There are two characteristics of a reaction

$$A + B \rightleftharpoons C + D \quad (10)$$

that are of principal interest: one is the *extent* to which the reactants A and B are transformed into the products C and D; the second is the *rate* at which the reaction proceeds.

5-2 Equilibrium

The familiar types of equilibrium reactions of acids and bases have been discussed in Chapter 4. Many of the reactions of organic compounds that involve the making and breaking of covalent bonds [for example, (4) and (5)] are equilibrium reactions that proceed, or can be made to proceed, essentially to completion.

The equilibrium constant of reaction (10) is defined by the expression

$$K = \frac{[C][D]}{[A][B]} \tag{11}$$

and the equilibrium constant, K, is related to the free energy change in the reaction by the equation

$$-\Delta F = RT \log_e K \tag{12}$$

where R is the gas constant and T is absolute temperature. Thus, in a reaction that liberates energy (an exergonic reaction) ΔF is negative (or $-\Delta F$ is positive) and K is greater than one. When ΔF is positive, K is less than one. A graphical representation of energy changes in reactions of several types is shown in Figure 5-1.

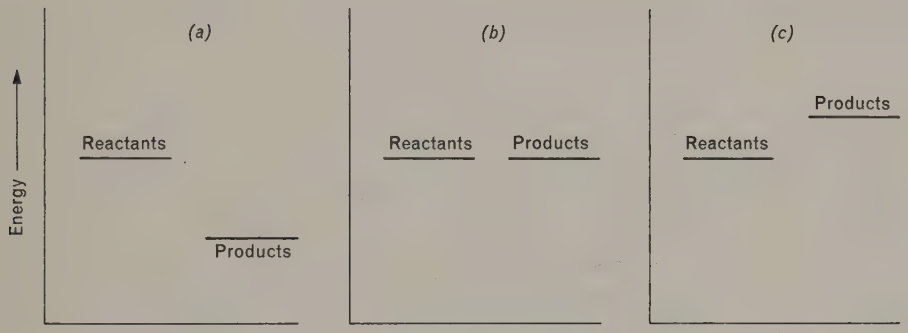


Figure 5-1
Energy changes in reaction: (*a*) exergonic, $K > 1$; (*b*) $K = 1$; (*c*) endergonic, $K < 1$.

A familiar example of an equilibrium reaction in organic chemistry is the reaction of an alcohol and a carboxylic acid to form an ester. In the case of ethyl acetate, the reaction is the following:

$$\underset{\text{Ethanol}}{CH_3CH_2OH} + \underset{\text{Acetic acid}}{CH_3COOH} \rightleftharpoons \underset{\text{Ethyl acetate}}{CH_3COOC_2H_5} + H_2O \tag{13}$$

The equilibrium constant for this reaction is expressed by the equation

$$K = \frac{[\text{ethyl acetate}]\,[H_2O]}{[\text{ethanol}]\,[\text{acetic acid}]} \tag{14}$$

If a moles of ethanol and b moles of acetic acid are allowed to react, when equilibrium is attained there will be x moles of the ester, x moles of water, $(a - x)$ moles

Table 5-1
Ester concentrations in ethanol–acetic acid mixtures at equilibrium at 25°C. Starting concentration of acetic acid = 1.

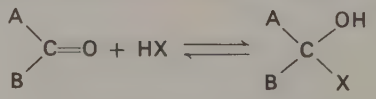
Starting concentration of ethanol	*Ester*	
	Observed	*Calculated*
0.10	0.05	0.05
0.50	0.41	0.42
1.00	0.66	0.67
2.00	0.86	0.85
8.00	0.97	0.97

of ethanol, and $(b - x)$ moles of acetic acid present in the final mixture, so that

$$K = \frac{x^2}{(a - x)(b - x)} \tag{15}$$

A study of this reaction by M. Berthelot and L. St. Gilles showed that $K = 4$. Thus, if 1 mole each of the alcohol and acid react, the final mixture will contain 0.667 mole of ester (x, $a - x$, and so on are concentrations, and so a constant volume is assumed when moles are specified). Table 5-1 shows the results of a series of experiments with varying concentrations of the alcohol.* It is clear from these data that we can convert acetic acid almost completely into ethyl acetate by using a large excess of ethanol. Conversely, if a large excess of acetic acid were used, practically all of the ethanol would be esterified. In general, when the organic chemist prepares an ester by this method he uses a large excess of the cheaper or less valuable reagent; if his primary concern is the conversion of an acid into its ester, he uses the alcohol as the solvent and thus in large excess. In this way, the esterification of the acid will be, for all practical purposes, complete.

The measurement of equilibrium constants in organic reactions is often an excellent way of studying the effect of structure upon the course of a reaction. For example, in the general case of addition to a carbonyl compound,



(16)

* The course of a reaction such as esterification may be followed experimentally by withdrawing aliquot samples from time to time and determining the amount of acetic acid remaining by titration with standard alkali.

the addition of HX to the trigonal carbonyl group alters the configuration around the carbon atom from trigonal (planar, 120° bond angles) to tetrahedral (bond angles 109°). The equilibrium constants of this reaction, carried out with a series of compounds containing different groups A and B, can be taken as an index of the relative stability of the two configurational states, and thus as a measure of the effect of the substituents A and B upon the relative stability of the states. Some specific examples of this and of other uses of equilibrium data in studying chemical reactions will be given in later chapters.

5-3 Rates of reactions

The mathematical expressions for the equilibrium constant of a reaction do not contain terms involving time, and thus do not give information about how fast a reaction will proceed. Indeed, the rate of a given reaction can sometimes be varied over an enormous range by very small differences in reaction conditions. Hydrogen and oxygen combine to form water in a reaction for which the equilibrium constant is so large that the reaction may be said to go to completion. Yet a mixture of hydrogen and oxygen may remain unchanged for an indefinite period of time; but if a small amount of a catalyst (platinum) is added, or an electric spark is passed through the gases, an explosive reaction will occur. Similarly, the reaction of chlorine with methane

$$Cl_2 + CH_4 \rightleftharpoons CH_3Cl + HCl \qquad (17)$$

is so slow as to be nearly undetectable if a mixture of the dry gases is kept in the dark; but upon exposure to sunlight immediate reaction occurs.

Reactions between ions, and proton transfers between acids and bases, are usually very fast. In proton transfers the approach of the atom bearing an unshared electron pair is unimpeded because of the small size of the hydrogen atom and is aided by the fact that the hydrogen nucleus is not shielded by an external array of electrons. Free radical reactions, such as the combination of chlorine atoms to give molecular chlorine are usually very fast because the bond that results is formed by the overlap of external orbitals, and all that is required for reaction to occur is that the atoms or radicals collide. In the case of complex radicals (such as $CH_3\dot{C}HCH_3$, for example), a suitable orientation at collision is necessary, but this is a probability factor that is seldom important enough to slow the overall reaction to a marked degree.

When covalent molecules react with each other or with ions, the reaction rate is often slow enough to be measured in the laboratory. The reaction of ethanol and acetic acid discussed in Section 5-2 proceeds at a rate that is easily measured, and that can be changed by altering the reaction conditions. Pure acetic acid and pure ethanol react quite slowly at room temperature, and the reaction requires many days to reach

equilibrium. If a drop of sulfuric acid is added to the reaction mixture the reaction proceeds much more rapidly, and equilibrium may be reached in hours instead of days. This will be discussed further in Section 12-12.

5-4 Activation energy and the transition state

A typical reaction in which an organic compound undergoes rupture of one bond and formation of a new one is the following:

$$HO^- + CH_3Br \rightleftharpoons HOCH_3 + Br^- \tag{18}$$

This reaction belongs to a large class of organic reactions that are important both because of their wide practical application and because of the great amount of theoretical and experimental study that has been devoted to them. This is a typical example of a *nucleophilic displacement reaction*; it is so called because the attacking agent, hydroxide ion, is a nucleophile, and the reaction involves the formation of an oxygen-carbon bond with displacement of the bromide ion. In general terms, this reaction can be represented by

$$B: + CH_3{:}X \rightleftharpoons B{:}CH_3 + :X \tag{19}$$

where the symbol B: represents a nucleophile (a base), and :X, also a nucleophile, is called the *leaving group* (or sometimes the *departing group*).

The reaction of methyl bromide with hydroxide ion proceeds at a measurable rate, and one can follow it experimentally by periodically withdrawing an aliquot portion of the solution and performing a suitable analysis—for instance, acidimetric titration to determine the OH^- concentration, or argentimetric titration for bromide-ion concentration.

An examination of experimental data obtained in this way for reaction (18) discloses that:

1. The rate of the reaction (the rate of disappearance of OH^- ion or the rate of appearance of Br^- ion) is proportional to the concentration of both OH^- and CH_3Br:

$$\text{rate} = k[OH^-][CH_3Br] \tag{20}$$

where k is the *rate constant* for the reaction. Doubling the concentration of either doubles the rate of the reaction.

2. At given concentrations of the reactants, the rate of the reaction increases with increasing temperature.

The nature of this reaction and the stages through which it proceeds are described by a general theory called the *transition state theory*. According to this theory, reacting molecules collide to form an unstable combination called the *activated complex* or the *transition state*, which decomposes either in such a way as to yield the components from which it was formed, or in another way to yield new compounds, the products of the reaction.

The activated complex is a high-energy state of the system that is formed when molecules with sufficient energy collide. A graphical representation of the course of a reaction that proceeds through the high-energy transition state is shown in Figure 5-2.

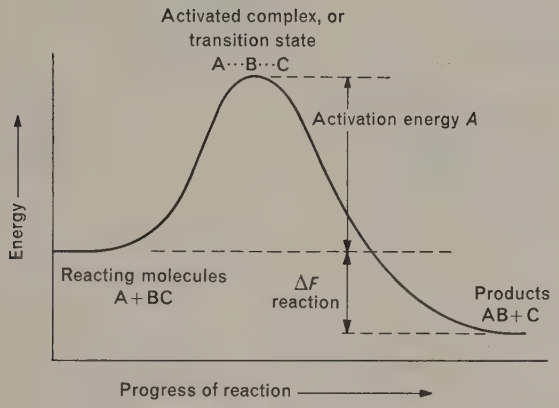


Figure 5-2
Energy diagram for reaction A + BC → AB + C.

What is the function of activation energy, and what is the activated complex? Why is the activated complex formed in some collisions and not in others? Why is the activated complex an unstable state of the system? In the following discussion we shall trace the course of events that take place in the formation of methanol and bromide ion from the reaction of methyl bromide and hydroxide ion (18), and try to answer these questions.

First of all, let us consider a system containing the reacting species methyl bromide and hydroxide ion. The molecules of these substances are in motion; they move from point to point, collide, and bounce from one another, from the walls of the vessel, and from solvent molecules. By the operation of the laws of chance, they move at various speeds. Some have low kinetic energy, some high. The differences in energies can be described by the Boltzmann distribution law, and the proportion of molecules with a given kinetic energy varies with temperature. It is reasonable to

assume that the higher the temperature, the greater the number of molecules with high kinetic energy. A graph of a Boltzmann distribution function at two temperatures is shown in Figure 5-3; it can be seen that at the higher temperature the fraction of molecules with high kinetic energies is larger.

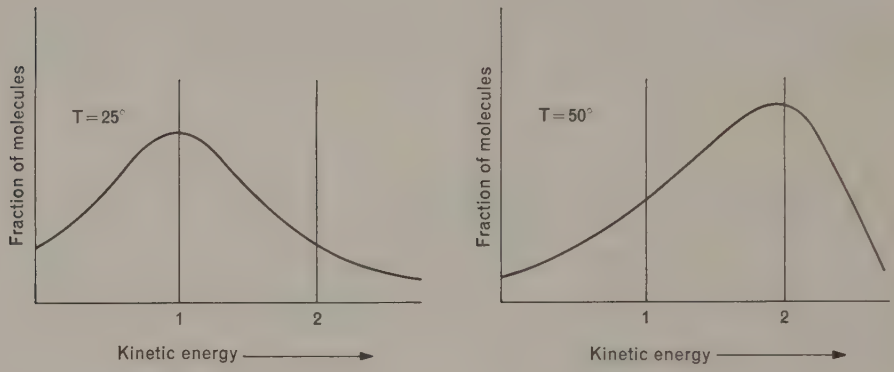


Figure 5-3
Distribution of energy among molecules and its dependence on temperature.

The collisions that occur between the hydroxide ions and the methyl bromide molecules may or may not lead to a chemical reaction. Collision must occur in such a way that the orbital overlap necessary for bond formation can occur, and thus collision must take place with proper orientation; further, it must take place with sufficient force to permit sufficient interpenetration of the two substances to bring them within overlap distance. Reaction can occur when an OH^- ion with sufficient energy collides with a CH_3Br molecule in such a way that a molecular orbital can begin to form between the carbon atom and the unshared pair of electrons on oxygen. Various possible modes of collision are pictured in Figure 5-4; of these, that marked (*c*) places the two molecules in a position to enter into a reaction.

But the four carbon orbitals in methyl bromide are filled, the octet is complete, and there appears to be no way in which a new bond can form. How can the hydroxide ion begin to engage in bonding with the "saturated" carbon atom? In our earlier discussion of covalent bonds it was pointed out that bonds between unlike atoms are polar in character, with the electron pair closer to the more electronegative atom. The molecular orbital that constitutes the carbon-bromide bond is not only distorted so that there is a greater share of the electron density at the bromine atom, but the carbon atom, because of its partial positive character, has some bonding capacity of its own. This is represented in Figure 5-5, where a lobe of the sp^3 orbital of the C—Br

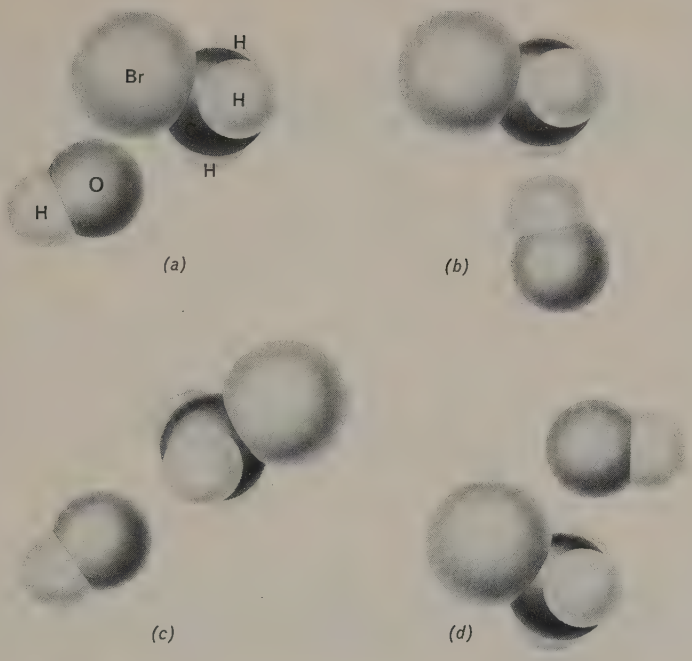


Figure 5-4
Various possible orientations of OH^- ions and CH_3Br molecules at collision.

bond extends in the direction away from this bond. The sequence of events that leads to reaction is pictured in Figure 5-5: the high-energy hydroxide ions strike the methyl bromide molecule (or the latter may be the energetic missile) with sufficient velocity to overcome the repulsive forces of the hydrogen nuclei; the orbital on oxygen that contains an unshared pair of electrons overlaps with the residual lobe of the carbon-bromine bond orbital; a very unstable (high energy) complex forms, in which OH^- has preempted somewhat more of the carbon orbital and bromine has relinquished some; and finally, either the OH^- ion recoils, or the bromine is expelled as the anion.

The decrease in energy in the overall process (ΔF reaction, Figure 5-2) is such that the equilibrium in reaction (18) lies far to the right. This means that the transition state decomposes into CH_3OH and Br^- more often than it reverts to OH^- and CH_3Br.

It is now apparent why an increase in concentration of OH^- or CH_3Br increases the rate of the formation of CH_3OH: at higher concentrations of the reactants there is a higher probability of collisions that form the activated complex. The effect of temperature is also understandable, since at higher temperatures there are relatively more molecules with sufficient energy to form the activated complex upon collision.

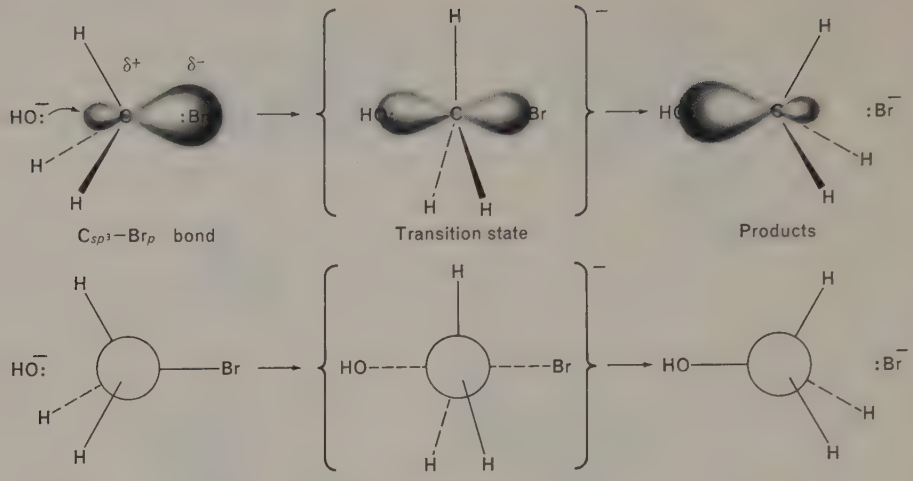


Figure 5-5
Stages in the reaction of methyl bromide with hydroxide ion. Note that in the transition state pictured, the three C—H orbitals are sp^2 in type. The fourth orbital, a p orbital of carbon, cannot contain more than two electrons; thus, the HO—C bond and the C—Br bonds cannot be full bonds. This can be expressed by saying that the oxygen and bromine atoms are partially bonded to carbon in the transition state.

Most organic reactions proceed through a transition state, the properties of which are seldom known in detail because the activated complex is a transitory species that cannot be isolated. Nevertheless, it is usually possible to write a structure that is a reasonable approximation of the transition state, and to use this hypothetical model as a basis for a consideration of its properties. The structures of transition states found in this text are of this kind: reasonable structural assignments whose value is their usefulness in helping one to reach an understanding of a reaction.

5-5 Competing reaction paths

It is frequently possible to devise, *a priori*, two reasonable and possible paths by which a reaction might proceed to yield a given product; and in some cases it is possible for a given pair of reactants to react in two different ways that lead to two different products. Often a consideration of the probable transition states for the possible reactions permits a decision as to the preferred course for the reaction. If the products of two competing reaction courses are of comparable structure and energy content, the preferred reaction will be the one whose transition state is at the lower energy level—that is, whose transition state is the most stable (Figure 5-6).

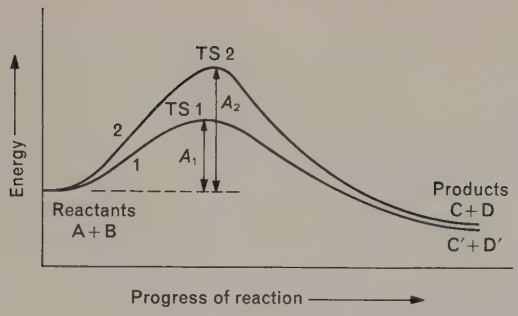


Figure 5-6
Energy profile of the reaction of A + B to yield different products by way of transition states 1 and 2 with activation energies A_1 and A_2.

The reason for the preference for the lower-energy transition state is found in a consideration of the expression for the dependence of reaction rate upon the energy of the transition state,

$$\text{rate constant } k = Ce^{-(A/RT)}$$

where C is a constant relating to effective collision frequency, A is the activation energy, R is the gas constant, and T is the absolute temperature. Since the activation energy is exponential in this expression, small changes in its value have profound effects upon the value of k; and, more important for our present purpose, an increase in the value of A causes a decrease in k. A simple numerical calculation will illustrate this point. Consider two reactions with activation energies of (1) 20,000 cal/mole and (2) 22,000 cal/mole.*

$$\frac{k_1}{k_2} = \frac{e^{-20{,}000/600}}{e^{-22{,}000/600}} = \frac{e^{-33.3}}{e^{-36.7}} = e^{3.4} = 30$$

Thus, the reaction rate is increased by a factor of 30 by a reduction in activation energy of only about ten percent.

In the hypothetical case for which the energy profiles are shown in Figure 5-6, the reaction that proceeds through transition state TS 1 to products C′ and D′ would proceed much faster than the alternative reaction through TS 2 to products C and D. If A_2 were 22,000 cal/mole and A_1 were 20,000 cal/mole, the ratio of product yields would be (C′ + D′)/(C + D) = 30.

*In the units used in this calculation, RT is approximately 600 cal/mole.

5-6 Multistage reactions

The displacement reaction (18) proceeds through a single transition state and thence to the products. Although a great many organic reactions are of this kind, many others proceed through a sequence of intermediate stages, with the formation of one or more discrete intermediates that can be assigned specific structures. Intermediates in a reaction may be of two kinds: *unstable* (that is, high-energy) *intermediates*, whose existence is transitory and can only be inferred from indirect experimental evidence; *stable intermediates*, which can often be isolated from the reaction mixture. Energy profiles for these reaction courses are shown in Figures 5-7 and 5-8. In Figure 5-7(*a*) the reactants combine to form the first transition state (TS 1), which then yields the intermediate product whose energy state is defined by the minimum in the curve. This intermediate then takes part in a second reaction, distinct from the first, leading through a second transition state (TS 2) to the final products of the reaction. Since transition state TS 1 is at a lower energy than TS 2, the reaction rate for the process R (reactants) $\rightarrow$ P (products) is governed by the (slower) rate of the second step, so that this step is called the *rate-determining step* of the overall reaction.

Figure 5-7(*b*) shows the energy profile of a two-step reaction in which the first step is rate determining.

Figure 5-8 shows the energy profile for a two-stage reaction in which a stable intermediate is formed. The energy difference between the reactants (R) and the intermediate (I) shows that the equilibrium R $\rightleftharpoons$ I lies on the side of the intermediate. The step I $\rightleftharpoons$ P is a separate reaction, proceeding through a second transition state,

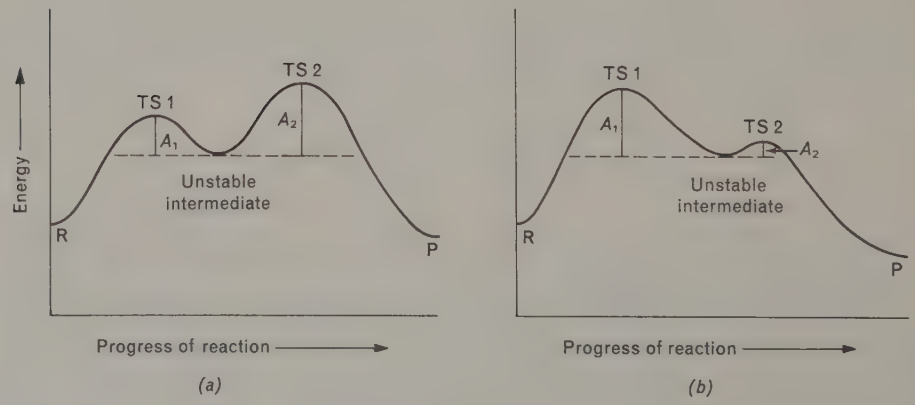


Figure 5-7
Energy profiles for reactions involving two transition states and an unstable intermediate. R = reactants, P = products, A = activation energies. (*a*) Second step is rate determining, $A_2 > A_1$. (*b*) First step is rate determining, $A_1 > A_2$.

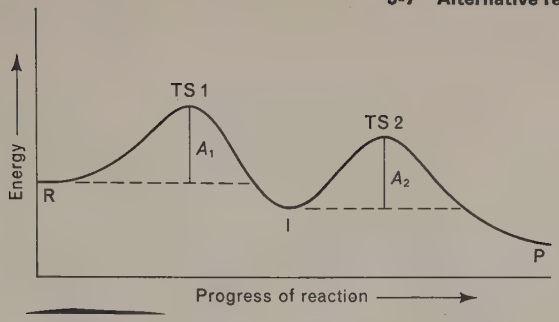


Figure 5-8
Energy profile for a two-step reaction in which a stable intermediate is formed.

and with its own equilibrium constant. Whether or not the intermediate accumulates in the reaction mixture depends upon the rate of its conversion into the final products and thus upon the relative activation energies of the two steps of the reaction.

5-7 Alternative reaction paths

The reaction between methyl bromide and hydroxide ion can be conceived of as proceeding in a way other than that described in Section 5-4. We might suppose that the reaction proceeds in two steps:

$$\text{Step 1:} \quad CH_3Br \longrightarrow CH_3^+ + :Br^- \tag{21}$$

$$\text{Step 2:} \quad CH_3^+ + OH^- \longrightarrow CH_3OH \tag{22}$$

Step 1 would, however, be expected to require a very high energy indeed, because the C—Br bond energy in methyl bromide, which is the energy absorbed by the reaction

$$CH_3Br \longrightarrow CH_3\cdot + \cdot Br \tag{23}$$

is 68 kcal/mole. This process is called *homolytic scission* of the bond. The energy required for Step 1, which is called *heterolytic scission*, would be greater than 68 kcal/mole, for it involves not only breaking of the C—Br bond but the separation of opposite charges.

Observed activation energies for reactions of the type exemplified by (18) are, however, in the region of about 20 kcal/mole. It can be concluded that the reaction course (21) and (22) cannot be the correct one.

In Figure 5-9 are shown two energy profiles for a reaction formulated in the general terms

$$A: + CH_3X \longrightarrow ACH_3 + :X \tag{24}$$

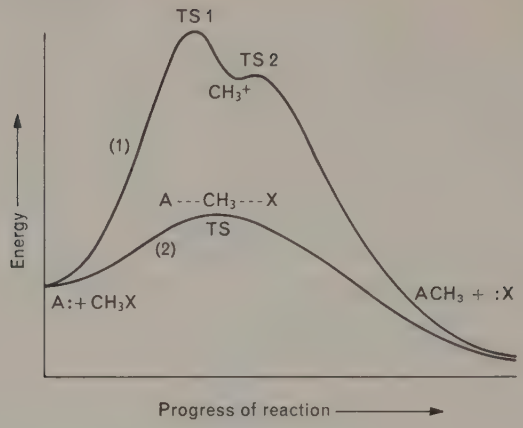


Figure 5-9
Energy profiles for two hypothetical pathways for the reaction A: + $CH_3X \rightarrow ACH_3$ + :X.
(1) Heterolytic dissociation-recombination.
(2) Bimolecular displacement.

The two reaction pathways represent (1) the dissociation-recombination course of (21) and (22); and (2) the bimolecular reaction of (18). It will be clear from this energy diagram that of the two alternative pathways, the bimolecular reaction, with the lower activation energy, would prevail.

Discussion of the *nucleophilic displacement reaction*, of which (18) is but one example, will be resumed in Chapter 7. It will be seen there that in the general reaction

$$B:^- + R:X \longrightarrow B:R + :X^- \qquad (25)$$

the nature of R determines whether pathway (1) or pathway (2) is followed, and that in many cases the dissociation-recombination pathway is indeed followed. An energy profile for a reaction of the general type (25) that does proceed through an ionization step, with R^+ an unstable intermediate, is shown in Figure 5-10. Structural factors—such as the nature of R in (25)—can determine whether a reaction proceeds by one pathway or another. Indeed, it is quite possible for a reaction to proceed by two pathways simultaneously, the same product being formed by both.

The descriptions of the course of reactions presented in the above discussion are called the *mechanisms* of the reactions. Much of the emphasis in the chapters to follow will be on the stepwise course, or the mechanism, of reactions. An understanding of the mechanisms of reactions, such as the dehydration of alcohols, the hydrolysis of acid derivatives, and aromatic substitution reactions, permits the chemist to under-

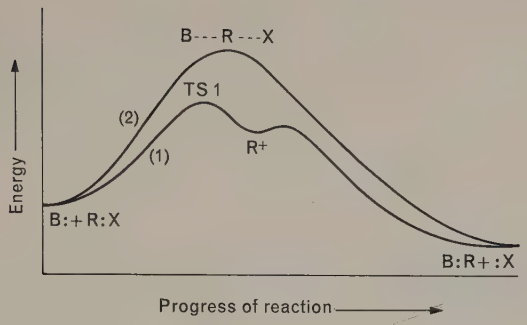


Figure 5-10
Energy profiles for two hypothetical pathways for the reaction $B^- + RX \rightarrow BR + X^-$ in which structural factors stabilize R^+ [path (1)] and increase the energy of the bimolecular transition state [path (2)].

stand and predict the course of chemical transformations. To the biologically oriented chemist, an understanding of organic reaction mechanisms will reveal that most of the chemical transformations occurring in living systems are comprehensible in terms of rational, mechanistically acceptable pathways.

6

Stereoisomerism. The arrangement of atoms in space

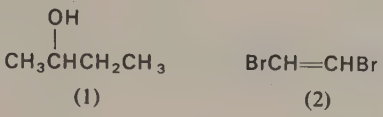
The concepts of the arrangement of organic molecules in space (stereochemistry), briefly introduced in Chapter 3, are developed in this chapter. Molecular configuration is an important property of the large majority of organic compounds. Stereochemistry involves not only the shapes of molecules, but the ways in which they react, for the relative positions of reacting groups has a profound effect upon the rate and result of a reaction.

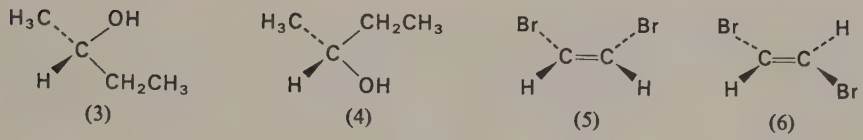
An important aspect of stereochemistry is the effect of the configuration of a dissymmetric molecule upon its behavior in biological reactions. Nearly all organic compounds produced by living organisms are optically active, because they are dissymmetric. Many drugs are capable of existing in enantiomeric (Section 6-4) or diastereomeric (Section 6-9) forms, and their physiological action is often critically dependent upon their configuration.

6-1 Molecular configuration

The conventional valence-bond formulas that are ordinarily used to represent organic compounds fail to show the three-dimensional aspect of their structures. When it is necessary or desirable to consider spatial relationships special devices of various

kinds are employed. For example, the formulas (1) and (2) for 2-butanol and 1,2-dibromoethane do not reveal the fact that each of these is a sterically noncommittal representation of two isomeric compounds:*





The two 2-butanols (3) and (4) are different compounds: they are *non-identical mirror images*. They are, however, identical in all chemical and physical properties except two:

1. One of them rotates the plane of vibration of polarized light to the left, the other an equal amount to the right. They are said to be *optically active*, and are called *optical isomers*.
2. They react at different rates with any reagent that is itself optically active.

The olefinic compounds (5) and (6) are *cis* (5) and *trans* (6) isomers. They are not optically active. They are commonly referred to as *geometrical isomers*. The inclusive term "stereoisomerism" is used to refer to both geometric and optical isomerism, for both depend upon the spatial arrangement in the isomers, of the same kinds of bonds between the same kinds of atoms. Since the term "stereoisomerism" is not definitive, the terms "*cis-trans* isomerism" and "optical isomerism" are ordinarily used.

6-2 Optical isomerism. Polarized light

Ordinary light is an advancing wave front in which the vibrations occur in all directions perpendicular to the direction of propagation. Each vibration may be looked upon as the resultant vector of two vibrations at right angles to one another:

* The conventional devices for writing formulas in three-dimensional representation were described earlier (Section 3-19) and should be referred to again at this time.

If the vibrations in one of the two directions are absorbed or selectively refracted, the resulting light ray vibrates in a single plane only and is said to be *plane polarized*:

This can be accomplished in several ways. A suitably oriented crystal of calcite (a form of $CaCO_3$) displays a different index of refraction for rays with one plane of vibration than for those vibrating in the other plane. This means that the two components of a light ray travel in calcite with different velocities, and that a properly cut calcite crystal can utilize this difference to separate them. The Nicol prism utilizes this property (called *double refraction*) of calcite to produce plane-polarized light by a combined refraction and reflection of one component of a light ray, with the result that the other is allowed to proceed through and emerge from the prism. The prism consists of two halves of a crystal of calcite, cut with precise angles and cemented together with a Canada balsam, a resin chosen for the particular value of its refractive index.

Another means of producing polarized light is by the use of a *dichroic* crystal. A dichroic crystal is one that has the property of absorbing the component vibrating in one plane more strongly than the component vibrating at right angles to it. A dichroic crystal of proper thickness will effectively remove one component by completely absorbing it, allowing the other to be transmitted to a useful extent (it, too, will be absorbed, but to a lesser degree). The widely used *Polaroid* material utilizes the dichroism of certain salts of quinine, properly oriented on a transparent support, to produce polarized light.

6-3 The measurement of optical rotation. The polarimeter

An "optically active" substance is one that rotates the plane of polarized light. The actual magnitude of this rotation can be measured with a device called a *polarimeter*. The polarimeter is a precision instrument, comprising the parts shown in Figure 6-1.

If the polarizer and analyzer are "crossed" at 90° with respect to one another, and no sample is interposed, no light will reach the eyepiece. If an optically active sample (usually dissolved in some optically *in*active solvent) is interposed, it rotates the plane of the polarized light entering it, so that the analyzer must be turned through an angle equal to the extent of the rotation in order again to produce a dark field in the eyepiece. The rotation is measured on a circular scale, calibrated in degrees, to which the analyzer is mounted. If the plane of polarization is rotated to the right, the sample is *dextrorotatory*; if to the left, *levorotatory*.

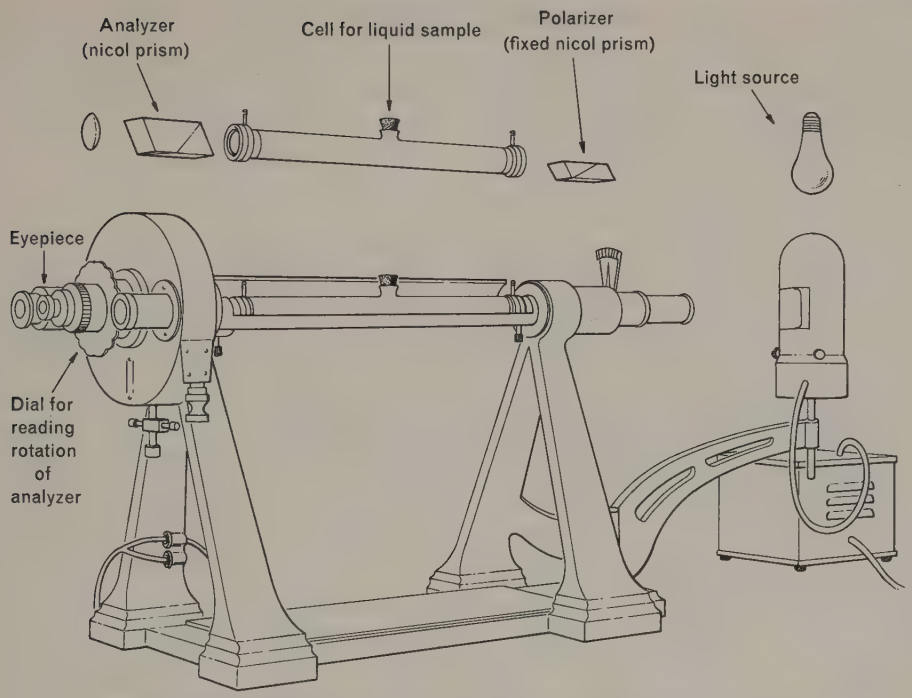


Figure 6-1
A polarimeter: schematic diagram with drawing of an actual instrument.

The degree to which the plane of polarization is rotated by a given substance depends upon the wavelength of the light, so monochromatic light (for example, that produced by a sodium lamp or a mercury or cadmium arc) is used in measurements of rotation.

With a particular optically active substance, the actual rotation in degrees is proportional to the concentration of the solution and the length of the light path through the solution. The actual rotation α is therefore

$$\alpha = kcl$$

If the concentration c is in grams per cubic centimeter and if l, the length of the tube that contains the sample, is measured in decimeters, the constant k is called the *specific rotation*, for which the symbol $[\alpha]$ is used. Then

$$k = [\alpha] = \frac{\text{observed rotation in degrees}}{\text{length in dm} \times \text{concentration of solution in g/cm}^3}$$

Optical rotations are reported as specific rotations, the temperature and wavelength of the light used being reported as in the following example; in addition, the concentration and solvent used are usually given:

$$[\alpha]_D^{20} = +18.5° \quad (c = 0.011 \text{ g/cm}^3, \text{ water})$$

This means that at 20°C, using the D line of sodium, a solution of 1.10 g of a substance in 100 ml of water had a specific rotation of 18.5° to the right (dextrorotatory). The concentration and solvent are given because with many compounds different rotations are observed with changes in concentration, and with different solvents.

6-4 Optical activity and molecular structure

Optical activity was first observed in 1811, when it was found that crystals of certain substances—notably quartz—existed in *enantiomeric* (sometimes, *enantiomorphic*) forms, one of which rotated the plane of polarized light to the right, the other to the left. Enantiomeric (Greek *enantios*, opposite) objects are those that are *nonidentical mirror images*; the right- and left-handed members of a pair of gloves and the pairs of objects pictured in Figure 6-2 are enantiomeric pairs.

The discovery of the optical activity of quartz was soon followed by observations of optical activity in solutions of organic compounds (for example, sugars, tartaric acid) and in liquid substances (for example, turpentine). The activity of quartz appears to reside in the particular crystal structure of this form of silica. However, since a homogeneous liquid or solution does not have the distinct structure possessed by a crystal, it must be concluded that the structural requirements for optical activity in these cases are to be found in the *arrangement of the atoms in the individual molecules*.

Discovery of optically active compounds continued throughout the first three-quarters of the nineteenth century, but until J. H. van't Hoff and A. Le Bel proposed

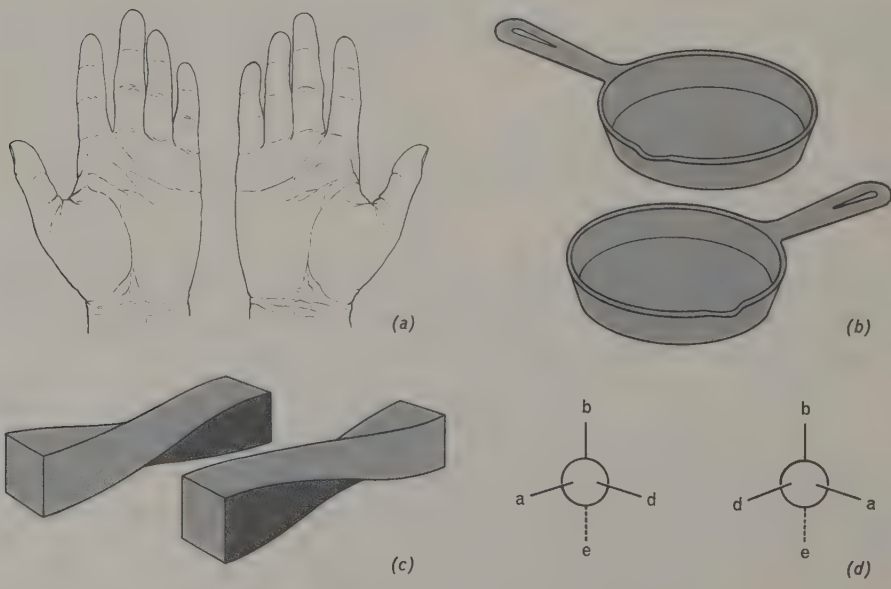
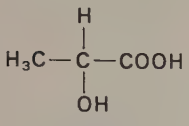


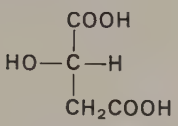
Figure 6-2
Enantiomeric pairs: non-identical mirror images.

their theory of the tetrahedral arrangement of the valence bonds of carbon in 1874, no satisfactory explanation for the phenomenon existed.

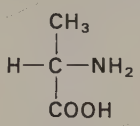
Van't Hoff and Le Bel observed that *in every known case of optical isomerism the compound contained at least one carbon atom to which four different atoms or groups were joined*; for example,



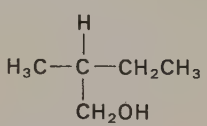
Lactic acid



Malic acid



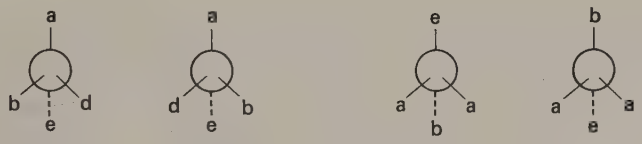
Alanine



"Active" amyl alcohol

It is significant that at the time of van't Hoff and Le Bel all of the known optically active compounds had been isolated from natural (plant or animal) sources.

The following two pairs of mirror images represent the compounds Cabde and Caabe:

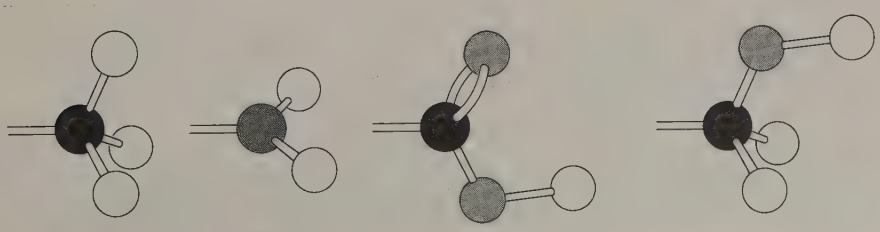


(7) (8) (9) (10)

Enantiomers Cabde — Not enantiomers Caabe

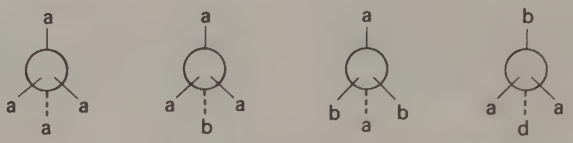
Forms (7) and (8) are not superposable, so that they are distinct isomers. In fact, they are enantiomers: one is dextrorotatory (+) and the other is levorotatory (−), although which is which must be determined by experiment. Examination of (7) and (8) discloses that they lack any element of symmetry. On the other hand, if groups b and e are themselves symmetrical, the compound Caabe possesses a plane of symmetry that bisects these groups. In that case (9) and (10) are superposable, and hence identical forms; they are not enantiomers.

The groups —CH_3, —COOH, —NH_2, and —CH_2OH are symmetrical; if they are represented in the following way, the page on which they are drawn represents the plane of symmetry:


—CH_3 —NH_2 —COOH —CH_2OH

Since they are free to rotate about the single bond that joins them to the rest of a molecule, we can regard these groups as equivalent to symmetrical spheres when estimating the stereochemical possibilities of that molecule.

A study of models of the following will show that all compounds of the types Ca_4, Ca_3b, Ca_2b_2, and Ca_2bd have a plane of symmetry (providing, of course, that none of the substituents a, b, and so on is itself dissymetrical):



All of these are drawn so that the plane of symmetry is vertical and at right angles to the page, passing through the groups at the top and bottom of each model.

The carbon atom (represented by the sphere) in (7) and (8) is called an *asymmetric carbon atom*; the presence of a single asymmetric carbon atom is a sufficient—*but not necessary*—condition for optical activity. *The necessary condition for optical activity is molecular asymmetry: the possibility of existence of two isomers as non-superposable forms that bear the relationship of an object to its mirror image.* The most frequently encountered examples of enantiomeric object and mirror image are compounds possessing one or more asymmetric carbon atoms, which makes it possible for the compounds to exist in *dextro*(rotatory) and *levo*(rotatory) forms [henceforth referred to as (+) and (−) forms].

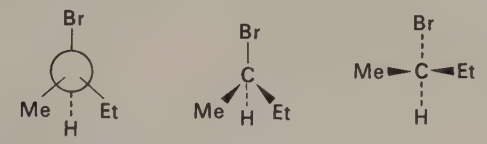
Exercise 1

What kind of isomerism could be expected if in the compound Caabd the carbon atom were (*a*) planar, with the four bonds at 90°, and (*b*) pyramidal, with the carbon atom at the apex of a regular pyramid?

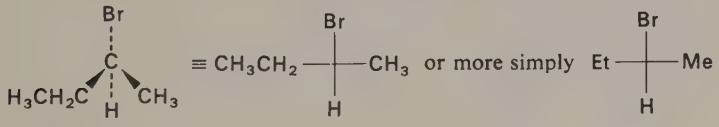
6-5 Representation of optical isomers. The Fischer projection and the Fischer transformation

The representation of three-dimensional structures by the "ball-and-stick" models, used in the preceding section, is too awkward and cumbersome a device for general use, and simpler and more convenient presentations are commonly employed. These

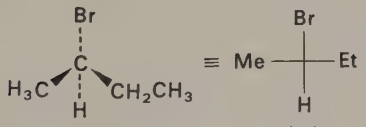
can be of several kinds; some of the most suitable are shown in the following, using one of the enantiomeric 2-bromobutanes as the example:



Although the dotted-and-heavy-bond formulas are often used, a simplified convention, called the *Fischer projection*, is also widely employed. This convention requires that the *horizontal bonds project toward the viewer, vertical bonds away from the viewer*. Thus, the enantiomeric 2-bromobutanes are drawn as follows:



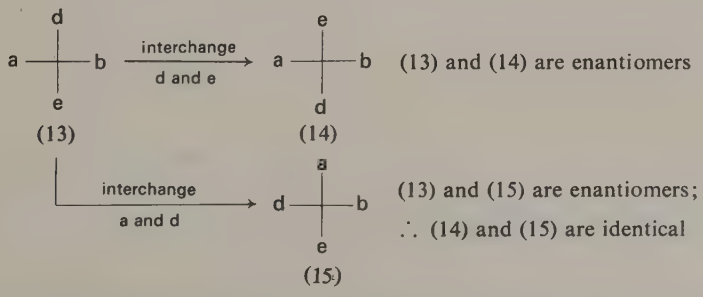
(11)



(12)

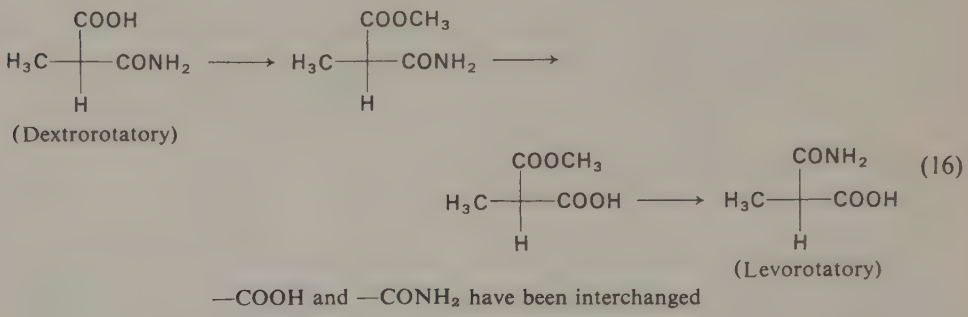
The simplified representation of asymmetric structures by the Fischer projection is efficient and convenient; it saves time and is readily comprehensible.

Fischer showed by experimental means that if any two groups in a compound Cabde are interchanged, the enantiomer results:



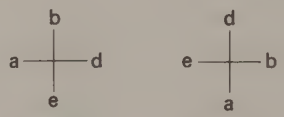
Although these relationships can be clearly recognized by manipulation of

models, Fischer demonstrated the transformation by an actual experiment:*

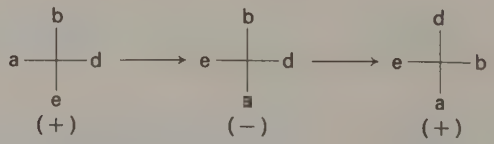


(16)

The chief utility of the Fischer transformation is in the ease with which structural formulas may be manipulated on paper. Suppose, for example, we wish to decide whether (17) and (18) are identical or enantiomers:



One can, of course, answer this question by constructing actual models and comparing them directly (but this is often inconvenient), or by drawing three-dimensional projection formulas and comparing them. Both of these procedures are quite unnecessary, however, for simple manipulation of the Fischer projection formulas by means of Fischer transformations provides the answer. It is to be noted that since a single interchange of any two groups yields the enantiomer, a *second interchange* of any two groups *returns the original configuration.* Let us arbitrarily call configuration (17) (+); its enantiomer is (−):

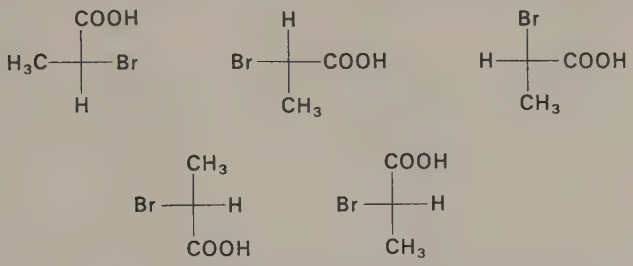


Thus (17) and (18) are the same.

* It would be premature to discuss at this time the details of the chemical procedures used in these functional-group alterations. They will become familiar to the student as the subject develops.

Exercise 2

Select the identical and enantiomeric forms of the following:



6-6 Other conventions for representing stereoisomeric structures

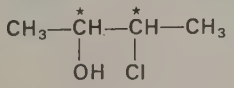
It is often preferable to represent stereochemical relationships by simple perspective drawings. Such formulas are not to be confused with Fischer projections. Let us consider the compound *cis*-1,2-cyclohexanediol, which can be drawn in any of the following ways:

(19) (20) (21) (22)

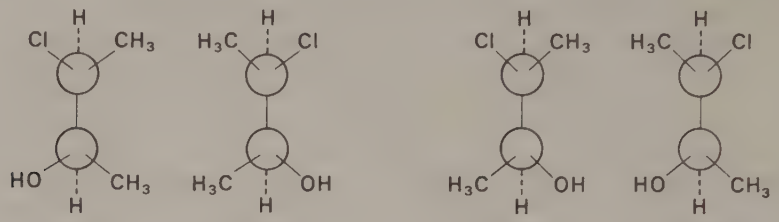
Formula (22) is a simplification of (20): formula (20) shows that the ring is viewed edge-on; in (22) this is understood. There is no satisfactory way of using a Fischer projection for a cyclic compound of this kind.

6-7 Two asymmetric carbon atoms

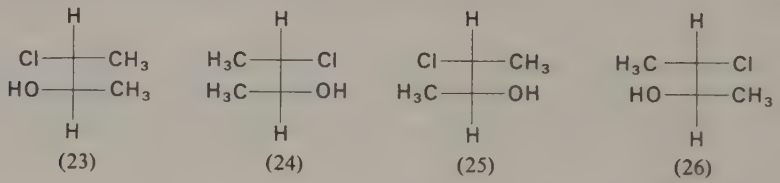
A compound such as 3-chloro-2-butanol has two asymmetric carbon atoms:



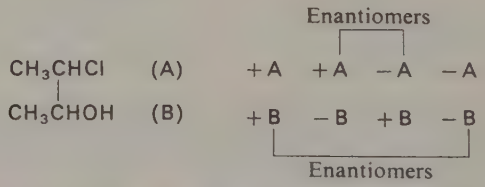
Projection formulas of models of the possible optical isomers may be drawn as follows:



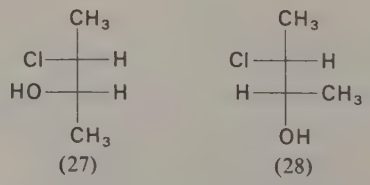
The Fischer projection can also be used to represent three-dimensional structures of this kind, as shown in the following diagrams. It should be remembered that *the Fischer convention requires that the horizontal lines represent bonds projecting toward the viewer*; the vertical lines project away from the viewer. Formulas (23) through (26) are thus represented as follows:



There are thus four optically active forms of 3-chloro-2-butanol. This can be shown in another way. If we call one of the asymmetric carbon atoms A and the other B, the following combinations are possible, since each asymmetric carbon atom can exist in a (+) and a (−) configuration:

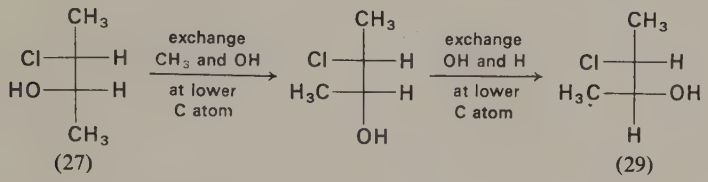


The Fischer transformation may be used at one asymmetric carbon of two. For example, let us ask if



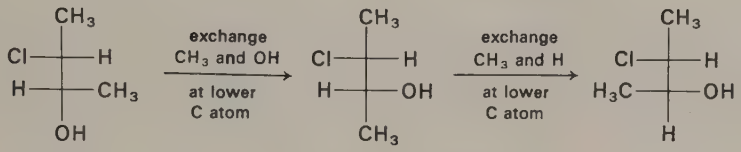
are the same compound.

Applying the Fischer transformation to the lower carbon atom of (27), we see that an exchange of CH_3 and OH followed by a second exchange of H and OH gives (29). Since we have not altered the top carbon atom and we have performed *two* exchanges on the lower carbon atom, (29) must be identical with (27):



(27) (29)

Performing a similar pair of exchanges at the lower carbon atom of (28) gives (30):



(28) (30)

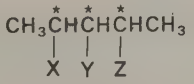
Because (29) and (30) are identical, it is apparent that (27) and (28) are the same.

Exercise 3

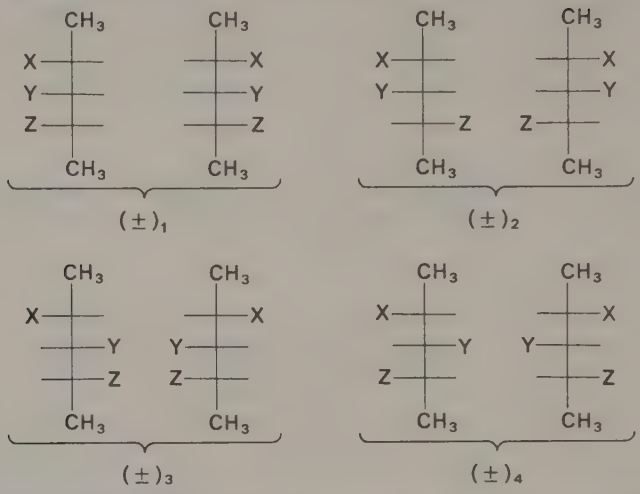
Which one of the four isomers (23)–(26) is represented by the one drawn as (27) = (28)?

6-8 More than two asymmetric carbon atoms

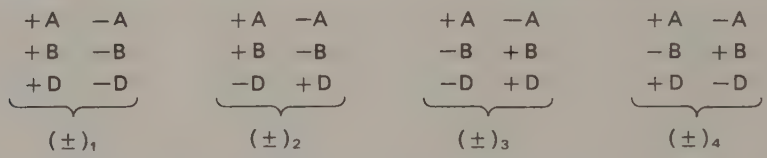
When *three* asymmetric carbon atoms are present, as in



the following projection formulas can be written:



Calling the three asymmetric carbon atoms A, B, and D, we have four enantiomeric pairs:



It is apparent that all the possible combinations are represented in this table, and that there are a total of eight possible optically active stereoisomers.

With four asymmetric carbon atoms, sixteen optically active isomers can exist [eight (±) pairs], and *for n asymmetric carbon atoms there are 2^n possible optical isomers.*

Exercise 4

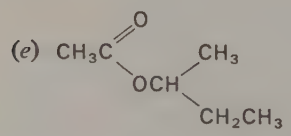
How many optically active isomers can exist for each of the following? Draw them in stereochemical notation (use Fischer projections where applicable):

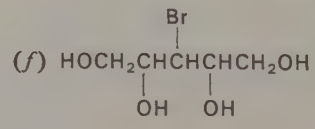
(*a*) CH_3CHCH_2Br with CH_3 below

(*b*) CH_3CHCH_2Br with CH_3CH_2 below

(*c*) $BrCH_2CHCl$ with CH_3 below

(*d*) $ClCH{-}CHCl$ with CH_3 and CH_2CH_3 below

(*e*) 

(*f*) 

(*g*) Cyclopropane-1,2-dicarboxylic acid (*cis* and *trans*)

(*h*) 1,2,3 tribromocyclohexane.

Exercise 5

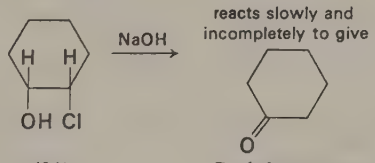
Look up the structural formula of cholesterol. Natural cholesterol is a single substance, and is optically active. How many optical isomers are possible for this structural arrangement? HINT: Find the number of asymmetric carbon atoms.

6-9 Diastereomers

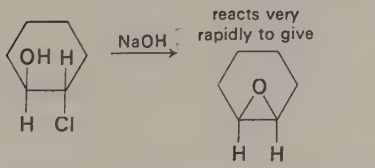
The compounds (23) and (25) are optical isomers, but they are not enantiomers. The same is true of the compounds +A+B+D, +A+B−D, +A−B−D, and +A−B+D in the preceding section.

The relationship between nonenantiomeric optical isomers is called *diastereoisomerism*, and the isomers are called *diastereoisomers*, or more commonly, *diastereomers*.

Diastereomers are usually different in physical properties and often show marked differences in chemical reactivity. *Cis*- and *trans*-2-chlorocyclohexanol, (31) and (32), are diastereomers; they react differently when treated with alkali:



(31) Cyclohexanone



(32) Cyclohexene oxide (1,2-epoxycyclohexane)

Each of the diastereomeric 2-chlorocyclohexanols exists in (+) and (−) modifications (of which only one is shown in the above formulas for each isomer). The (+) *cis* form, its (−) isomer, and the (±) mixture all react with alkali at identical rates to give the same product, cyclohexanone. The (−), (+), and (±) *trans* forms all react at the same rate (but different from that of the *cis* forms) to give the same product, cyclohexene oxide.

The difference in the reactivity of the diastereomeric 2-butene chlorohydrins will be discussed in detail in Section 10-19.

In the 2-chlorocyclohexanols the rigidity of the ring system requires that the

dispositions of the —OH and —Cl groups must remain *cis* or *trans*, and the *cis* compound *cannot* assume the favorable configuration required for the nucleophilic displacement of Cl^- by attack of $—O^-$, which requires the rearside attack by oxygen on the carbon atom holding —Cl. The *trans* compound possesses this favorable configuration, and thus yields the oxide very readily. In this case the *cis* compound actually undergoes not only a slower, but a different *kind* of reaction from that undergone by its diastereomer.

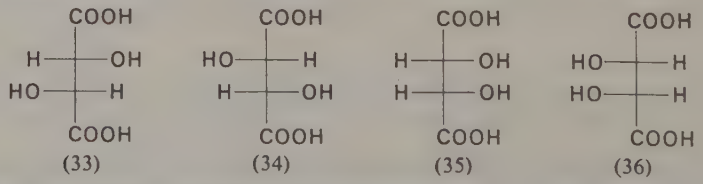
Diastereomeric compounds can be separated by the usual physical methods, such as distillation or fractional crystallization. It should be stressed that when diastereomeric compounds result from a chemical reaction of optically inactive reactants, the products are optically inactive: each of the diastereomers is obtained as a (±)-mixture, and if optically active compounds are desired the mixtures must be resolved (see Section 6-11).

Exercise 6

(*a*) What would be the result of reducing (±)-3-methyl-2-pentanone to the secondary alcohol (3-methyl-2-pentanol)? How many products would be formed? (*b*) What would be the result if optically active 3-methyl-2-pentanone were used? Formulate these reactions in stereochemical notation.

6-10 "Similar" asymmetric carbon atoms

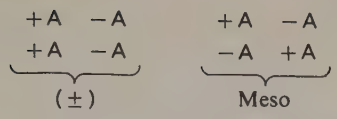
Tartaric acid contains two asymmetric carbon atoms, but to each of them are attached the same four substituents: H, OH, COOH, and —CH(OH)(COOH). The four apparent ways of arranging the groups in space can be represented as follows:



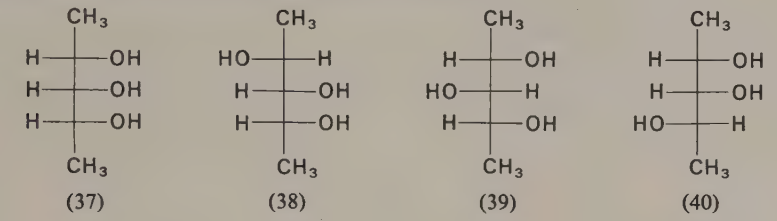
(33) (34) (35) (36)

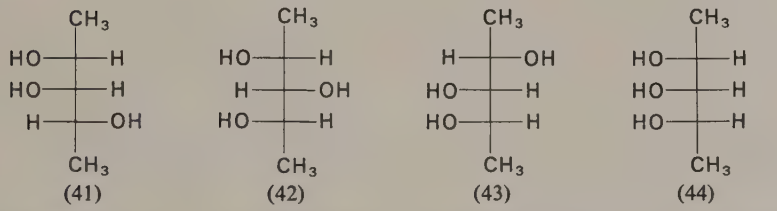
It can be seen that (33) and (34) are indeed enantiomers and represent (+) and (−) forms; but (35) and (36) are not enantiomers: they are identical, as can be seen by rotating one of them 180° *in the plane of the page*. Compound (35) [=(36)] is not optically active: it possesses a plane of symmetry. This compound is called *meso*-tartaric acid.

If the top asymmetric carbon atom is called A, the lower, which carries the same substituents, must also be designated as A. The (+), (−), and *meso* forms can then be represented:

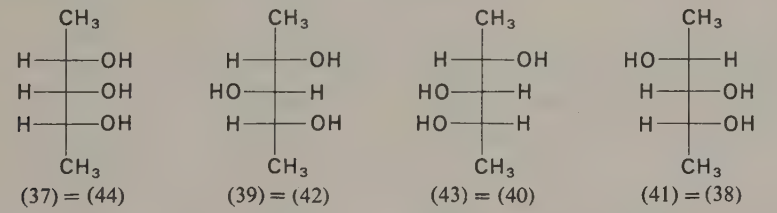


In compounds such as 2,3,4-pentanetriol the central carbon atom is called a *pseudoasymmetric* carbon atom. An examination of the various possible configurations of the hydroxyl groups in this triol will provide a good exercise in determining the number of isomers that can exist. Let us first write down in a systematic way all possible configurations of the three CHOH groups:





How many of these represent identical compounds? According to the convention we use for writing these formulas, we can turn any of them through 180° *in the plane of the page*. (But not out of that plane!) Thus, we see that (37) and (44) are the same; so are (38) and (41), (39) and (42), and (40) and (43). We are left with only four different configurations from the above set of eight:



Since the mirror image of (44) is (37), and these are identical, this must be a symmetrical compound. It is a *meso* form. The same is true of (39) = (42). In these *meso* compounds it can be seen that a plane of symmetry bisects the molecule through the central —CHOH group.

The pair (43) = (40) and (41) = (38) is an enantiomeric pair. Neither has an element of symmetry; they are mirror images, and they are not identical.

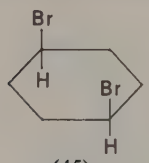
Thus, there are four 2,3,4-pentanetriols: two different *meso* compounds, one dextrorotatory compound, and its enantiomeric levorotatory compound.

It can be seen that if the two groups at the ends of the molecule were not identical, all eight of the configurations corresponding to (37)–(43) would be different. In this case there would be three different asymmetric carbon atoms, thus $2^n = 8$ possible stereoisomers and no *meso* compounds.

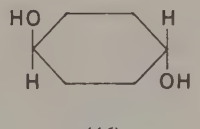
Exercise 7

Draw all of the possible configurations of 2,3,4-tribromohexane, and find the enantiomeric pairs. Are there any *meso* forms?

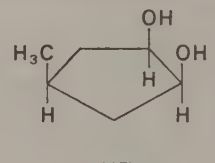
With some practice in visualizing formulas as three-dimensional projections the student will find it easy to discern whether elements of symmetry are present. For instance, the following represent nonresolvable (*meso*) compounds:



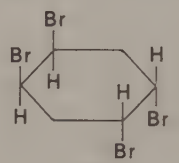
(45)



(46)



(47)



(48)

Exercise 8

Find the plane of symmetry in each of the compounds (45)–(48).

6-11 Resolution of optical isomers

A mixture containing equal amounts of two enantiomers is called a *racemic mixture*. The separation of a racemic mixture into the separate (+) and (−) isomers is called *resolution*. Since the melting points, solubilities, ionization constants (if acids or bases), and all other physical properties of (+) and (−) isomers are identical (except the direction in which they rotate the plane of polarized light), they cannot be separated by distillation, crystallization, differential partition between solvents, or any other such means. A rare exception is encountered in the case of those racemic mixtures that crystallize into hemihedral, enantiomorphic crystals that can be separated by hand.

Since diastereomers can be separated by physical means, the conversion of enantiomers into *diastereomeric derivatives* allows their separation, usually by simple crystallization. Subsequent decomposition of the separated derivatives allows the recovery of each enantiomer in the optically active state.

The selection of the particular means of converting the *dl*-mixture* into a mixture

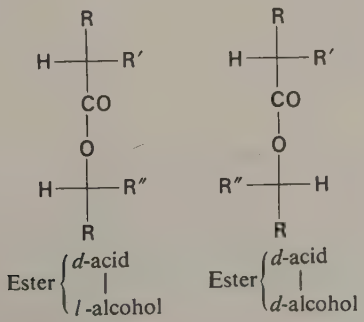
* The symbols *d* and *l* are often used in place of (+) and (−) in discussing optical isomerism. Present-day custom tends toward the use of the (+)-(−) symbolism, but it is sometimes more convenient to use the alternative notation. Since the two symbols mean the same thing, either may be chosen. The reason for the abandonment of the *d-l* notation is that another kind of configurational notation, in which the letters D and L are used, is also employed. While *d* stands for "dextrorotatory," D does not. The use of D and L will be explained in Section 6-15.

Table 6-1
Methods of resolution of racemic mixture

	dl-Pair		*Resolving agent*		*Diastereomers*
1.	*d*-acid *l*-acid	+	*d*-base	→	salt: *d*-acid-*d*-base salt: *l*-acid-*d*-base
2.	*d*-amine *l*-amine	+	*l*-acid	→	salt: *d*-amine-*l*-acid salt: *l*-amine-*l*-acid
3.	*d*-alcohol *l*-alcohol	+	*d*-acid	→	ester: *d*-acid-*d*-alcohol ester: *d*-acid-*l*-alcohol
4.	*d*-alcohol *l*-alcohol	+	anhydride or chloride of *d*-acid	→	as in 3
5.	*d*-ester acid *l*-ester acid	+	*d*-base	→	as in 1
6.	*d*-ketone *l*-ketone	+	*l*-hydrazide	→	*d*-ketone-*l*-hydrazone *l*-ketone-*l*-hydrazone

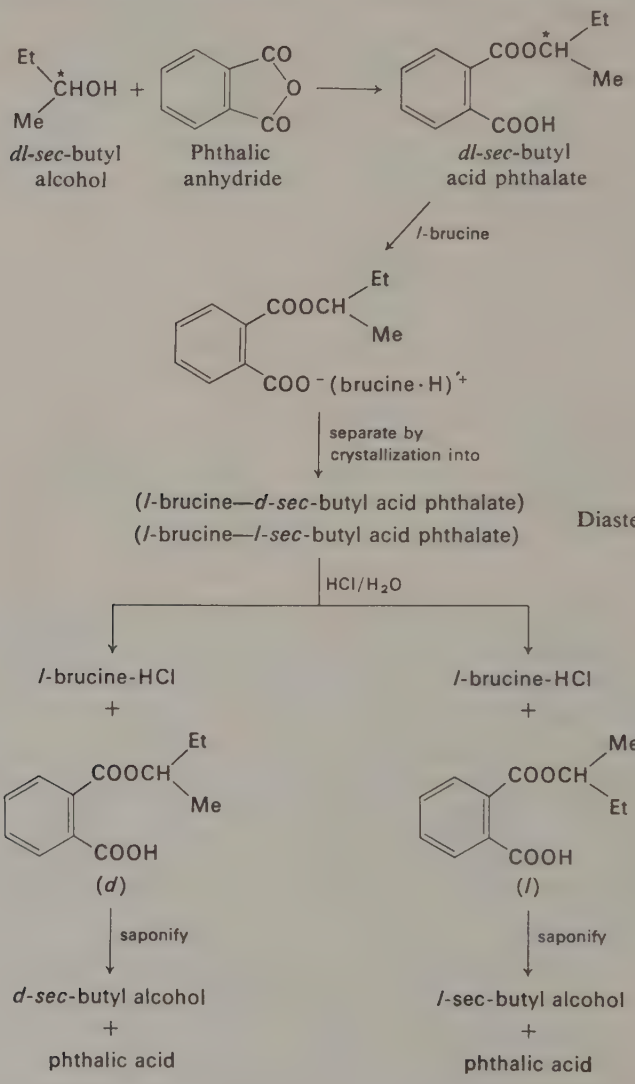
of diastereomers depends upon the chemical nature of the compound to be resolved and the physical properties of the resulting diastereomers. It is usually desirable to prepare one or both diastereomers that are crystalline compounds. General examples of resolution procedures are given in Table 6-1.

That *d*-A-*d*-B and *l*-A-*d*-B (where A = acid, B = base, as in example 1, Table 6-1) are not enantiomeric can be appreciated when it is recognized that the mirror image of *d*-A-*d*-B is *l*-A-*l*-B. This is also shown in example 3: if we write the Fischer projection formulas for the two esters (49) it is easy to see that they are not enantiomers, but diastereomers:



(49)

Since salts are readily prepared, are usually crystalline, and are easily reconverted into their component acids and bases, the most widely used methods of resolution are variations of example 1 in Table 6-1. Compounds that are not acids can often be converted into acidic derivatives, these resolved, and the separate diastereomers then reconverted into the original compound to give the separate enantiomers. For example, *sec*-butyl alcohol can be resolved by means of the following scheme:

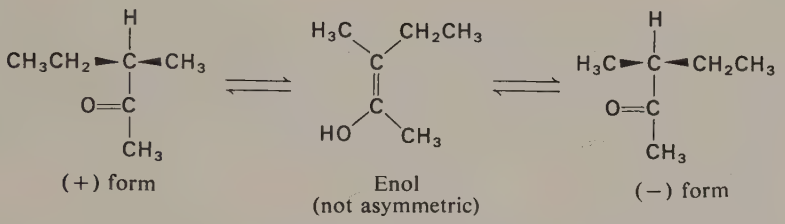


6-12 Racemization

Racemization is the process whereby an optically active (*d* or *l*) compound is converted into a mixture of equal amounts of the *d* and *l* forms, with the result that

optical activity disappears and the observed rotation drops to zero. If an optically active compound enters into an equilibrium in which it forms, and is reformed from, a symmetrical compound, racemization takes place.

Compounds in which the asymmetric carbon atom contains a readily ionizable hydrogen atom are usually racemized with ease by the action of alkali. The enolic form that is present in the equilibrium mixture (even if in very small concentration) is a symmetrical molecule, and returns, upon reversion to the ketone, to both enantiomeric configurations. For example, optically active 3-methyl-2-pentanone can racemize in the following way:



(51)

Racemization can occur by other mechanisms, but whatever the manner in which it takes place, the *existence of a symmetrical intermediate* that can return to both enantiomers of the original compound can account for the disappearance of optical activity.

Many compounds are optically very stable. Optically active 3-methylhexane would not be expected to undergo ready racemization, for this would involve the breaking of strong bonds. Such bond breaking would not be expected to occur under conditions short of those that would bring about extensive destruction of the compound. On the other hand, compounds in which the asymmetric carbon atom bears a readily ionizable hydrogen atom, as in the case of the ketone shown in (51), usually racemize with ease in the presence of alkali.

Exercise 9

Explain why the enol shown in (51) cannot be optically active. What element of symmetry does it possess?

6-13 Optical isomerism without an asymmetric carbon atom

Although by far the greater number of known optically active compounds owe their asymmetry to the presence of one or more asymmetric carbon atoms, optical activity can exist in the absence of an asymmetric carbon atom, as a result of *asymmetry of the molecule as a whole*, or as a result of the *asymmetry of an atom other than carbon*.

Molecular asymmetry is found in allenes of the type RCH=C=CHR, the enantiomeric forms of which are shown in Figure 6-3.

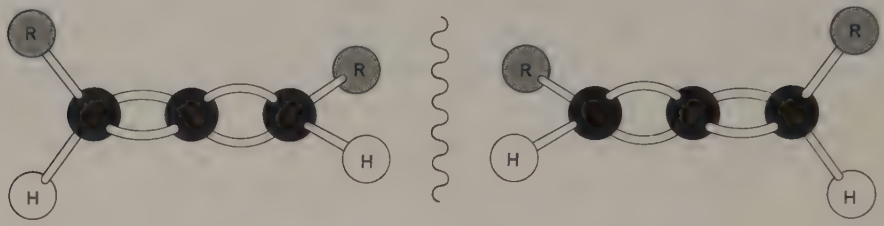
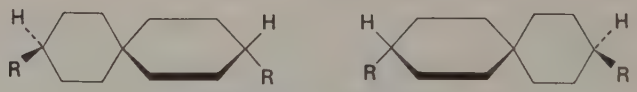


Figure 6-3
Enantiomeric allenes RCH=C=CHR.

Exercise 10

Can the allene $(CH_3)_2C{=}C{=}CHCH_2CH_3$ exist in enantiomeric forms? Why?

Molecular asymmetry analogous to that possessed by properly constituted allenes is also observed in bicyclic (spirane) systems of the following type:

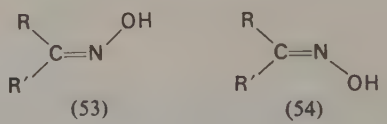


(52)

Enantiomeric spiranes

In a spirane such as the one shown the two rings are disposed at right angles to one another.

Stereoisomerism due to atoms other than carbon. Oximes. The oximino grouping $\diagdown C{=}N{-}OH$ can assume two stereochemical forms



(53) (54)

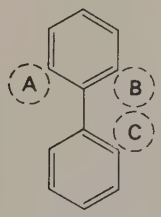
and many oximes exist in two forms, called *syn* and *anti*, corresponding to *cis* and *trans*. In (53), the hydroxyl group is *syn* with respect to R; in (54), it is *anti* with

respect to R and *syn* with respect to R′. If R and R′ are symmetrical, neither of the oximes is asymmetric. They are geometrical isomers.

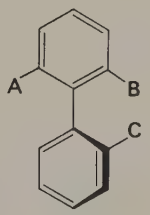
Exercise 11

If R and R′ were symmetric, why would neither (53) nor (54) be resolvable into enantiomeric forms? Illustrate with suitable perspective drawings, and explain.

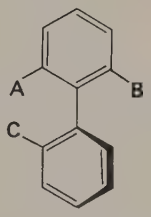
Optical activity in substituted biphenyls. Optical isomerism that is the result of restricted rotation about a single bond is uncommon, but is encountered in certain appropriately substituted biphenyl derivatives. The following generalized structures show the nature of the isomerism that is observed in compounds of this type:



(55)



(56)



(57)

If A, B, and C are sufficiently bulky atoms or groups, the lower benzene ring cannot rotate freely with respect to the upper ring, and thus forms (56) and (57) can exist separately. They are enantiomers, separated by an energy barrier whose height is a measure of the ease with which substituent C can pass A or B. If at any time the two rings were to become coplanar, as in (55), any movement from this position could as easily yield (56) as (57); an equal number of the two enantiomeric forms would be formed, and racemization would result.

Figure 6-4 is a diagram of the energy barriers to the rotation of three hypothetical biphenyl derivatives:

1. If A, B, C, and D are all small in size (for example, hydrogen or fluorine atoms), there is a small energy barrier to the passage of these substituents past each other, and rotation of the rings takes place with comparative ease. Such compounds are not resolvable.

2. If A, B, and C are large enough (with D small) to *restrict* rotation by passage of C past A or B, but not to *prevent* it, the enantiomeric forms [as (56) and (57) above] can be isolated, but racemization would be expected to occur at a measurable rate.

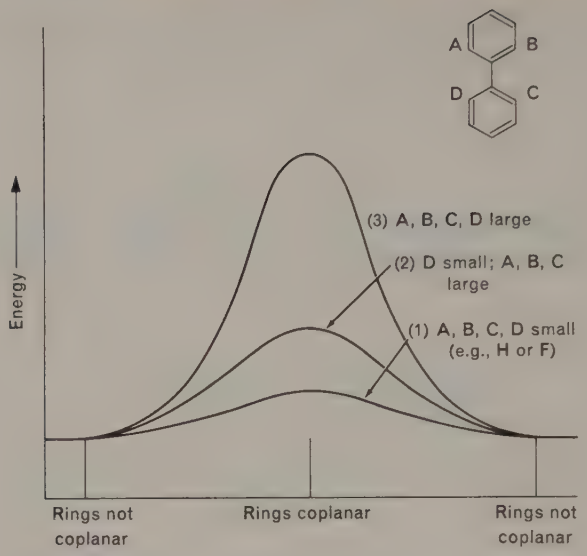
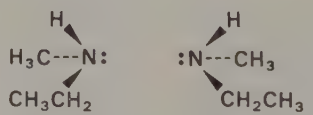


Figure 6-4
Energy diagram for rotation of a biphenyl about the single bond.

3. If A, B, C, and D are all large groups whose bulk prevents their passage by one another, the activation energy for racemization is high, and the compounds are optically stable. Racemization occurs very slowly unless sufficient energy is supplied, as by elevation of the temperature.

6-14 Stereochemistry of amines and ammonium salts

The bond angles in ammonia and amines are found to have values near the tetrahedral value. For example, in dimethylamine the C—N—C bond angle is about 111 ± 3°, and in triethylamine the C—N—C angle is about 113 ± 3°. It might be expected that tertiary amines having three different groups attached to nitrogen would be capable of existing in enantiomeric forms. We can draw such a pair of enantiomers for methylethylamine:

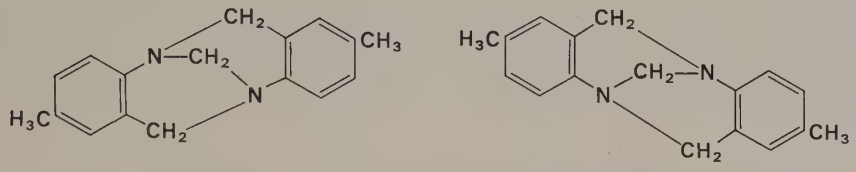


(58) (59)

The fact is that no such resolution has been accomplished. The explanation for the nonresolvability of tertiary amines of this kind is that the energy barrier to the

interconversion of the two enantiomeric species, through a planar (and thus symmetrical) intermediate state, is so low that the thermal energy at ordinary temperatures is sufficient to cause the interconversion. If we could carry out the necessary experiments at a sufficiently low temperature, resolution of a tertiary amine could probably be accomplished.

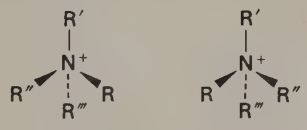
A tertiary amine that has been resolved is the complex compound known as *Troeger's base*. In this, the cage-like structure holds the molecule with sufficient rigidity that the enantiomers shown in the following formulas can be obtained and preserved as separate, optically active compounds:



(60) (61)

Enantiomers of Troeger's base

In quaternary ammonium compounds, the four bonds to the nitrogen atom are tetrahedrally disposed. Thus, there exist the same possibilities for stereoisomerism as in the case of the tetrahedral carbon atom. Stable, optically active enantiomeric forms of ammonium salts of the following kind are known:



(62) (63)

Enantiomers

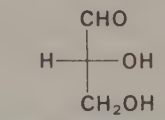
The four valences are tetrahedrally disposed (sp^3 hybridization), and the isomerism is like that due to tetracovalent, asymmetric carbon atoms.

6-15 Relative and absolute configuration

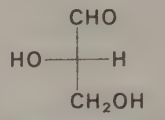
The terms "dextro" and "levo," applied to optically active compounds, refer to the direction of rotation of the plane of polarized light, as determined experimentally. There is no generally useful way of determining *a priori* which of two enantiomers will be the dextrorotatory isomer. The configurations of organic compounds are usually determined by relating them, by experimental means, to some standard substance, the configuration of which is known.

A reference substance widely used for this purpose is glyceraldehyde. The

dextrorotatory isomer of glyceraldehyde is designated the D *isomer*, its enantiomer the L *isomer*:

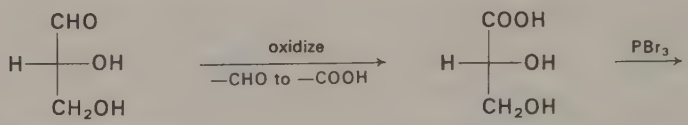


D-(+)-glyceraldehyde
(64)



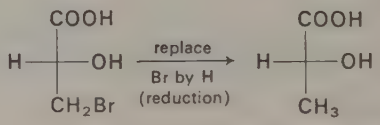
L-(−)-glyceraldehyde
(65)

Thus, if the groups attached to the asymmetric carbon atom of D-glyceraldehyde can be altered to produce new compounds, or if other compounds can be degraded to glyceraldehyde, then the configurations of corresponding asymmetric carbon atoms can be established, *relative to the configuration of* D-*glyceraldehyde*:



D-(+)-glyceraldehyde
(64)

D-(−)-glyceric acid
(66)



D-(−)-lactic acid
(68)

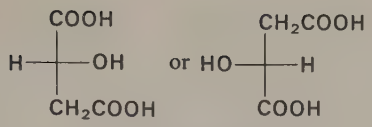
(67)

Since nothing in the transformation (64)–(68) has affected the disposition of the four bonds to the central asymmetric carbon atom, all of the compounds in the above series have the same *relative configuration*. It should be noted that D-glyceric acid and D-lactic acid are *levorotatory*, while the D-glyceraldehyde to which they are related chemically is *dextrorotatory*. Thus, the sign of rotation is not an indication of configuration. Indeed, it is proper to designate both the configuration (D or L) and the actual sign of rotation (+ or −) when these are both known.

It should now be apparent why the designations *d* and *l* are being replaced in current usage by the designation (+) and (−) (see the footnote to Section 6-11): it would be awkward to speak of D-*l*-tartaric acid or of D-*d*-malic acid.

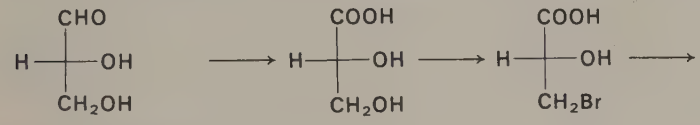
The more complex the compounds that can be related to D-glyceraldehyde, the easier becomes the task of determining further relative configurations, since, as the number of reference compounds of known configuration becomes larger, new relationships can be established rapidly.

There is occasionally an element of arbitrariness in the assignment of relative configurations. For example, D-(+)-malic acid can be written in either of two ways:

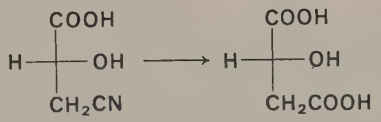


D-(+)-malic acid (69)

The form on the left implies that it was derived from D-(+)-glyceraldehyde (64), while the form on the right seems to have been derived from L-(−)-glyceraldehyde. Further, while D-(+)-glyceraldehyde can be transformed into malic acid as follows,

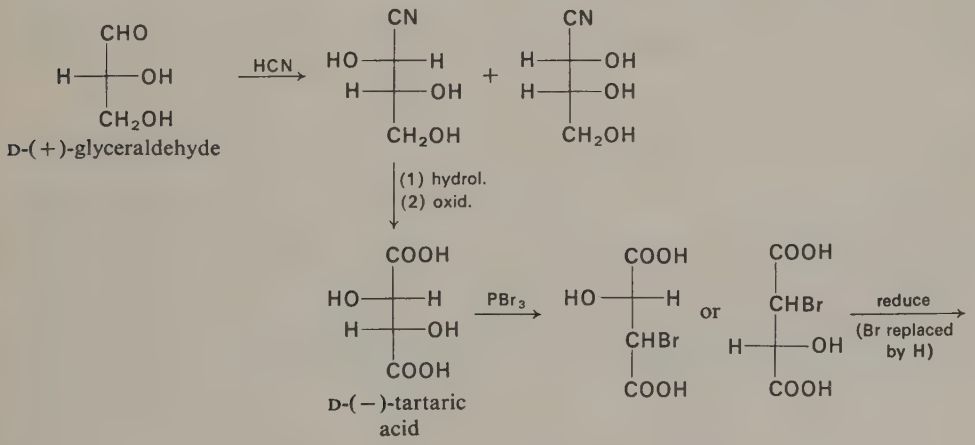


D-(+)-glyceraldehyde (70)

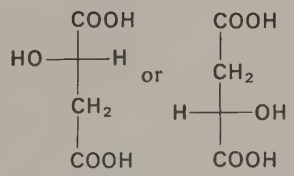


D-(+)-malic acid (natural)

a *different* malic acid can be formed from D-(+)-glyceraldehyde in the following way:



D-(−)-tartaric acid



L-(−)-malic acid (71)

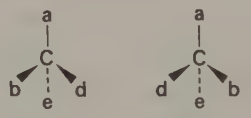
Identical

It can be seen that both D-(+)- and L-(−)-malic acid can be derived *chemically* from D-(+)-glyceraldehyde; therefore it is necessary to specify how the transformation is to be brought about. The convention has been adopted of designating as D-malic acid that one in which —COOH is derived directly from —CHO of D-glyceraldehyde.

After a system of relative configurations has been established, the determination of the *absolute configuration of any one compound in the series* can establish the absolute configuration of them all. In fact, absolute configurations have been assigned to a great many compounds, since the absolute configuration of (+)-glyceraldehyde is known. It was a happy turn of events that (+)-glyceraldehyde has been shown by experimental means to have the *absolute configuration* (64), which was first assigned *arbitrarily* to the dextrorotatory isomer, and hence is indeed D-(+)-glyceraldehyde. This result was obtained by applying X-ray analysis to dextrorotatory tartaric acid, which can be related to glyceraldehyde by chemical transformation.

6-16 The RS system of nomenclature

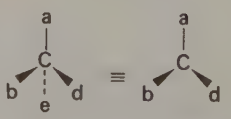
A general system of configurational nomenclature devised by R. S. Cahn (England), C. K. Ingold (England), and V. Prelog (Switzerland) is now widely used. In the compound Cabde, the groups can be arranged in two ways:



(72) (73)

If we assign a priority order, or *sequence rule*, that states that b takes priority over a, a over d, and d over e, we can express the difference between (72) and (73) in the following way:

1. Draw the three-dimensional figure so that it is seen with the lowest priority group (e) pointing away from the observer [as in (76)]:



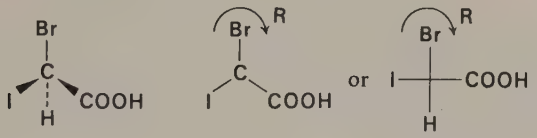
(72) (74)

2. Determine whether the path that is traveled in going from the group of highest priority (b) toward the group of next priority (a) is clockwise (*rectus*, or R) or counter-

clockwise (*sinister*, or S). In (72) [= (74)] the order of priority is (by definition) b > a > d; thus (72) has the R configuration, and (73) has the S configuration.

When using this system to name actual compounds, a certain priority order, or a set of sequence rules, must be followed:

1. Groups attached to the asymmetric carbon atom have priority in the order of decreasing atomic number of the atom bound to carbon. Thus, in iodobromoacetic acid, IBrCHCOOH, the order is I > Br > C > H:



(75) (76)

[Note that the Fischer projection shown in (76) is just as convenient as the perspective drawing (75), as indicated by the arrow in (76).]

2. If two or more of the atoms (first set) attached to the asymmetric carbon atom have the same atomic number (this is usually carbon), the priority order is determined by the atoms (second set) attached to these. Thus $—CH_2OH$ takes priority over $—CH_3$; $—CH_2OH$ over $—CH_2NH_2$; $—CH_2Cl$ over $—CH_2OH$; $—CH_2CH_3$ over $—CH_3$ (= $—CH_2—H$), and so on.

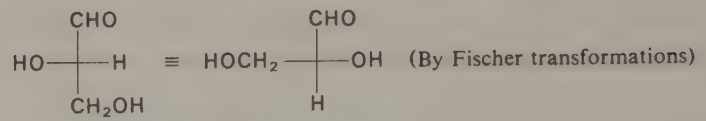
3. If the second set of atoms are the same in two groups, the number of such atoms determines priority. Thus, $—CH(OCH_3)_2$ over $—CH_2OCH_3$; $—CHCl_2$ over $—CH_2Cl$; $—CH(CH_3)_2$ over $—CH_2CH_3$; but $—CH_2Br$ over $—CHCl_2$ or $—CCl_3$ (rule 1).

4. Rule 3 is extended to the third, fourth, and other positions if necessary. Thus, $—CH_2CH_2CH_3$ over $—CH_2CH_3$; $—CH_2CH_2CH_2Cl$ over $—CH_2CH_2CH_2CH_2Cl$.

5. When the atom attached to the asymmetric carbon atom is bound to other atoms by a double or triple bond, the atom at the end of the multiple bond is counted twice (double bond) or three times (triple bond): thus $C{\equiv}CH$ over $—CH{=}CH_2$; $—CH{=}O$ over $—CH_2OH$; $—CH{=}NCH_3$ over $—CHCH_3$ (that is, $—CH$ with N and N over $—CH$ with $NHCH_3$ and C the $—CH$ grouping).

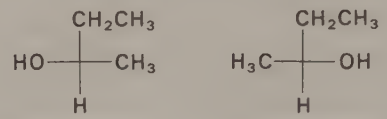
Some examples are the following:

L-(−)-glyceraldehyde sequence: OH, CHO, CH_2OH, H



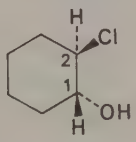
L-(−)-glyceraldehyde = (S)-glyceraldehyde

2-butanol sequence: OH, CH_2CH_3, CH_3, H



(77)

trans-2-chlorocyclohexanol

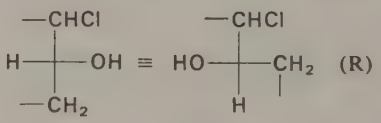


C-2 sequence: Cl, CHOH, CH_2, H

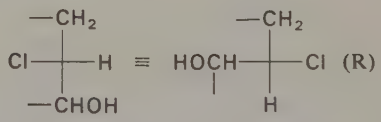
C-1 sequence: HO, CHCl, CH_2, H

(78)

For the configuration shown in (78), asymmetric carbon atom 1 can be arranged:

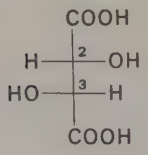


Carbon atom 2 can be arranged:



Thus, (78) is (1R,2R)-2-chlorocyclohexanol. Its enantiomer is (1S,2S)-2-chlorocyclohexanol.

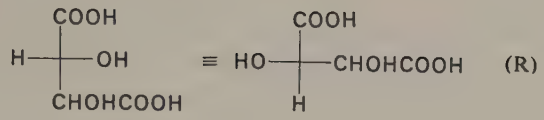
L-(+)-tartaric acid



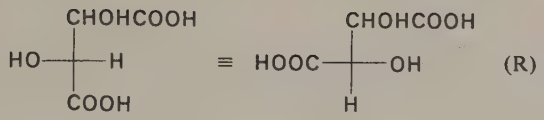
C-2 and C-3 sequence: OH, COOH, CHOH(COOH), H

(79)

carbon 2:



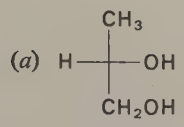
carbon 3:

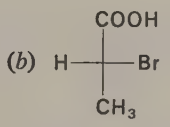


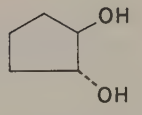
Thus, L-(+)-tartaric acid is (2R,3R)-2,3-dihydroxybutanedioic acid.

Exercise 12

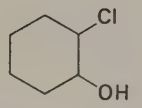
Name the following compounds by the RS system:







(*d*) D-(−)-lactic acid (*e*) L-(+)-malic acid



6-17 Molecular asymmetry in biological systems

The fact that enantiomeric and diastereomeric compounds differ in reactivity with asymmetric reagents is of supreme importance in biological systems. Of the products of the synthetic activities of living organisms, those that have the capability of existing in stereoisomeric forms are nearly always produced naturally as only one of the two or more possible stereoisomers. A naturally occurring compound containing an asymmetric carbon atom is nearly always found to be optically active when it is isolated from its natural source; usually only one of a number of possible diastereomers or *cis-trans* isomers is produced in a living organism; and so on.

Enzymes, the catalysts in metabolic reactions, are asymmetric molecules. As proteins, they are composed of L-amino acids joined in peptide linkages (Chapter 37); the folding and coiling of the polypeptide chains form uniquely organized assemblages of groups into sites of distinctive stereochemical structure.

The stereochemical specificity of biochemical processes has been recognized in an empirical way for over a century. The following are some examples:

(*a*) Pasteur observed that (±)-ammonium tartrate was metabolized by *Penicillium glaucum* (a mold), but that only the (+) form was utilized, the (−) form remaining unaltered.

(*b*) When (±)-malic acid is injected into a rabbit, only the (−) enantiomer appears unchanged in the urine; the (+) form is metabolized.

(*c*) β-Glucosidase, an enzyme occurring in the intestine of snails and in the seeds of almonds, catalyzes the hydrolysis of β-D-glucosides but not of α-D-glucosides (Chapter 14).

(*d*) The enzyme fumarase catalyzes the hydration of fumaric acid (the *trans* acid) to give L-malic acid. It does not act upon maleic acid (the *cis* acid).

(*e*) Epinephrine, one of the hormones involved in the activity of the nervous system, can exist in enantiomeric forms. The *natural* hormone (isolated from animal kidney) is the levorotatory (−) form. The (+) form (synthetic) is about 1/30 as active.

Many other physiological responses depend for their expression upon the stereochemistry of the agent that causes them. Many amino acids have characteristic tastes, the nature of which depends upon their stereochemistry (see Table 6-2).

Table 6-2
The stereochemistry and taste of some amino acids

	L *Series*		D *Series*	
Amino acids	*Rotation*	*Taste*	*Rotation*	*Taste*
alanine	+	nil	−	sweet
valine	+	nil	−	sweet
leucine	−	bitter	+	sweet
isoleucine	+	bitter	−	sweet
asparagine	−	nil	+	sweet
tyrosine	−	bitter	+	sweet
histidine	−	nil	+	sweet
tryptophan	−	bitter	+	nil

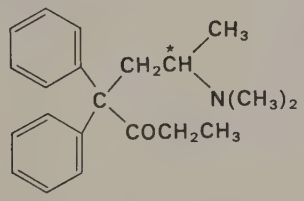
These observations are epitomized in a statement of Pasteur: "La matière nerveuse est une matière dissymmetrique comme toutes les substances primordiales de la vie."

6-18 Stereoisomerism and activity of drugs

Many drugs, medicinals, and other physiologically active compounds can exist in enantiomeric or diastereomeric forms, which usually show wide differences in physiological activity. While compounds of this kind isolated from natural sources

are of one stereoisomeric structure only, synthetic compounds are usually prepared either as the racemic (±) compound or as a mixture of diastereomers. It is often necessary or desirable to resolve the racemic mixture or to separate the diastereomers in order to separate the inactive or less active isomer from the active compound.

An example is the well-known synthetic analgesic compound methadone. Methadone has morphine-like properties and is used as a clinical analgesic. It has the following structure, which can exist in enantiomeric forms (the asymmetric carbon atom is denoted by the asterisk):

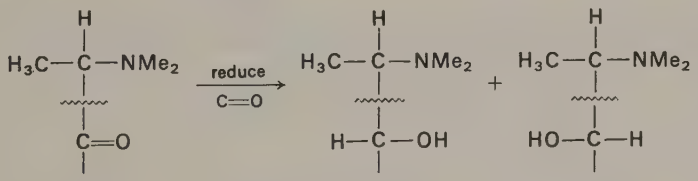


(80)

When tested for analgesic potency, (−)-methadone was found to be about twice as active as morphine, while its enantiomer was not analgesic:*

Compound	*Analgesic activity*
morphine	1
(−)-methadone	2.2
(+)-methadone	0
(±)-methadone	1.4

A series of diastereomeric amino alcohols, called methadols, can be obtained by reduction of the carbonyl group of methadone. Each enantiomer of methadone of course yields two epimeric alcohols:



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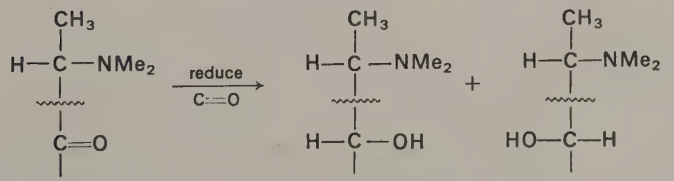


(82)

* Tests for analgesic activity vary in method and provide varying results. Thus, figures for potency are not absolute; they differ according to the test method used, and disclose only relative activities.

These amino alcohols are named α- and β-methadol, and thus there exist α(−)-, α(+)-, β(−)-, and β(+)-methadol. These, too, are potent analgesic compounds, the activities of some of which, compared with morphine (= 1), are as follows:*

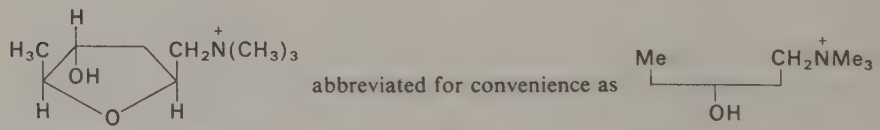
Compound	ED_{50}(*mg/kg*)
morphine	2.3
(±)-methadone	1.6
α(−)-methadol	3.5
β(−)-methadol	7.6
α(+)-methadol acetate	0.3
β(−)-methadol acetate	0.4

It should be apparent from the foregoing discussion that changes in stereochemistry can have a profound effect upon biological activity.

6-19 Muscarine and its stereoisomers

A well-studied case of the relationship between stereoisomerism and physiological activity is that of (+)-muscarine, the toxic principle of the poisonous mushroom, *Amanita muscaria* L. Muscarine is a quaternary ammonium compound with acetylcholine-like activity. It is a highly toxic compound with a lethal dose of about 15 micrograms for a 20-gram mouse.

(+)-Muscarine has the structure and stereochemistry shown below. Only the cation is shown; the compound would ordinarily be dealt with experimentally as muscarine chloride, muscarine bromide, and so on.

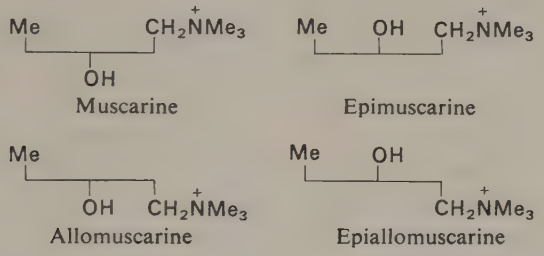


Muscarine (cation)

Muscarine possesses three asymmetric carbon atoms, and thus there are eight possible stereoisomeric compounds of the same gross structure. These are named and have the

* ED = effective dose; thus, a higher ED means a lower activity. ED_{50} is the dose that is effective for 50 percent of the subjects in an experiment.

stereochemistry shown in the following formulas, abbreviated as above:



Exercise 13

Redraw the complete (cyclic) structures of these stereoisomers in the form shown above for the muscarine cation.

The other four are the enantiomers of these.

All of the stereoisomers have been synthesized, and compared in physiological tests. One of the results of acetylcholine-like action is a drop in blood pressure; this provides one means of comparing the activity of the compounds in the series:

Dose in γ/kg, of (±)-compounds required for equal lowering of cat blood pressure	
muscarine	0.01
epimuscarine	3.0
allomuscarine	1.7
epiallomuscarine	1.0

It has been observed that the natural compound is 100 to 300 times as active as its non-natural stereoisomers.

Stereochemical specificity is even more dramatically shown by the fact that the non-natural enantiomer, (−)-muscarine, is nearly inactive. Some other comparisons, using a different test system, are shown in Table 6-3. *Muscarone*, which contains a —C(=O)— group in place of the —CHOH— group of muscarine, is four times as active as muscarine itself, showing that the presence of the alcoholic hydroxyl group is not in itself essential for activity of the muscarine type.

Table 6-3
Relative biological activities of acetylcholine, some stereoisomers of muscarine, and muscarone

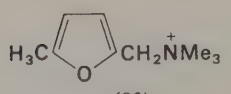
Compound	*Equiactive dose*
acetylcholine	4.2
(+)-muscarine	1.0 (comparison standard)
(−)-muscarine	400
(±)-muscarine	2.5
(±)-epimuscarine	750
(±)-allomuscarine	420
(±)-epiallomuscarine	250
(−)-muscarone	0.25

Exercise 14

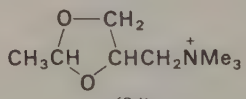
It is occasionally observed that a *dl* drug is less than one-half as active as the optically active form. Can you suggest a possible reason for this?

6-20 Synthetic muscarine analogues

The structural requirement for acetylcholine-like activity appears to be a quaternary ammonium grouping (—NMe_3^+) at an optimal distance from an oxygen-containing functional entity. This structural requirement is somewhat flexible, and several related potent acetylcholine-like compounds are known. Indeed, two compounds with high muscarinic activity, (83) and (84), bear a remarkable resemblance to muscarine itself:



(83)



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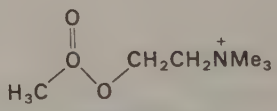


Acetylcholine

Exercise 15

How many stereoisomeric forms are possible for (84)? Draw the perspective structure for the isomer that you would expect to be most like muscarine in physiological potency.

Exercise 16

Look up the formula for morphine. How many asymmetric carbon atoms are present? How many stereoisomers are possible?

Exercise 17

Look up the formula for Demerol (meperidine). Compare the structures of morphine, Demerol, and methadone. Aside from the fact that they are all tertiary amines, can you find a structural feature that the three have in common?

Problems

1. Write projection formulas showing all of the stereoisomeric forms of each of the following:

(*a*) $(CH_3)_2CHCOOH$

(*b*) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCOOH$

(*c*) $HOCH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle OH}{\overset{|}{C}}}}COOH$

(*d*) $HOCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$

(*e*) $CH_3\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$

(*f*) $CH_3CH{=}CHCH_2OH$

(*g*) $CH_3CH{=}C\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

(*h*) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

(*i*) $CH_3\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

(*j*) 1,3-dibromocyclobutane

2. (*a*) Write the structures for all of the heptanes (C_7H_{16}), marking asymmetric carbon atoms with an asterisk and indicating enantiomeric pairs; (*b*) do the same for all of the six-carbon alcohols, $C_6H_{13}OH$.

3. Which of the following allenes are capable of existing in enantiomeric forms? Indicate the kind of symmetry that is present in those that are nonresolvable.

(*a*) $CH_3CH{=}C{=}CH_2$

(*b*) $CH_3CH{=}C{=}CHCH_3$

(*c*) $(CH_3)_2C{=}C{=}CHCH_3$

(*d*) $(CH_3)_2C{=}C{=}C(CH_3)_2$

(*e*) $CH_3\underset{\displaystyle Br}{\underset{|}{C}}H{=}C{=}CH_2$

4. Draw projection formulas for the following compounds: (*a*) (R)-2-bromobutane, (*b*) (2R,3S)-2-bromo-3-methyl-pentane, (*c*) (S)-*sec*-butyl acid phthalate, (*d*) *meso*-tartaric acid, (*e*) (1S,2S)-cyclohexane-1,2-diol.

5. Treatment of (R)-2-bromopentane with sodium acetate gives a compound $C_7H_{14}O_2$. Name the product and give its configuration in the RS notation.

6. A specimen of alanine (2-aminopropanoic acid) was found to be optically active and dextrorotatory. Can we call this D-alanine with this information alone?

7. If (±)-2-methylbutanoic acid were esterified by reaction with (+)-2-butanol, how many optically active compounds would be present in the final equilibrium reaction mixture?

7

The nucleophilic displacement reaction. Substitution at the sp^3 carbon atom

In this chapter is described one of the most common types of organic reactions, the nucleophilic displacement reaction, so called because one reactant is a *nucleophile* (Section 7-2, and defined in Section 4-6), which attacks a second reactant to *displace* a group or atom. The nucleophilic displacement reaction is one of the most valuable synthetic reactions used by the organic chemist, providing methods for the synthesis of ethers, alcohols, alkyl halides, amines, and a number of other compound classes.

Several topics that have been discussed in the previous chapters bear on the nucleophilic displacement reaction. Among these are the degree of basicity of the *nucleophilic reagent*; the effect of molecular structure upon the *rate* of the reaction; the *mechanism* of the reaction; and the *stereochemistry* of the reaction.

A new concept—stabilization by charge delocalization, or resonance—is introduced to provide a way of accounting for differences in rate and mechanism. This concept is developed more fully in Chapter 9, where it can be referred to concurrently with the study of this chapter.

7-1 The nucleophilic displacement reaction

One of the most common reactions in organic chemistry is that in which an atom or group possessing an unshared (non-bonding) electron pair attacks a carbon or other atom that is deficient in electrons, to form a covalent two-electron bond. The electron deficiency may be complete (the carbon atom may bear a positive charge), or it may

be partial (the carbon atom may be electron-deficient because of polarization of the bond to another atom).

In its most general form, this kind of reaction is central to most of the bond-forming processes encountered in organic chemistry. It can be recognized as a feature of addition reactions, substitution reactions, elimination reactions, and rearrangement reactions. In this chapter we shall examine one of these: the *replacement* of an atom or group, along with its binding electron pair, by attack of an atom or group that provides an electron pair for the formation of the new bond.

The most general expression for this reaction is

$$Y: + R:X \rightleftharpoons Y:R + :X \qquad (1)$$

7-2 The nucleophilic agent Y:

The characteristic feature of Y: in (1) is its possession of an unshared pair of electrons. It is therefore a base in the most general meaning of this term, and is capable of accepting a proton. Since the proton is the bare nucleus of the hydrogen atom, the term *nucleophile* is applied to atoms or groups Y:.

Basicity is a measure of nucleophilicity towards the proton, and is assessed in terms of the equilibria between proton acceptors and proton donors (Chapter 4). Nucleophilicity towards carbon, which will be our principal concern, roughly parallels the basicity of Y:; and while there are departures from this generalization, strong bases (for example, HO^-, CH_3O^-) are usually better nucleophiles than weak bases (for example, Cl^-, H_2O).

Table 7-1
Some typical nucleophilic displacement reactions

Y: (*nucleophile*)	+ R:X	→ Y:R	+ :X (*leaving group*)
1. $Br:^-$	+ $CH_3OH_2^+$	→ $Br:CH_3$	+ H_2O
2. $HO:^-$	+ CH_3Br	→ $HO:CH_3$	+ Br^-
3. $H_3N:$	+ CH_3I	→ $H_3\overset{+}{N}:CH_3$	+ I^-
4. $CH_3O:^-$	+ CH_3Cl	→ $CH_3O:CH_3$	+ Cl^-
5. $CH_3COO:^-$	+ CH_3CH_2Br	→ $CH_3COO:CH_2CH_3$	+ Br^-
6. $I:^-$	+ CH_3Br	→ $I:CH_3$	+ Br^-
7. $(CH_3)_2S:$	+ CH_3I	→ $(CH_3)_2\overset{+}{S}:CH_3$	+ I^-
8. $CH_3S:^-$	+ CH_3CH_2Br	→ $CH_3S:CH_2CH_3$	+ Br^-
9. CN^-	+ CH_3CH_2I	→ $NC:CH_2CH_3$	+ I^-
10. N_3^-	+ CH_3Br	→ $N_3:CH_3$	+ Br^-
11. $CH_3—\overset{H}{\underset{\vert}{O}}:$	+ $CH_3OH_2^+$	→ $CH_3\overset{H}{\underset{\vert}{\overset{+}{O}}}:CH_3$	+ H_2O

Table 7-1 is a list of the more common nucleophiles and some displacement reactions of type (1). No single charge type characterizes the nucleophile: both neutral molecules and anions may be nucleophilic, and reagents of both classes are used in preparative applications of the nucleophilic displacement reaction.

It has been found that the nucleophilic reactivity of the atoms within a single group of the periodic table increases with the size of the atom. Thus, $I^- > Br^- > Cl^-$; and $CH_3S^- > CH_3O^-$. The higher nucleophilicity of the larger atoms is laid to two factors: (1) the deformability of the external orbitals, or the polarizability of the electrons involved in bonding to the carbon atom; and (2) the less extensive solvation of larger atoms than smaller atoms.

It can be inferred from this that nucleophilicity should be enhanced in a solvent of low solvating power. This is found to be the case: dimethyl sulfoxide, $(CH_3)_2SO$, is a solvent in which the rates of nucleophilic displacement reactions are greatly increased, compared with those in such solvents as water or alcohols.

In general, the anions (conjugate bases) of strong acids such as HNO_3 (NO_3^-), H_2SO_4 (HSO_4^-), HCl (Cl^-) and H_3O^+ (H_2O) are poor nucleophiles. This is in accord with the generalization that nucleophilicity parallels basicity. Indeed, as will be seen in the following section, these groups are usually regarded as the displaceable groups corresponding to :X in (1).

7-3 The leaving (departing) group :X

The groups :X in (1) that are expelled from RX by the attack of the nucleophile are in most cases the anions of strong acids and therefore are exceedingly weak bases and poor nucleophiles. Since the equilibrium (1) expresses a competition of Y: and :X for R, it is to be expected that a strongly nucleophilic Y: will effect an essentially complete displacement of a weakly nucleophilic :X. In Table 7-2 are listed some of the common *displaced, or leaving, groups*. One of these is the nitrogen molecule, N_2,

Table 7-2
Some typical leaving groups :X in the reaction
$Y: + R:X \rightarrow Y:R + :X$

RX	*Displaced group* :X	*Conjugate acid* H:X
RCl	Cl^-	HCl
RBr	Br^-	HBr
$RNR'_3{}^+$	NR'_3	$HNR'_3{}^+$
$RSR'_2{}^+$	SR'_2	$HSR'_2{}^+$
$ROH_2{}^+$	OH_2	H_3O^+
$ROSO_2R'$	$R'SO_2O^-$	$R'SO_2OH$
$ROSO_2OR'$	$R'OSO_2O^-$	$R'OSO_2OH$
$RN_2{}^+$	N_2	$HN_2{}^+$
$ROP_2H_3O_6$	$^-OP_2H_3O_6$*	$H_4P_2O_7$

* This is the pyrophosphate anion, a group of great importance in biological displacement reactions (see Chapter 8).

which is the conjugate base of the hypothetical strong acid HN_2^+. Since the neutral nitrogen molecule has no observable basic character it is displaced with ease. The manner of formation of compounds of the class RN_2^+ will be described in Chapter 32.

The order of ease with which some representative groups can be displaced is

$$N_2 > OSO_2R^- > I^- \sim Br^- > NO_3^- > Cl^- > OH_2 \sim SR_2 > NR_3 \gg OR^-$$

It should be noted that the least readily displaced groups in this series, NR_3 and OR^-, are relatively strong bases.

7-4 The mechanism of the nucleophilic displacement reaction

The S_N2 mechanism. The reaction of methyl bromide with the hydroxide ion has been described in Chapter 5. This is a bimolecular reaction, the rate of which is dependent upon the concentrations of both CH_3Br and OH^-:

$$\text{rate} = k[CH_3Br][OH^-] \qquad (2)$$

This reaction course is indicated by the symbol S_N2, for substitution (S), nucleophilic (N), and bimolecular (2). The term S_N2 refers to the observed facts that the reaction proceeds through a transition state in which both CH_3Br and HO^- participate. The energy required for the breaking of the C—Br bond is partly provided by the energy of the concomitant formation of the O—C bond. This is illustrated by the diagram in Figure 5-5, and by the energy profile of Figure 5-9 (2).

An important feature of the bimolecular displacement reaction is that since the incoming nucleophile forms a bond to the side of the carbon atom opposite the one from which the leaving group is displaced, the configuration of the groups attached to the carbon atom is *inverted.* Inversion always occurs in the S_N2 displacement reaction. This will be discussed further in Section 7-9.

The S_N1 mechanism. When *t*-butyl bromide is allowed to react with dilute aqueous alkali the product is *t*-butyl alcohol. The overall process

$$(CH_3)_3CBr + OH^- \longrightarrow (CH_3)_3COH + Br^- \qquad (3)$$

is identical with the overall hydrolysis of methyl bromide. The kinetics of this reaction are, however, quite different from those of the bimolecular hydrolysis of methyl bromide. It is found that the rate of the reaction (3) is independent of the concentration of hydroxide ion, and depends only upon the concentration of *t*-butyl bromide. The *rate-determining* step of reaction (3) must involve only the alkyl halide; this can be accounted for by a *slow* ionization step, followed by a fast second step in which OH^- participates:

$$(CH_3)_3Br \overset{\text{slow}}{\rightleftharpoons} (CH_3)_3C^+ + Br^- \quad \text{(Rate-determining)} \qquad (4)$$

$$(CH_3)_3C^+ + OH^- \overset{\text{fast}}{\rightleftharpoons} (CH_3)_3COH \qquad (5)$$

An energy profile for this reaction is shown in Figure 5-10(1), in which transition state 1 (TS1) leads to the reactive carbonium ion intermediate of equilibrium (4). It is clear that *t*-butyl alcohol cannot be formed faster than $(CH_3)_3C^+$ is produced by ionization (solvolysis) of the halide.

This kind of displacement reaction is called S_N1, the "1" indicating that the rate-determining step is unimolecular.

7-5 Displacement reactions in synthesis

Many synthetic procedures of wide usefulness in organic chemistry have as their central process the nucleophilic displacement reaction. It will be useful here, before discussing some of the other factors that influence this reaction, to describe some synthetic methods for the preparation of a number of important classes of compounds by the use of the S_N2 displacement reaction. A variety of types of groups :X in RX have been chosen for these examples; in each it is to be noted that the group R is primary (that is, $R = R'CH_2$). Specific examples are used, but each may be regarded as a prototype of a general procedure.

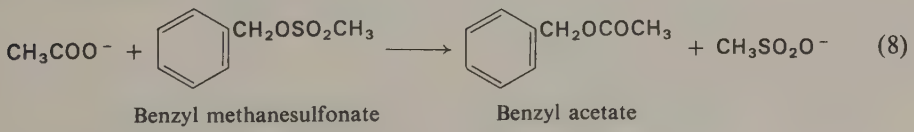
(*a*) Preparation of alkyl bromides by the reaction of an alcohol with an inorganic bromide in strongly acidic solution (chlorides and iodides can be prepared in an analogous way):

$$Br^- + RCH_2OH_2^+ \longrightarrow RCH_2Br + H_2O \qquad (6)$$

(*b*) Preparation of ethers:*

$$(CH_3)_2CHO^- + CH_3I \longrightarrow (CH_3)_2CHOCH_3 + I^- \qquad (7)$$

(*c*) Preparation of esters:



(8)

Benzyl methanesulfonate — Benzyl acetate

(*d*) Preparation of alcohols (hydrolysis of alkyl halides):

$$\underset{\text{1-bromobutane}}{CH_3CH_2CH_2CH_2Br} + OH^- \longrightarrow \underset{\text{1-butanol}}{CH_3CH_2CH_2CH_2OH} + Br^- \qquad (9)$$

(*e*) Synthesis of nitriles (alkyl cyanides):

$$\underset{\text{1-bromopentane}}{CH_3CH_2CH_2CH_2CH_2Br} + CN^- \longrightarrow \underset{\text{1-cyanopentane}}{CH_3CH_2CH_2CH_2CH_2CN} + Br^- \qquad (10)$$

---

* Reagents such as alkoxide ions, RO^-, are associated with some inorganic cation. Thus $(CH_3)_2CHO^-$ would be provided by a solution of $(CH_3)_2CHO^-Na^+$ in isopropyl alcohol. Similarly, such anionic reagents as $RCOO^-$, CN^-, RS^- are the nucleophilic species in solutions of their salts (for example, potassium cyanide, sodium acetate, and so on). Since the cation is unchanged in the reaction, it seldom needs to be made a part of the equation.

(*f*) Preparation of dialkyl sulfides:

$$CH_3S^- + CH_3CH_2Br \longrightarrow \underset{\text{Methyl ethyl sulfide}}{CH_3SCH_2CH_3} + Br^- \qquad (11)$$

(*g*) Preparation of sodium alkanesulfonates:

$$\underset{\substack{\text{Sulfite}\\\text{(as sodium sulfite)}}}{SO_3^=} + CH_3I \longrightarrow \underset{\substack{\text{Methanesulfonic}\\\text{acid (anion)}}}{CH_3SO_2O^-} + I^- \qquad (12)$$

(*h*) Preparation of amines:

$$NH_3 + CH_3CH_2I \longrightarrow \underset{\substack{\text{Ethylamine}\\\text{(protonated)}}}{CH_3CH_2NH_3^+} + I^- \qquad (13)$$

In the presence of an excess of ammonia, free ethylamine will be formed by the simple proton exchange

$$CH_3CH_2NH_3^+ + NH_3 \rightleftharpoons CH_3CH_2NH_2 + NH_4^+ \qquad (14)$$

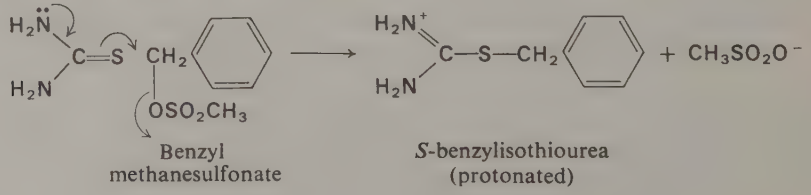
and the ethylamine, also a reactive nucleophile, can then react further with the ethyl iodide that is present

$$CH_3CH_2NH_2 + CH_3CH_2I \longrightarrow CH_3CH_2\overset{+}{N}H_2CH_2CH_3 + I^- \qquad (15)$$

Further proton exchange and further reaction with ethyl iodide leads to further alkylation of the amine to give as the final result a mixture of $EtNH_2$, Et_3N, and $Et_4N^+I^-$ (Et=—CH_2CH_3). Thus, this method of preparing amines has obvious practical disadvantages. Other methods will be described later.

(*i*) Preparation of isothioureas:

Thiourea, $S{=}C(NH_2)_2$, is an excellent nucleophile, the sulfur atom acting as the nucleophilic center. It reacts with alkyl halides and sulfonic esters. The nucleophilicity of the sulfur atom is aided by the ability of the —NH_2 group to provide electrons in the manner shown.



Benzyl methanesulfonate — *S*-benzylisothiourea (protonated) (16)

Exercise 1

For each of the reactions (6) to (16) identify the nucleophilic reagent Y:, the departing group :X, and the R group corresponding to the general expression $Y: + R:X \rightarrow Y:R + :X$.

7-6 The role of the solvent

The solvent in which a nucleophilic displacement reaction occurs can have a profound influence upon the reaction. A change in the solvent medium can

(*a*) alter the nucleophilicity of the nucleophilic agent or alter the relative nucleophilicity of a series of agents;
(*b*) alter the rate at which a displacement reaction proceeds; or
(*c*) change the mechanism of the reaction so that a displacement reaction that is S_N1 in one solvent may become S_N2 in another, or *vice versa.*

Two properties of organic solvents are of most importance in these effects: their dielectric constant and their ability to solvate ions by hydrogen bonding or dipole interaction. There are many subtle factors involved in solute-solvent interaction, and only some of the more conspicuous will be dealt with here. We shall deal chiefly with the effect of the solvent upon the rate and mechanism of the displacement reaction.

The reaction of *t*-butyl bromide has been described as proceeding through a rate-determining ionization. This dissociation is more properly termed *solvolysis*, for the solvent participates in the reaction in a manner that can be expressed as

$$(CH_3)_3Br + (\text{solvent}) \rightleftharpoons (CH_3)_3C^+(\text{solvated}) + Br^-(\text{solvated}) \qquad (17)$$

Solvation, by dispersal of the ionic charge in the ion-solvent complex, lowers the energy necessary for separation of the R^+ and X^- ions. Water and water-alcohol mixtures promote ionization by virtue of a high dielectric constant, and by hydrogen bonding and dipolar association of ion-solvent molecules. Such a system is shown in Figure 4-1.

A good ionizing solvent can be expected to favor reaction by the S_N1 mechanism. The hydrolysis of *t*-butyl chloride is in fact 10^4 times faster in aqueous (50%) ethanol than in pure ethanol. In anhydrous acetone, a solvent that does not promote ionization, *t*-butyl chloride reacts—for example, with iodide ion as the nucleophile—at a very slow rate. Moreover, nucleophilic displacement reactions of *t*-butyl chloride and other alkyl halides in anhydrous acetone proceed chiefly by the S_N2 mechanism.

We can summarize solvent effects in the following way:

1. If a given nucleophilic displacement reaction can, for structural reasons

(discussed further on), proceed by either the S_N1 or S_N2 route, the S_N1 process is favored by a good ionizing medium.

2. In a poorly solvating medium such as anhydrous acetone the reaction may be forced to proceed by the S_N2 course; in some cases structural factors may allow this to occur only very slowly.

The structural factors alluded to here will be considered in the following sections.

7-7 The effect of the structure of R in RX in displacement reactions

The S_N2 reaction. The overall rate of a nucleophilic displacement reaction does not indicate the mechanism (S_N1 or S_N2) by which it proceeds. Methyl bromide and *t*-butyl bromide both react very rapidly in dilute aqueous-alcoholic alkali; yet the first reaction proceeds by the S_N2 route, the second by the S_N1 route. Ethyl bromide and isopropyl bromide react at rates that are neither very fast nor very slow; a careful kinetic analysis of these hydrolyses shows that ethyl bromide reacts principally by the S_N2 mechanism but that the isopropyl bromide reaction shows "mixed" kinetics.

When the reaction

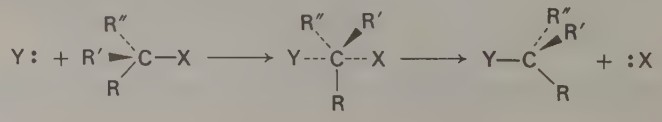
$$RBr + I^- \longrightarrow RI + Br^- \tag{18}$$

is carried out in anhydrous acetone solution, a poor ionizing medium, the carbonium ion pathway (S_N1) is suppressed, so that the S_N2 mechanism prevails. Table 7-3

Table 7-3
Relative rates of reaction for RBr + I → RI + Br under S_N2 conditions

R	*Relative rate*
CH_3—(methyl)	200,000
CH_3CH_2—(ethyl)	1,000
$(CH_3)_2CH$—(isopropyl)	12
$(CH_3)_3C$—(*t*-butyl)	1

shows how increasing substitution on the carbon atom at which displacement occurs affects the rate of reaction. It is evident that replacement of the hydrogen atoms of $—CH_3$ by methyl groups strongly retards the reaction. This can be readily understood if the nature of the S_N2 reaction is recalled:



(19)

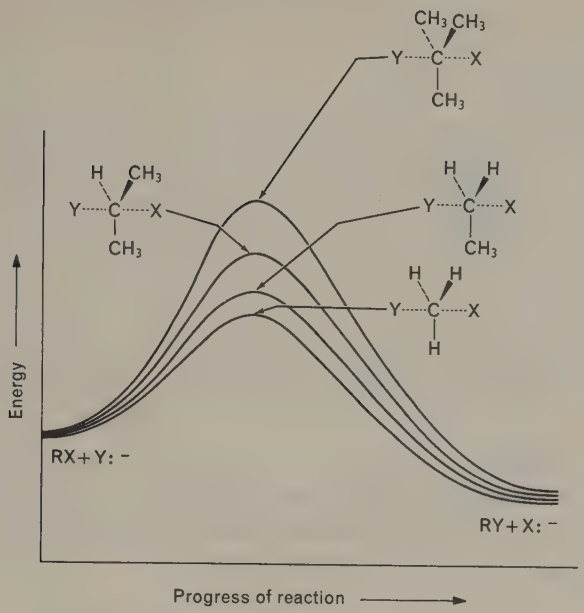


Figure 7-1
Energy profiles for S_N2 displacement reactions in the series CH_3Br, CH_3CH_2Br, $(CH_3)_2CHBr$, $(CH_3)_3CBr$. Overall free-energy change is arbitrary.

The formation of the transition state requires that Y: approach to within bonding distance. When R, R′, and R″ are all hydrogen atoms the approach of Y: is relatively unimpeded. As substitution progresses through ethyl (R = CH_3, R′ = R″ = H) and isopropyl (R = R′ = CH_3, R″ = H) to *t*-butyl (R = R′ = R″ = CH_3), penetration of Y: to within bonding distance is impeded, and greater activation energy is required to enable Y: to pass through the protective shield of substituents. The energy profiles of Figure 7-1 show how the activation energy required for attainment of the bimolecular transition state rises with increasing substitution at the reaction center.

Very important structural effects upon reaction rates in S_N2 displacement reactions are also observed with increasing substitution in the position β to the reaction center. In the compounds shown in Table 7-4, an increase in the number of methyl substituents on the β carbon atom [none in $\overset{\beta}{C}H_3\overset{\alpha}{C}H_2Br$, three in $(CH_3)_3CCH_2Br$] is accompanied by a dramatic fall in the rate of the reaction

$$RBr + C_2H_5O^- \longrightarrow ROC_2H_5 + Br^-$$

Neopentyl halides, $(CH_3)_3CCH_2X$, react very slowly by both S_N1 and S_N2 mechanisms. For reactions of the S_N2 type, the reason can best be seen by an examination of a molecular model, a drawing of which is shown in Figure 7-2. Approach of the nucleophile Y: to the rear side of the carbon atom holding the Br atom is greatly hindered

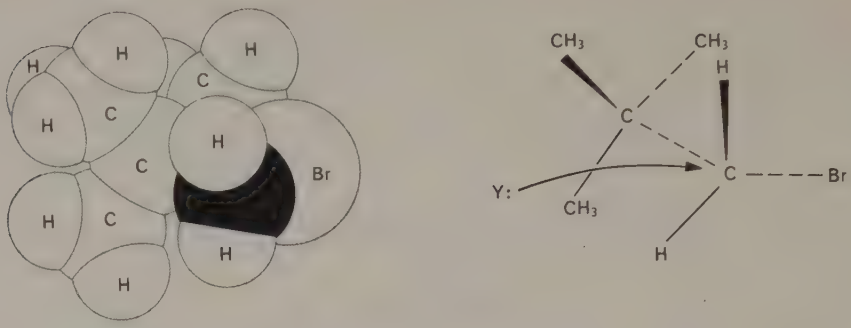


Figure 7-2
Molecular model of neopentyl bromide, showing sterically hindered environment of the reaction center —CH_2Br.

by the β-methyl groups; the nucleophile can approach to within bonding distance only by overcoming severe inter-group interactions. The energy required for this penetration is reflected in a high activation energy required to reach the transition state, with a consequent reduction in reaction rate.

Table 7-4
Relative rates of the reactions
$RBr + C_2H_5O^- \rightarrow ROC_2H_5 + Br^-$
for primary alkyl bromides

R	*Relative rate*
CH_3CH_2—	500,000
$CH_3CH_2CH_2$—	28,000
$(CH_3)_2CHCH_2$—	4,000
$(CH_3)_3CCH_2$—	1

Reaction of neopentyl halides by the S_N1 route is also slow, because of the inherent instability of the primary carbonium ion, $(CH_3)_3CCH_2^+$. Reaction by this pathway can occur, however, but with rearrangement (a 1,2-shift of —CH_3). This will be discussed in Chapters 9 and 34.

The S_N1 reaction. The foregoing discussion has shown why CH_3Br reacts rapidly and $(CH_3)_3CBr$ slowly by the S_N2 pathway. On the other hand, CH_3Br reacts very slowly by the S_N1 route, while $(CH_3)_3CBr$ reacts rapidly by this mechanism. This means that there is little tendency for the reaction

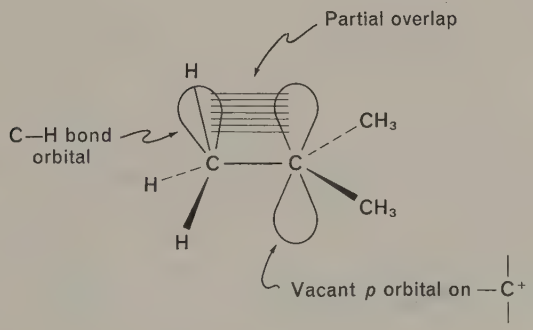
$$CH_3Br \xrightarrow{\text{solvent}} CH_3^+ + Br^- \qquad (20)$$

while the corresponding dissociation of the *t*-butyl halide provides an easy pathway for rapid displacement of the halogen.

Why is $(CH_3)_3C^+$ so much "better" (that is, stable) a carbonium ion than CH_3^+?

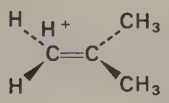
The methyl carbonium ion, CH_3^+, would be expected to be quite unstable. It has an unfilled valence orbital and a localized positive charge. It would be expected to have a strong attraction for an atom with an unshared electron pair; conversely, CH_3X would be loath to part with :X. Experimental evidence supports these views: the methyl carbonium ion has little tendency to form.

The $(CH_3)_3C^+$ ion also has an unfilled orbital and a positive charge; yet it is clearly more stable than CH_3^+. It is evident that the three methyl groups are a stabilizing factor. The stabilizing effects of the methyl groups in the *t*-butyl carbonium ion can be attributed to their ability to delocalize, or disperse, the positive charge. They can do this by utilizing the electrons in the H—C bonds in a manner shown in the following diagram:



(21)

This contribution, regarded in the extreme, can be represented formally as

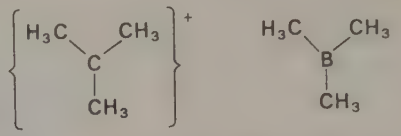


(22)

No such species as (22) actually exists as a discrete entity; but it is apparent that partial contributions of this kind by nine C—H orbitals permits the positive charge to be distributed over the whole *t*-butyl group. This charge dispersal, or delocalization, is a stabilizing factor; it is clear that the positive charge of the *t*-butyl carbonium ion is not confined to the central carbon atom. It is also apparent that no such charge dispersal is possible in the CH_3^+ ion. Here the charge is constrained to exist as a localized charge on the carbon atom.

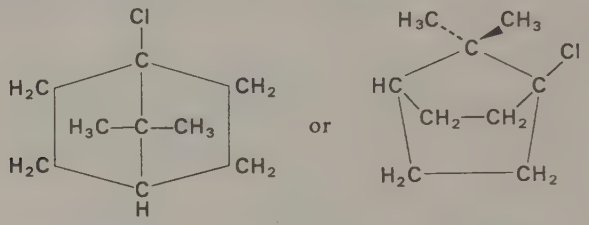
An important corollary to this description of the *t*-butyl carbonium ion is that for effective use of the C—H orbitals to delocalize charge, as pictured in (21), *the ion must be "flat," that is, trigonally symmetrical and planar.* The three carbon-carbon

bonds are thus sp^2 in type, and the $(CH_3)_3C^+$ ion must resemble the trimethylboron molecule, with which it is isoelectronic:



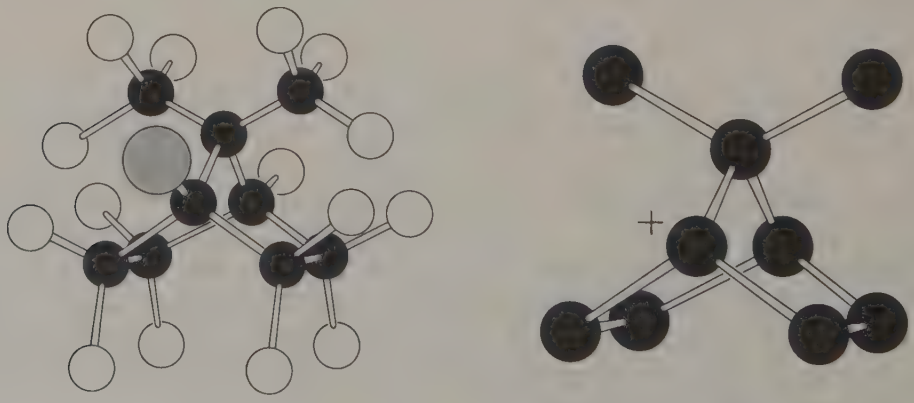
(23)

What if the carbonium carbon atom *cannot* assume a planar configuration? From the foregoing discussion, it may be concluded that the ability of the ion to become planar is a necessary condition for its formation. That this is indeed true is very elegantly shown by the behavior of the compound



(24)

A drawing of a molecular model of this compound is shown in Figure 7-3. This compound is remarkably inert to the displacement of the halogen: it is unaffected by heating with 30% KOH for 21 hours, and does not react with boiling alcoholic silver nitrate (no silver chloride is formed). It is clear that the carbonium ion that would be formed by ionization of the halogen cannot assume a planar configuration because the rigid cage-like structure of the molecule does not permit it to "flatten" out.



(a) (b)

Figure 7-3
Ball-and-stick models of (*a*) cyclic compound (24) and (*b*) the carbonium ion that would be formed by ionization of Cl. In (*b*) the hydrogen atoms have been omitted to show the carbon skeleton more clearly.

In Figure 7-3 are shown ball-and-stick models of the bicyclic chloro compound (24) and of the carbonium ion that would be formed by ionization of the halogen. It is also evident that neither solvent molecules nor a nucleophilic reagent would be able to penetrate inside of the cage to solvate or attack the rear side of the carbonium carbon atom; thus, neither S_N1 nor S_N2 displacement can occur.

7-8 Stabilization of the carbonium-ion intermediate

Ethers containing a halogen atom on the carbon atom adjacent (α) to the oxygen atom are very reactive by both nucleophilic displacement mechanisms. An example is chloromethyl ether, CH_3OCH_2Cl, which undergoes hydrolysis at a rapid rate. The reactivity of this compound under conditions favoring the bimolecular displacement reaction need not be dwelt upon because it is clear that the overall geometry of this halide is very similar to that of 1-chloropropane, and thus that nucleophilic attack at $—CH_2Cl$ is not subject to unusual steric interference.

In contrast to 1-chloropropane, whose reaction by way of a carbonium ion intermediate is very slow (the primary carbonium ion, $CH_3CH_2CH_2^+$, has no marked stabilizing features), chloromethyl ether is very reactive by the S_N1 route. This suggests that the transition state leading to the carbonium ion $CH_3OCH_2^+$ is at a relatively low energy level.

The reason for this stability can be seen by an examination of Figure 7-4. The hypothetical unstabilized form (*a*) would not be expected to be more stable than the

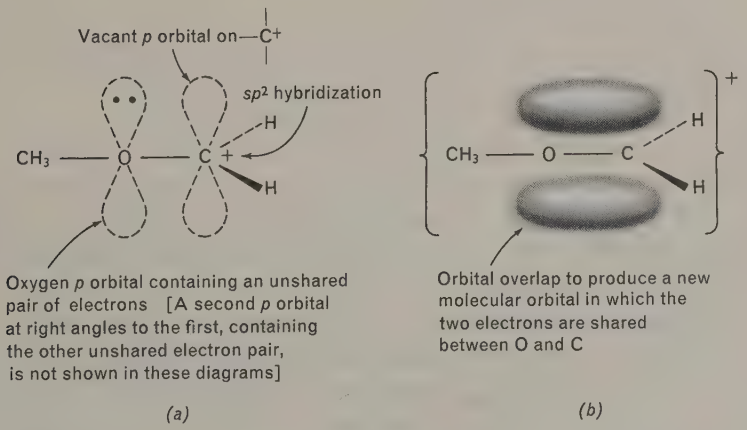


Figure 7-4
Stabilization of the carbonium ion $CH_3OCH_2^+$ by charge delocalization: (*a*) the hypothetical "free" carbonium ion; (*b*) the actual ion with charge delocalized by orbital overlap.

primary propyl carbonium ion. The actual stabilized ion shown as (*b*) can be represented by the formal structure

$$\{CH_3O{-}CH_2{}^+ \longleftrightarrow CH_3\overset{+}{O}{=}CH_2\} \tag{25}$$

The double-headed arrow is a special symbol that represents the kind of charge delocalization shown in Figure 7-4(*b*). Its use will be further discussed in Chapter 9.

Exercise 2

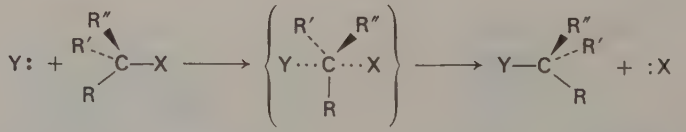
Show by an appropriate counting of the electrons in $CH_3\overset{+}{O}{=}CH_2$ why the positive charge is placed on oxygen.

Exercise 3

Would you expect $CH_3CH{=}CHCH_2Cl$ to show high or low reactivity in the S_N1 displacement reaction? Why? HINT: The π orbital of the carbon-carbon double bond is formed by the overlap of contiguous *p* orbitals, as in Figure 7-4. See also Figure 10-1.

7-9 The stereochemistry of the nucleophilic displacement reaction

An important feature of the bimolecular nucleophilic displacement reaction is shown in the equation



(26)

The configuration at the carbon atom has been *inverted* in the displacement of :X; the carbon atom has been "turned inside out" like an umbrella in a high wind. Although the product YC—RR′R″ is not the enantiomer of RR′R″—CX, the two have enantiomeric *configurations.*

Numerous experimental observations confirm that the picture of the reaction shown in (26) is correct: every substitution that follows the mechanistic course shown in (26) is accompanied by inversion at the carbon atom at which the substitution takes place. A demonstration of this inversion has been accomplished in the manner shown in Figure 7-5.

The conversion of the alcohol with an optical rotation of $+33°$ into its optical enantiomer, with rotation $-33°$, shows that *inversion of configuration has taken place*

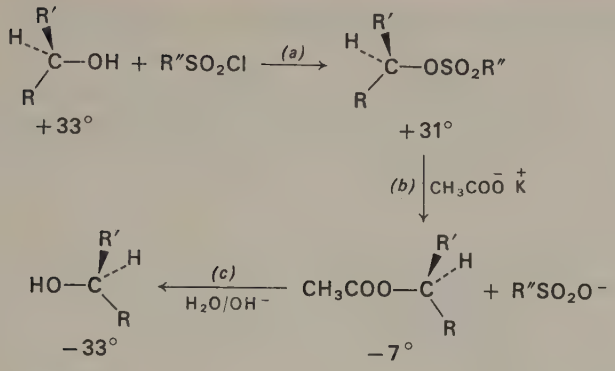


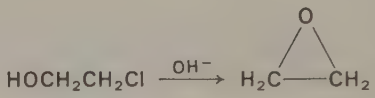
Figure 7-5
A demonstration of the inversion that takes place at the carbon atom involved in an S_N2 reaction:
(*a*) The conversion of the alcohol to the sulfonic acid ester does not involve a breaking of the C—O bond; thus there is no change in the configuration at the asymmetric carbon atom.
(*b*) This is the displacement step, involving the attack of the nucleophile (acetate ion) and displacement of $R''SO_2O^-$
(*c*) The alkaline hydrolysis of the ester (the acetate) does not affect the C—O bond, and thus there is no inversion at this step.

at some point in this series of reactions. Since it is known from much evidence that the formation of the sulfonic ester (*a*) and the hydrolysis of the acetate (*c*) do not involve inversion, the inversion must have occurred in the step (*b*) involving the displacement of $R''SO_2O^-$ by attack of the acetate ion.

The stereochemical course of the unimolecular (S_N1) displacement reaction is neither so clear cut nor so predictable. The solvated carbonium ion may combine with the nucleophile at either side, with the result that the configuration of the product may be partially inverted with respect to that of the starting material, largely inverted, or inverted to a very small extent only (*retention* of configuration). The reason for this variability in the stereochemical result is that the carbonium ion may be symmetrically solvated on both sides, in which case the entering group may attack with equal probability at either side; or the nucleophile may attack at a stage in which solvation is heavier on one side than the other, in which case a predominance of one enantiomer may result; or the nucleophile may attack at a stage at which the leaving group is held in a "solvent cage" and has not left the vicinity of the carbon atom, in which case it will impede attack of the nucleophile at the "front" face, and thus promote predominant attack at the rear face, with inversion. These variable factors will be affected by experimental conditions: the nature of the solvent, the nature of the nucleophile and of the leaving group, and the conditions under which the reaction is performed. The usual stereochemical result in the S_N1 reaction is that some inversion occurs but the product is a mixture of both enantiomers.

7-10 Internal nucleophilic displacement. Ring formation

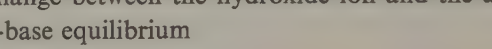
If the attacking nucleophilic center and the carbon atom that carries the leaving group are a part of the same molecule, the displacement reaction leads to the formation of a cyclic product. An example of this is the formation of an ethylene oxide from a β-halo alcohol:



$$HOCH_2CH_2Cl \xrightarrow{OH^-} H_2C\text{—}CH_2 \quad (O) \tag{27}$$

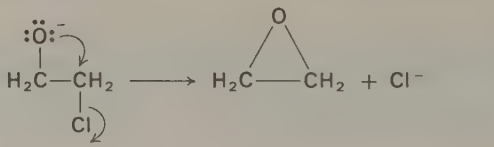
The steps in this reaction are the following:

1. The proton exchange between the hydroxide ion and the alcoholic hydroxyl group leads to the acid-base equilibrium



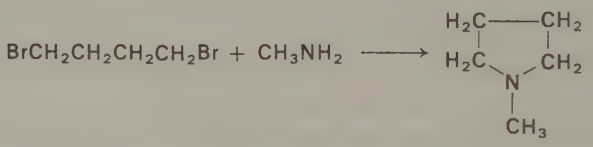
$$HO^- + HOCH_2CH_2Cl \rightleftharpoons {}^-O\text{—}CH_2CH_2Cl + H_2O \tag{28}$$

2. The conversion of —OH into —O^- greatly enhances the nucleophilic character of the oxygen atom, with the result that an *internal* nucleophilic displacement can occur:



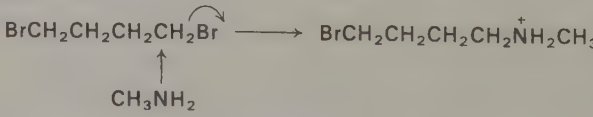
$$H_2C\text{—}CH_2 \quad (:\ddot{O}:^-,\ Cl) \longrightarrow H_2C\text{—}CH_2 \quad (O) + Cl^- \tag{29}$$

The reaction of a dihalide with ammonia or an amine can lead to ring formation by a comparable route:



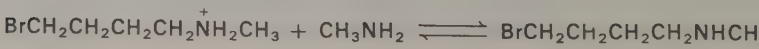
$$BrCH_2CH_2CH_2CH_2Br + CH_3NH_2 \longrightarrow \begin{matrix} H_2C\text{—}CH_2 \\ | \quad\quad | \\ H_2C \quad N \quad CH_2 \\ \quad\quad | \\ \quad\quad CH_3 \end{matrix} \tag{30}$$

1. The initial displacement reaction is the quite unexceptional step



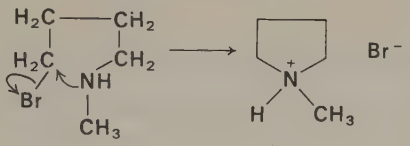
$$BrCH_2CH_2CH_2CH_2Br \xrightarrow{CH_3NH_2} BrCH_2CH_2CH_2CH_2\overset{+}{N}H_2CH_3 + Br^- \tag{31}$$

2. Proton exchange between the product of reaction (31) and excess CH_3NH_2 generates the free amine:



$$BrCH_2CH_2CH_2CH_2\overset{+}{N}H_2CH_3 + CH_3NH_2 \rightleftharpoons BrCH_2CH_2CH_2CH_2NHCH_3 + CH_3\overset{+}{N}H_3 \tag{32}$$

3. Internal nucleophilic displacement in the bromo amine leads to ring formation:



(33)

The cyclic ammonium salt is but the protonated amine; in practice the reaction mixture would be made alkaline with aqueous sodium hydroxide and the cyclic amine isolated by extraction with some suitable organic solvent.

The synthetic method illustrated by equations (31) to (33) is a general and valuable procedure for the practical preparation of cyclic amines; it is most widely used for the preparation of five- and six-membered rings. Variants are possible and practicable: for example, the treatment of the following bromo-substituted ammonium salt with alkali leads to ring closure (intramolecular alkylation) to form *N*-methylpiperidine:

$$BrCH_2CH_2CH_2CH_2CH_2\overset{+}{N}H_2CH_3 \xrightarrow{NaOH} \textit{N}\text{-methylpiperidine} \qquad (34)$$

Exercise 4

Formulate the steps summarized in (34) and write the structure of *N*-methylpiperidine. Why will the ammonium salt not cyclize before alkali is added?

7-11 Nucleophilic displacement reactions in living organisms

Because of their wide variety and fundamental importance, nucleophilic displacement reactions in biological systems deserve special attention. Despite the somewhat complex structures of some of the participants in these reactions, it is appropriate to introduce the subject at this early point because it is a logical development of the concepts discussed in this chapter, and because it provides an excellent example of the interpretation of cellular metabolism in rational, mechanistic terms. This will be the subject of Chapter 8.

Problems

1. Show all the details in the preparation of 1-bromopropane by the reaction of 1-propanol with a mixture of NaBr, H_2O, and H_2SO_4.

2. Explain why $ClCH_2OCH_2CH_3$ is hydrolyzed more rapidly than its isomer $CH_3OCH_2CH_2Cl$.

3. Allyl halides ($CH_2{=}CHCH_2X$) are very reactive by the S_N1 displacement reaction. Suggest a reason for stabilization of the $CH_2{=}CHCH_2^+$ ion.

4. Write equations for the reactions between each of the following pairs of compounds (assume that the reactions are carried out in alcoholic or aqueous-alcoholic solutions).
   (*a*) ethyl bromide and potassium acetate
   (*b*) allyl chloride and trimethylamine
   (*c*) 1-bromopentane and potassium cyanide
   (*d*) methyl iodide and potassium *t*-butoxide [$(CH_3)_3CO^-K^+$] in *t*-butyl alcoholic solution
   (*e*) benzyl bromide and sodium hydroxide
   (*f*) ethyl methanesulfonate ($CH_3SO_2OC_2H_5$) and diethylamine

5. Draw estimated energy profiles for the alkaline hydrolysis (by dilute aqueous alcoholic sodium hydroxide) of 2-bromopropane, showing the two chief mechanistic pathways.

6. What would be the product formed by the reaction between 3-methyl-4-dimethylamino-1-butanol and concentrated HBr, followed by the addition of sodium hydroxide solution to the point of alkalinity?

7. Arrange the following compounds in the order of their reactivity with trimethylamine, assuming the S_N2 mechanism: (*a*) *t*-butyl bromide, (*b*) allyl chloride, (*c*) 1-chloropropane, (*d*) 2-chloropropane, (*e*) 3-bromo-3-methyl-1-butene.

8. Arrange the compounds in Problem 7 in the order of their reactivity in an S_N1 displacement reaction.

8

Nucleophilic displacement reactions in biological systems

The versatility and generality of the nucleophilic displacement reaction is nowhere better illustrated than in biological systems. It was seen in Chapter 7 that most nucleophilic displacement reactions result in the alkylation of the nucleophile. For this reason, the reactions described in this chapter are often referred to simply as *biological alkylation* reactions. Although products of a wide range of structural types are formed by reactions of this class in living systems, all are variants of the same reaction. Although many biological alkylation reactions are catalyzed by unique and often specific enzymes, the mechanistic aspect of all of them at the site of reaction is substantially the same.

8-1 The scope of biological alkylation reactions

The metabolic processes of living organisms include a wide array of reactions that are readily recognized as nucleophilic displacement reactions. Many of these processes are enzyme-mediated, but the discrete functional entities involved in the synthetic steps that we shall deal with here are alkylating agents and nucleophilic substrates.

Four principal categories of reactions of this kind can be recognized:

1. *Modification or deactivation of enzymes* due to the alkylation of nucleophilic centers that are needed for normal enzyme activity.*

* The *acylation* of enzymes, although not strictly a nucleophilic displacement reaction in the usual use of the term, should also be included here. One aspect of this will be discussed in Section 8-5.

2. *The toxic action of organic compounds* whose chemical properties define them as alkylating or acylating agents. Among these are such toxicants as methyl bromide, methyl sulfate, α-halogen ketones, "mustard gas," phosphorus insecticides, and certain α,β-unsaturated carbonyl compounds.

3. *Alkylating agents are used therapeutically*, particularly in tumor chemotherapy. Since these compounds also have toxic effects on normal metabolic tissue, they are remindful of the saying, "Drugs are poisons and *vice versa*."

4. *Alkylation reactions in normal primary and secondary metabolism* of living organisms, leading to the biosynthesis of *C*-, *N*-, and *O*-methylated compounds, *O*- and *C*-prenylated* compounds, and carbon-carbon unsaturation.

8-2 Biological "leaving groups"

Nucleophilic displacement reactions have been defined as the attack of a reagent having an unshared electron pair upon an electron-deficient center, with the prior (S_N1) or simultaneous (S_N2) expulsion of what has been called the "leaving" or "departing" group. Leaving groups are characteristically the weakly nucleophilic conjugate bases of strong to moderately strong acids, and in many cases contain the positively charged atoms O, N, or S (as in RO^+H_2, $RO^+R'_2$, $RS^+R'_2$, $RN^+R'_3$, where attack is at R, and OH_2, OR'_2, SR'_2, and NR'_3 are displaced).

In biological alkylation reactions of normal metabolism, the various structures of the "leaving" groups are of course those that evolutionary development has selected for the needs of growth and reproduction. They bear a striking resemblance to those that the organic chemist has discovered by experimental and theoretical study.

8-3 Biological methylation reactions

The most prevalent of the natural biological alkylation processes is the transfer of methyl groups from a methyl donor to a nucleophilic site. The principal source of methyl groups is *methionine*, but transfer of the methyl group from methionine *itself* is a highly unfavored process, for the reaction (using an amine as a typical nucleophile)

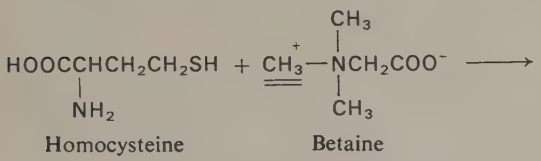
$$R_3N + CH_3SCH_2CH(NH_2)CHCOOH \rightleftharpoons R_3\overset{+}{N}{-}CH_3 + {}^-SCH_2CH_2CH(NH_2)COOH \qquad (1)$$

Methionine

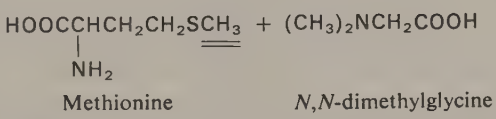
* "Prenyl" is a useful name for the γ,γ-dimethylallyl group, $(CH_3)_2C{=}CHCH_2{-}$, which is so called because of its structural resemblance to isoprene.

is energetically unlikely, and it would be expected that the equilibrium represented by the equation would lie almost completely to the left.

Indeed, one of the biological sources of methionine is the methylation of the sulfur atom of homocysteine by a quaternary ammonium methyl donor (transferred CH_3 group underlined); this is reaction (1) from right to left:

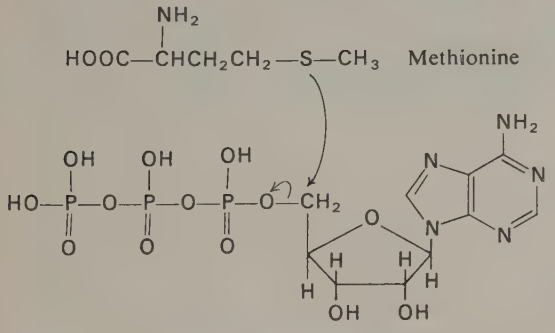


Homocysteine Betaine



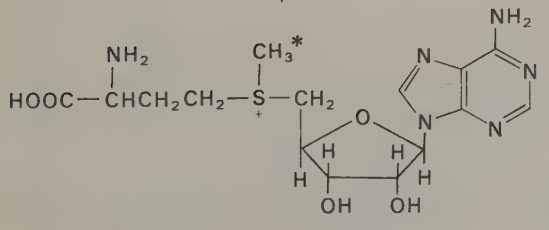
Methionine *N*,*N*-dimethylglycine (2)

Methionine, therefore, is not itself a methyl donor. But conversion of CH_3S— into the sulfonium grouping CH_3—$\overset{+}{S}$— yields the so-called *activated methionine*. This is an effective methyl donor, and can transfer the methyl group to a wide variety of nucleophiles by a simple nucleophilic displacement. The sulfonium derivative of methionine is formed in nature by the alkylation of sulfur by the adenine-ribose unit derived from adenosine triphosphate (ATP):



Methionine

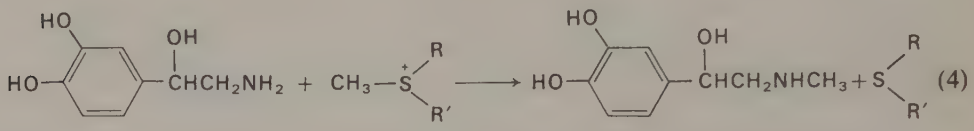
Adenosine triphosphate (ATP) (3)



S-adenosylmethionine (*S*-AdM)

*CH_3 = methyl group to be transferred to a nucleophilic center

S-Adenosylmethionine (*S-AdM*) is a methyl sulfonium compound of the general structure $CH_3S^+R_2$, and an effective methyl donor in nucleophilic displacement reactions. It is the source of biological methyl groups in a wide variety of compounds. A typical example of the reaction is the formation of adrenaline (epinephrine) from noradrenaline (norepinephrine):



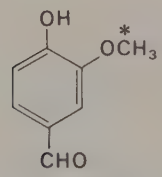
(4)

(*S*-AdM)

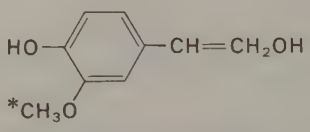
R = —$CH_2CH_2CHCOOH$ (with NH_2) R′ = 5-(ribose-adenine)

It is to be noted that although the active methylating agent is *S*-adenosylmethionine (*S*-AdM), the complete system involved in the methylation of any given substrate is a specific enzyme of which *S*-AdM is the coenzyme or prosthetic group. In the case of the norepinephrine-epinephrine reaction, the enzyme is called *phenylethanolamine N-methyltransferase*. Other methyltransferases abound in living systems, notably in plants, in which countless *N*-methylated compounds (for example, alkaloids) and *O*-methylated compounds are found.

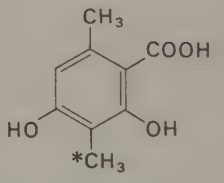
O-Methyltransferases catalyze the methylation of the hydroxyl groups of phenols by the agency of *S*-AdM. Methyl ethers of phenolic compounds of many kinds are well known products of higher plants. Moreover, carbon-methylation also occurs, the nucleophile being a carbon anion formed at the enzymatic reaction site. In the examples given below, all of the —CH_3 groups marked by * are derived from

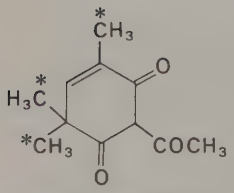


Vanillin

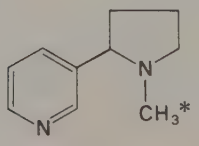


Coniferyl alcohol

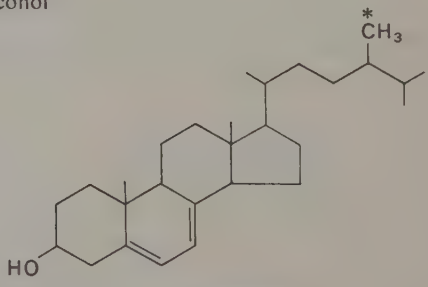




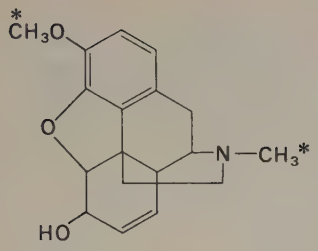
Dehydroangustione



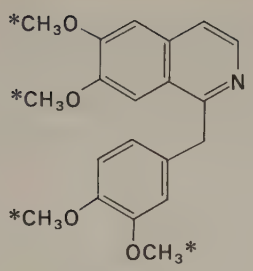
Nicotine



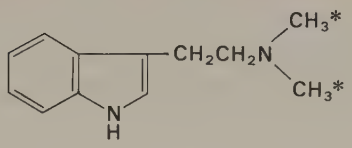
Ascosterol



Codeine



Papaverine

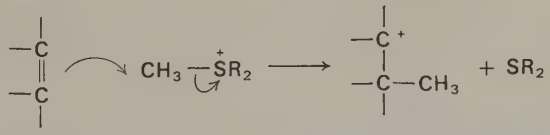


Dimethyltryptamine

methionine by way of *S*-AdM. Proof of this has been obtained from *in vivo* experiments in which $^{14}CH_2$-labeled methionine has been administered to a living plant or other organism and the $^{14}CH_3$-labeled methylation product isolated and identified.

It is noteworthy that while *N*-, *O*-, and *C*-methylated compounds are widely distributed in nature, other simple *N*-, *O*-, and *C*-alkyl derivatives (for example, $\diagdown N—CH_2CH_3$ compounds and *O*-ethyl ethers) are not found. Thus, "*one-carbon metabolism*" is alone; the similar generation and transfer of other alkyl groups is not known, with the unique exception of the five-carbon (γ,γ-dimethylallyl) groups to be described below.

The sterol ascosterol, shown in the above list of examples, deserves special comment. The "extra" methyl group (marked *) of the side chain of ascosterol is normally lacking in the side-chains of sterols, and has been shown to be derived from methionine. In this case, the carbon-carbon double bond has acted as a nucleophile to accept the methyl group from *S*-AdM. Numerous other steroidal compounds are known that contain "extra" methyl groups of this kind. The generalized process can be written as follows:



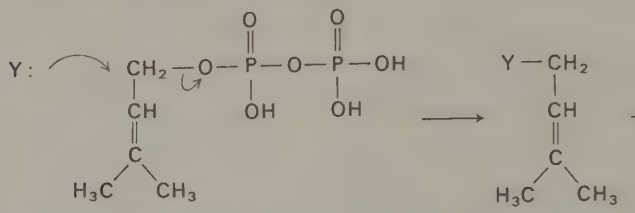
(5)

(followed by loss of H^+ and, in some cases, double-bond migration).

8-4 Prenylation of carbon and oxygen

γ,γ-Dimethylallyl (prenyl) pyrophosphate, a primary precursor in the natural synthesis of terpenes, sterols, carotenoids, and many other products of cellular metabolism, is an alkylating agent ideally designed to meet the requirements of nucleophilic displacement reactions. It possesses an effective leaving group, the pyrophosphate ion, attached to the allylic group $(CH_3)_2C{=}CHCH_2—$. Allyl halides and sulfonic esters of allylic alcohols are well known to be highly reactive in displacement reactions with nucleophiles and react readily by either S_N1 or S_N2 routes.

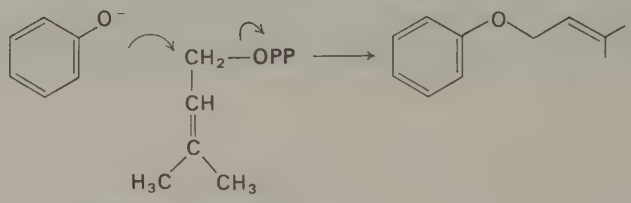
The appearance of the prenyl group in naturally occurring compounds of many structural classes attests both to the ubiquity of prenyl pyrophosphate as a natural synthetic "reagent" and to its capacity for alkylating a wide variety of nucleophilic centers. The most general expression for the reaction is



(6)

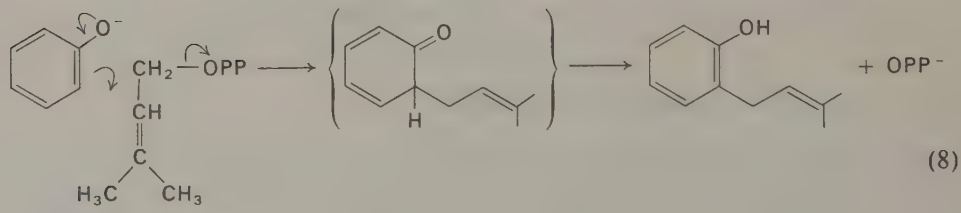
where the nucleophilic center is represented by Y:, which may be either neutral or anionic. Because these reactions are natural processes occurring with the catalytic assistance of an enzymatic milieu,* it is impossible to specify the degree to which the reaction is S_N1 or S_N2 in type, but an understanding of the overall result does not depend upon knowledge of this detail.

The prenylated compounds most common in nature are those in which the oxygen of a phenol, the carbon of an enolate anion, or a carbon-carbon double bond act as nucleophilic agents. Thus, *O*-prenyl ethers, *C*-prenylated phenols, and compounds in which two or more five-carbon units are combined are well known. The alkylation (prenylation) reactions leading to these are summarized in the following expressions (where OPP is an abbreviation for pyrophosphate):



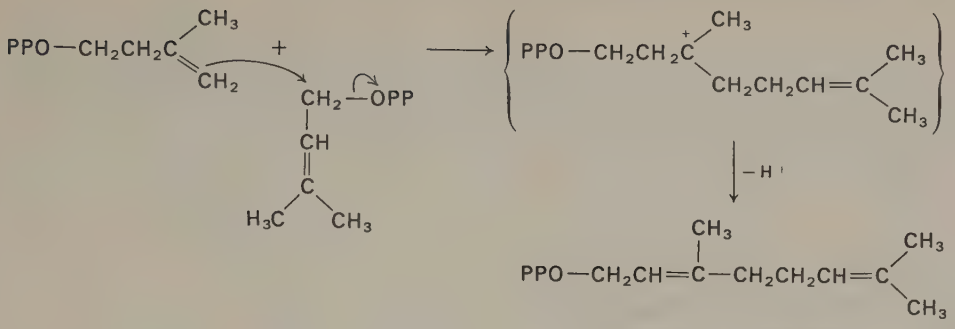
(7)

Prenyl pyrophosphate



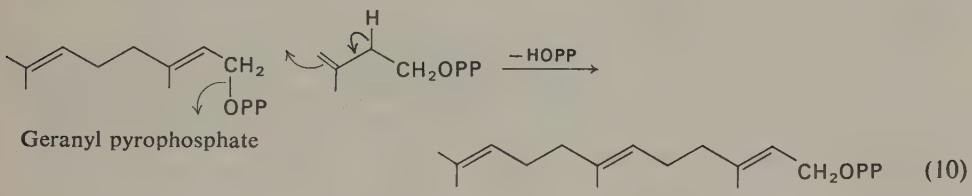
(8)

* One cannot make a simple comparison between those reactions that occur in aqueous or other protic solutions and those occurring at an enzyme surface, for the proton-accepting and -donating properties of elements of a peptide chain may be greatly modified in what may be an aprotic or lipoid environment.



Geranyl pyrophosphate (9)

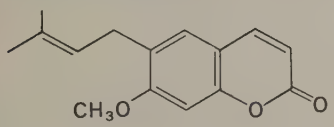
The C_{10} compound geranyl pyrophosphate, formed in the last of the above reactions, is also an allylic pyrophosphate, structurally quite analogous to prenyl pyrophosphate and capable of engaging in alkylation reactions of the same kind:



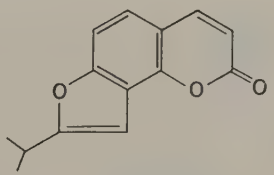
Geranyl pyrophosphate (10)

$$C_{10} + C_5 \longrightarrow C_{15}$$

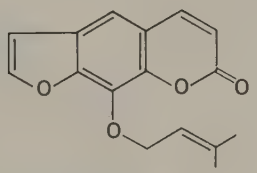
The following compounds are examples of *O*- and *C*-prenylated compounds, the natural synthesis of which involves prenyl pyrophosphate or geranyl pyrophosphate:



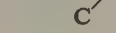
Suberosin

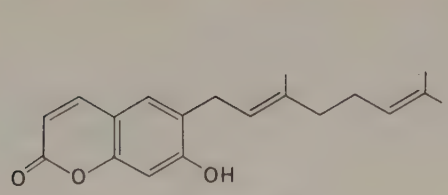


Oroselone

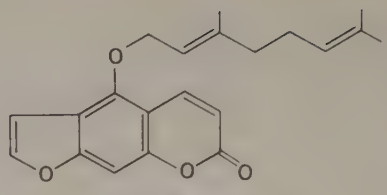


Imperatorin*

* It should be added that the two carbon atoms of the furan ring in imperatorin and other benzofurans of the same type are also derived from an initial prenylation. The three carbon atoms of the  unit are lost in subsequent metabolic reactions.



Ostruthin



Bergamottin

8-5 Alkylation of "active sites" of enzymes

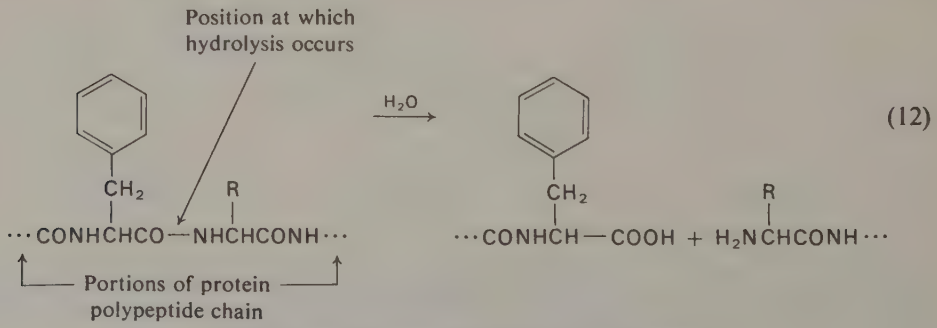
Certain functional groups, such as —SH, —OH, and —NH (which are clearly nucleophilic), are known to be essential to the catalytic action of many enzymes. They are components of the "active site" of these enzymes, and are known to participate in the reactions by which the substrate undergoes chemical change. It has been observed that when some enzymes are treated with chemical reagents, catalytic activity is lost, and the enzyme is said to be inactivated. Many of these enzyme inhibitors are alkylating agents.

Iodoacetic acid and iodoacetamide are well-known inhibitors of many enzymes whose catalytic activity requires that free —SH groups be present. They are widely used in studies of enzyme action. Alkylation of —SH by iodoacetamide is a straightforward nucleophilic displacement reaction

$$\text{Enz—SH} + \text{ICH}_2\text{CONH}_2 \longrightarrow \text{Enz—SCH}_2\text{CONH}_2 + \text{HI} \qquad (11)$$

The reaction is not reversible, and results in loss of enzymatic activity.

Chymotrypsin is an enzyme with both esterase and peptidase activity, that is, a capacity for catalyzing the hydrolysis of the —NHCO— (peptide) linkage in proteins. It shows a special degree of specificity toward the particular —NHCO— grouping shown in the following equation:

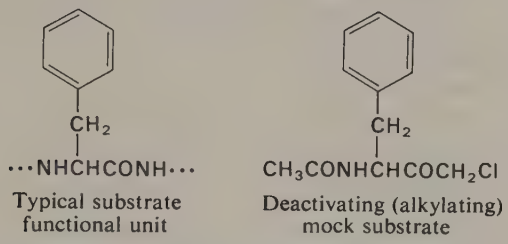


(12)

Chymotrypsin-catalyzed hydrolysis of a peptide

Because of the preference of chymotrypsin for the peptide bond in a position adjacent

to the $C_6H_5CH_2\underset{|}{C}H$— group, it appears that the enzyme has a site with special affinity for this group. A "mock" substrate, a chloroketone containing this same structural unit and having alkylating ability, is found to inactivate the enzyme by forming a covalent bond with a nucleophilic grouping necessary for enzymatic activity.



The nucleophilic grouping that is alkylated by the chloroketone is believed to be the —NH grouping of a histidine unit in the protein chain of chymotrypsin.

Other hydrolytic enzymes with specificity for particular portions of a polypeptide chain can be deactivated, in a similar manner, by α-chloroketones with structures corresponding to the specific requirements of the active sites on the enzymes.

Deactivation of enzymes is brought about by (highly toxic) derivatives of phosphoric acid such as tetraethyl pyrophosphate, diisopropyl fluorophosphonate (DFP), and other compounds of a large group known as "nerve gases." Deactivation is effected by nucleophilic displacement on phosphorus (with displacement of fluoride ion when the toxic agent is DFP), with the result that the enzyme is *phosphorylated.* In these cases the nucleophilic group that is phosphorylated is the hydroxyl group of a serine unit of the polypeptide chain. This has been established in the case of chymotrypsin by degradation of the inactivated enzyme and isolation of the phosphorylated serine, $HOOC\underset{|}{\underset{NH_2}{CH}}CH_2O\overset{\downarrow}{\underset{O}{P}}(OiPr)_2$ (when the toxic agent is DFP).

8-6 Correspondence between toxicity and alkylating ability

Many quite ordinary compounds of unexceptional structure are highly toxic to living organisms. Among these are methyl bromide, dimethyl sulfate, diazomethane, other low-molecular-weight reactive alkyl halides, and chloromethyl ethers.*

Methyl bromide, for example, is highly toxic to man, animals, and plant life. It is used as a soil fumigant and insecticide, and also to inhibit the germination of

* It has been reported that mixtures of formaldehyde and HCl vapor react to give a low but dangerous concentration of bis-chloromethyl ether, $ClCH_2OCH_2Cl$, a toxic and carcinogenic compound.

grain in storage. Studies with isotopically labeled methyl bromide have shown that it acts as a biological methylating agent. The particular nucleophilic centers in the living cells that are methylated are not known with certainty, but it appears unlikely that methyl bromide would show much discrimination among the several kinds of nucleophilic groupings found in the cellular components of living systems. Methyl chloride is also toxic; but since chlorides are known to be less reactive than bromides in nucleophilic displacement reactions, methyl chloride would be expected to be less toxic than methyl bromide. This is the case. Methyl iodide, as would be expected, is somewhat more toxic than the bromide.

Dimethyl sulfate and methyl esters of sulfonic acids, both widely used in organic synthesis as methylating agents, are also toxic. These compounds are somewhat less hazardous by reason of their relatively low volatility, but they should be handled and used with care.

Lacrimators (tear gases) are compounds used as anti-personnel agents, whose toxicity is manifested in severe irritation of mucous tissues, eyes, and skin. Typical lacrimators are α-halogen substituted ketones, such as chloroacetophenone and bromoacetone, and α-bromophenylacetonitrile, all of them very reactive toward nucleophilic agents. Acrolein, an α,β-unsaturated aldehyde (CH_2=$CHCHO$) and a severely lacrimatory substance, can also "alkylate" by addition of nucleophiles according to the Michael-like (Chapter 25) reaction

$$RSH + CH_2{=}CHCHO \longrightarrow RSCH_2CH_2CHO \qquad (13)$$

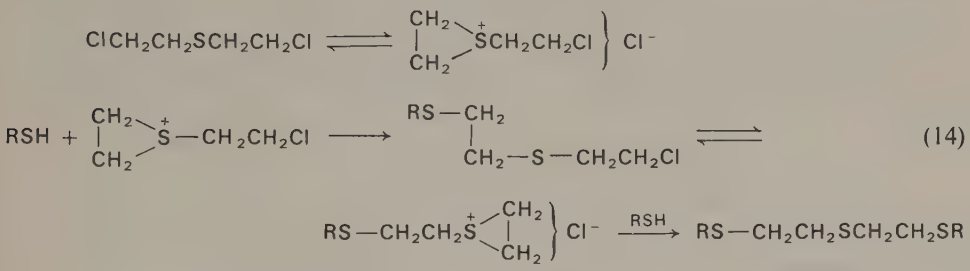
The exact nature of the tissue-lacrimator reaction is not known in detail, but it is highly probable that these compounds exert their effects by alkylating nucleophilic sites of protein substrates, thus disturbing the normal functioning of the tissues of which they are a part.

8-7 Mustard gas and related compounds

"Mustard gas" is an oily liquid compound having the structure $ClCH_2CH_2SCH_2CH_2Cl$ (β,β′-dichlorodiethyl sulfide). It is highly toxic, and has found extensive use as a war gas. It damages mucous tissue and can cause severe disablement and death. That mustard gas is a very effective alkylating agent has been demonstrated in intensive studies of its chemistry and physiological action.

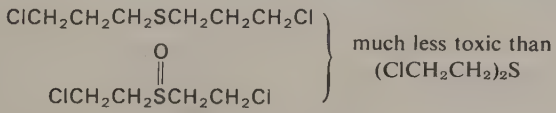
The reaction of mustard gas with nucleophilic reagents proceeds by way of the intermediate formation of a cyclic sulfonium salt, which is the active alkylating agent. It will be apparent that mustard gas can act as a *bifunctional* alkylating agent, in which both chlorine atoms can be replaced in sequential stages. Using a thiol as a

typical nucleophilic agent (an enzyme or protein —SH group is an equivalent biological reagent), the reaction can be formulated as follows:

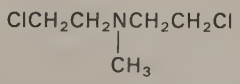


(14)

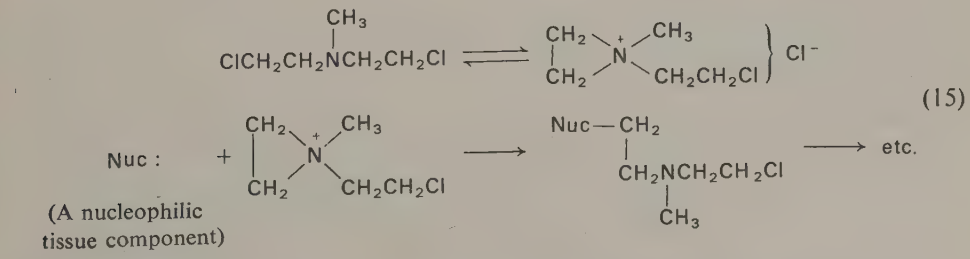
The high degree of reactivity of *S*-mustard as an alkylating agent can be attributed to the assistance of the internal nucleophile, sulfur, in eliminating the chlorine atom to form the extremely reactive three-membered cyclic sulfonium salt. If the sulfur is so situated that only the sterically less favored four-membered ring can be formed, or if the nucleophilicity of the sulfur atom is reduced by converting it into the less nucleophilic sulfoxide, toxicity is greatly diminished or is essentially absent:



As is to be anticipated, if sulfur is replaced by another sufficiently nucleophilic atom similar physiological activity is observed. Nitrogen-mustards, of which the simplest analog to *S*-mustard is



are also toxic, and have been used in chemical warfare. They can act as alkylating agents by a reaction that is a parallel of that displayed by *S*-mustard:



(15)

Nitrogen-mustards are also bifunctional alkylating agents; a second alkylation, following the one shown, can occur as in the case of *S*-mustard.

Exercise 1

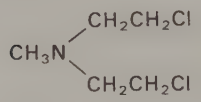
Which of the following compounds would you expect to be less or more active physiologically (that is, toxic) than $(ClCH_2CH_2)_2NCH_3$: (*a*) $(ClCH_2CH_2)_2\overset{+}{N}(CH_3)_2$, (*b*) $(ClCH_2CH_2CH_2)_2NCH_3$, (*c*) $(ClCH_2CH_2)_2N(\rightarrow O)CH_3$, (*d*) $(HOCH_2CH_2)_2NCH_3$, (*e*) $(ClCH_2CH_2)_2NCOCH_3$.

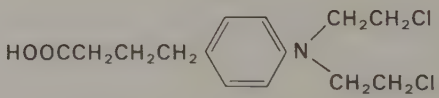
8-8 Therapeutic applications of biological alkylating and acylating agents

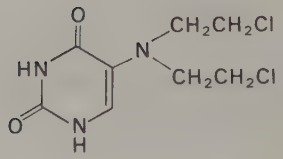
Early studies of the physiological actions of sulfur- and nitrogen-mustards, stimulated by concern arising from their use as poison gases in warfare, revealed certain significant properties of these compounds. They were observed to damage lymphoid tissue and the rapidly proliferating bone marrow. They also produced effects similar to some of those caused by exposure to X-radiation. Their toxicity to tissues characterized by rapid growth suggested the possibility that they might show preferential toxicity to tumor cells. This was found to be the case, and they were introduced into cancer chemotherapy. Although their efficacy in the treatment of malignancy is limited, they have found a secure place in treatment of cancer, and many compounds of the nitrogen-mustard class are clinically useful drugs.

Most of the effective drugs of this class are bifunctional alkylating agents. The simplest compound of the type, $ClCH_2CH_2N(CH_3)CH_2CH_2Cl$, is the prototype, and has found clinical usefulness. Since alkylation can be accomplished by a variety of agents, the clinically most valuable anti-tumor compounds of this kind belong to a wide range of structural classes. All of them in the examples given below are bifunctional alkylating agents:

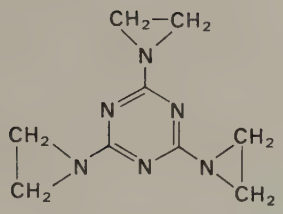
Nitrogen mustards

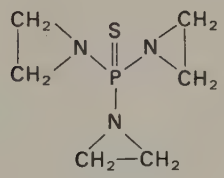




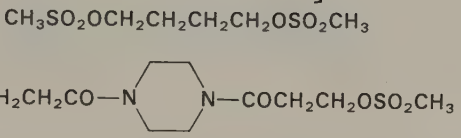


Ethyleneimines

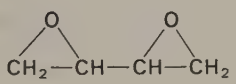


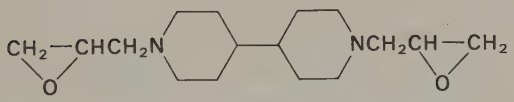


Esters of methanesulfonic acid



Epoxides (some anti-tumor activity but not much used in therapy)





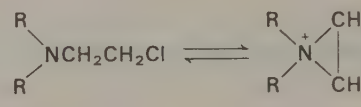
It should be noted, however, that some monofunctional agents (for example, *n*-butyl-sulfonates) also show some anti-tumor activity.

The specific sites at which these compounds alkylate tissue (enzyme, protein, nucleic acid) nucleophiles are not always known with precision. It has been suggested that the reactive sites are on the purine and pyrimidine rings of nucleic acids. Since the reproductive and metabolic mechanisms of living organisms depend upon the cellular nucleic acids, alteration of the structural organization of these molecules by attachment of the alkylating agents could disrupt these functions. The fact that the most effective agents are bifunctional (and thus can bond to two separate nucleic acid chains, or to two separate sites of a single chain) suggests that they can prevent the hydrogen bonding between two DNA chains and thus make impossible the conditions required for their normal replication.

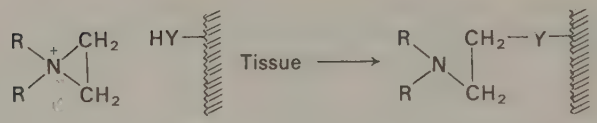
Other kinds of compounds, which are not alkylating agents, are also used in cancer chemotherapy, but a discussion of these is not relevant to the present topic of discussion.

8-9 Monofunctional alkylating agents of the β-chloroethylamine class

An outgrowth of the search for physiologically active alkylating agents of the nitrogen-mustard type was the discovery that certain *monofunctional* chloroethylamines cause interesting, and in some cases therapeutically valuable, physiological responses. One of these, *N*,*N*-dibenzyl-β-chloroethylamine (*Dibenamine*), possesses the property of counteracting the effects of epinephrine (adrenalin), and causes a lowering of blood pressure. Anti-adrenalin (sympatholytic) compounds that are not alkylating agents are known, and have found use in therapy, but their hypotensive effects soon disappear because of the reversible nature of the drug-receptor reaction and eventual diffusion of the drug from the active site. Dibenamine and its analogs, however, have effects that are prolonged and irreversible. The most probable explanation is that these β-chloroethylamines are alkylating agents, and combine permanently with some element of the tissue (designated below as some nucleophilic group HY—) by a covalent bond:



(16)



(17)

To summarize the foregoing discussion, it is recognized that proteins, enzymes (which are proteins), and nucleic acids possess a variety of nucleophilic substituents, among them —SH, —NH_2, and —OH groups. Reactions of these with alkylating agents having structures ranging from the simple compound methyl bromide to bifunctional alkylating agents of the nitrogen-mustard type can alter their normal metabolic functions and cause profound physiological responses. Toxic manifestations of many kinds are seen, ranging from trivial irritation, to disturbance of nerve action, to death. In some cases the influence of such agents upon metabolic systems can be beneficial, leading to useful therapeutic applications.

Problems

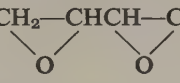
1. Which of the following would you choose as possible candidates for cytotoxic or antitumor agents:
   (a) $CH_3OCH_2CO(CH_2)_4COCH_2OCH_3$ (*b*) $ClCH_2CO(CH_2)_4COCH_2Cl$

(*c*) $CH_2{=}CHCO(CH_2)_4COCH{=}CH_2$ (*d*) $CH_2{=}CHN(CH_3)_2$
(*e*) $CH_3SO_2O(CH_2)_4OSO_2CH_3$ (*f*) $HO(CH_2)_6OH$

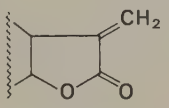
2. Write the equations for the reactions (if any) of the compounds in Problem 1 with dimethylamine.

3. What would you predict to be the result of treating $CH_3SO_2OCH_2CH_2OH$ with alkali?

4. The methyl ester of CH_3SO_3H is toxic. Write the equation for its reaction with a sulfhydryl compound RSH.

5. How would an epoxide—for example,  —react with a nucleophilic center such as an —SH group?

6. Certain compounds containing the structural element



have been found to have cytotoxic and antitumor activity. Show how this structural unit could act as an alkylating agent.

9

Resonance stabilization. Charge delocalization

It was shown in Chapter 5 that organic reactions usually proceed through a *transition state* in which the reacting molecules possess a greater energy (activation energy) than the initial reactants. Although it is only in rather simple systems that this increase in energy is amenable to precise calculation, it is possible for the organic chemist to estimate relative activation energies and thus to understand why some reactions are faster than others, why a catalyst (such as a mineral acid) speeds up a reaction, why one of two apparently similar reactions proceeds and the other does not, and why one of two possible products is formed in preference to the other.

These deductions depend upon an understanding of how the bonding electrons (present in the bonds between atoms) and the non-bonding electrons (present as unshared electrons upon such atoms as oxygen and nitrogen) are distributed within a molecule. In this chapter it will be shown that the conventional (Lewis) structures used for many organic compounds, while convenient, are often inaccurate, and that a proper understanding of the true structures usually leads to an enlarged understanding of the properties and chemical behavior of organic compounds.

It should be noted here that some of the principles dealt with in this chapter have been introduced as necessary parts of earlier discussions (for example, in Chapter 7). It will be advantageous for the student to review those sections (7-7 and 7-8) in which relative stabilities of carbonium ions were discussed.

9-1 Resonance. Electron delocalization

The terms "resonance energy," "resonance hybrid," and "resonance stabilization" are familiar ones in organic chemistry. In order to use them with meaning and precision it is necessary to understand the concepts to which they relate and to recognize the circumstances to which they apply.

Much chemical behavior is best explained—often only implicitly—in terms of changes in energy during chemical reactions: (1) the energy required to proceed from initial reactants to an activated complex, or transition state, which is related to the rate of a reaction; and (2) the overall energy change from reactants to products, which is related to the equilibrium constant for a reaction. Concepts of *resonance stabilization* —or, as we shall see, *charge delocalization* or charge dispersal—provide a means of understanding the influence of molecular structures, transition states, and products upon the rate and course of a reaction.

9-2 The resonance hybrid

Consider the two isomeric compounds

$$\underset{(1)}{CH_3OCH_2CH_2Cl} \quad \text{and} \quad \underset{(2)}{CH_3CH_2OCH_2Cl}$$

Both of these are primary alkyl chlorides. Both undergo nucleophilic displacement reactions to give products in which —Cl has been replaced by the nucleophilic reagent. Both react readily by the S_N2 mechanism; but although (2) reacts rapidly in S_N1 displacement reactions, the reaction of (1) by the S_N1 mechanism is so slow as to be negligible. The conclusion from this is that the dissociation of (2)

$$CH_3CH_2OCH_2Cl \rightleftharpoons CH_3CH_2O\overset{+}{C}H_2 \;\Big|\; Cl^- \qquad (3)$$

proceeds through a transition state of lower energy than the dissociation of (1):

$$CH_3OCH_2CH_2Cl \rightleftharpoons CH_3OCH_2\overset{+}{C}H_2 \;\Big|\; Cl^- \qquad (4)$$

Why is the carbonium ion formed in (3) a "better" (that is, more stable) carbonium ion than the other?

An examination of the structure R—O—CH_2^+ discloses that the positive charge is not constrained to exist only upon the carbon atom. The unshared electron pair on the oxygen atom can be used to fill the vacant *p* orbital on the electron-deficient carbon atom, thus being shared between carbon and oxygen:

$$\underset{(a)}{CH_3CH_2-\ddot{O}-CH_2^+} \longleftrightarrow \underset{(b)}{CH_3CH_2-\overset{+}{\ddot{O}}=CH_2} \qquad (5)$$

The symbolism used in (5) should be noted. The curved arrow is used to indicate a process; it is not a bond, but simply indicates how a bond is to be formed. The double-headed arrow is a symbol to indicate that the cation has neither structure (*a*) nor structure (*b*): the ion is a *resonance hybrid* with a structure that can best be expressed by (*5a* ↔ *5b*). An alternative is to write

$$CH_3CH_2-\overset{+}{\overbrace{O=\!=\!=CH_2}} \qquad (6)$$

but it will soon be recognized that this is needlessly explicit. As familiarity with this concept grows, it will no longer be necessary to write (*5a* ↔ *5b*) or (6). *Either* 5*a* or 5*b* can be used to represent the cation, so long as its true nature is understood. In fact, it is seldom necessary to write all of the structures that make up a resonance hybrid; in most cases any one of them is adequate, for any one implies the others.

Upon examining the ion $CH_3OCH_2CH_2^+$ formed in (4), it should be evident that no such charge dispersal (delocalization) can occur: the electron pair on oxygen is separated from the carbonium carbon atom by a —CH_2— group, and thus cannot act as in (5). One might say that in (4) the positive charge has "no place to go"; there is no other acceptable structure for the ion $CH_3OCH_2CH_2^+$ that differs only in the location of the positive charge.

Charge delocalization is a stabilizing factor. Figure 9-1 is an energy diagram for processes (3) and (4) as S_N1 displacement reactions. Since the transition state for (3)

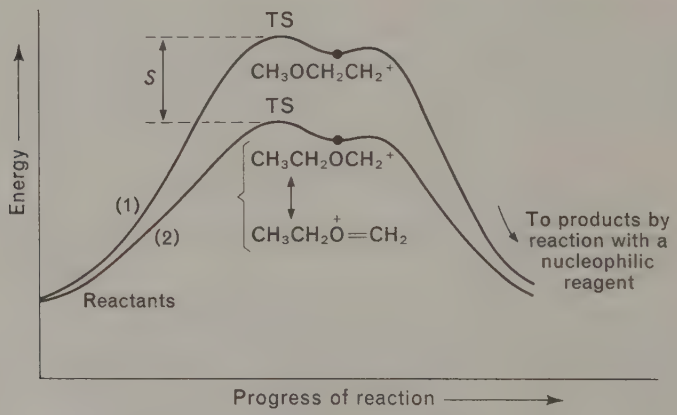


Figure 9-1
Energy diagrams for the rate-determining step $RCH_2Cl \rightleftharpoons RCH_2^+ + Cl^-$ for (1) $CH_3OCH_2CH_2Cl$ and (2) $CH_3CH_2OCH_2Cl$ in S_N1 nucleophilic displacement reactions. S = resonance stabilization by charge delocalization in the ion $CH_3CH_2OCH_2^+ \leftrightarrow CH_3CH_2\overset{+}{O}=CH_2$. (*Note*: the *transition states* leading to the respective cations have structures related to the *intermediates* $CH_3OCH_2CH_2^+$ and $CH_3CH_2OCH_2^+$, and thus differ by about the same energy S.)

is stabilized by charge delocalization it is at a lower energy; thus, reaction by process (3) requires less activation energy and is the faster of the two S_N1 displacement reactions.

The structures *5a* and *5b* are called *contributing structures*. The true structure of the ion, which we may regard for the present as (6), is intermediate between *5a* and *5b*; thus the term "resonance hybrid."

It is fundamental to recognize that a given ion or compound is only *one substance with one structure*. Therefore all of the structural formulas used to represent a resonance hybrid are expressions for the same thing. It will become apparent that it is not necessary to write all of the contributing structures, which would be tedious, but only to select the most usefully illustrative of them. Ordinarily (*5a* ↔ *5b*) would be written simply as $CH_3CH_2OCH_2^+$, chiefly because in its subsequent reaction with a nucleophile $Y:^-$ the bond is formed to carbon:

$$CH_3CH_2OCH_2^+ + Y:^- \longrightarrow CH_3CH_2OCH_2Y$$

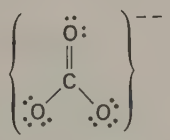
Exercise 1

Why would the formula $CH_3CH_2\overset{+}{\underset{\cdot\cdot}{O}}{=}CH_2$ be a less appropriate choice? In other words, why does the reaction

$$CH_3CH_2\overset{+}{\underset{\cdot\cdot}{O}}{=}CH_2 + Y:^- \longrightarrow CH_3CH_2{-}\underset{\cdot\cdot}{O}(Y){=}CH_2$$

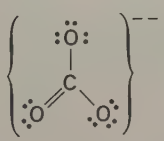
not need to be considered?

Let us examine some additional examples. The carbonate ion, CO_3^{--}, written as a Lewis structure would be



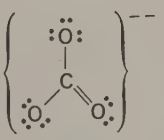
(*7a*)

It is at once apparent, however, that the structures



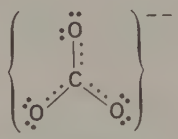
(*7b*)

and



(*7c*)

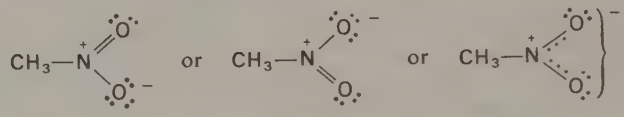
are equally valid, and that all three of the oxygen atoms are identical. A structural formula for CO_3^{--} that corresponds to (6) above is



(7*d*)

which indicates that all of the oxygens are equivalent; each oxygen may be regarded as having $\frac{2}{3}$ of a (−) charge; and the ion has three *identical* C—O bonds and not two C—O bonds and one C=O bond.

The compound nitromethane, CH_3NO_2, may be written as

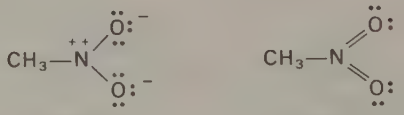


(8*a*) (8*b*) (8*c*)

It is ordinarily written simply as (8*a*) or (8*b*).

Exercise 2

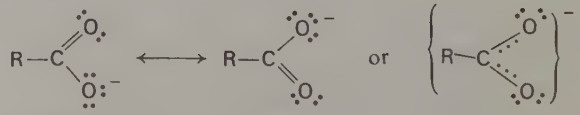
Can you suggest why a structure (8*d*) or (8*e*) would not be included in the description of the resonance hybrid?



(8*d*) (8*e*)

(Note that in all of the structures (8*a*)–(8*e*), all of the electrons of the oxygen atoms are accounted for.)

The carboxylate anion is



(9*a*) (9*b*) (9*c*)

It is ordinarily written simply as $RCOO^-$ or RCO_2^-.

Exercise 3

The structure of methyl nitrite, CH_3ONO, can be written in some detail as $CH_3—\ddot{O}—\ddot{N}=\ddot{O}:$, but more precisely by the contributing structures

$$CH_3—\ddot{O}—\ddot{N}=\ddot{O}: \longleftrightarrow CH_3—\ddot{O}=\ddot{N}—\ddot{O}:$$
$$(a) \qquad\qquad (b)$$

As (*b*) is written, it should also bear a (+) and a (−) charge. Where are these to be placed?

9-3 Resonance stabilization. Delocalization energy

The heat of formation of an organic compound can be measured experimentally. From measurements of the heat of formation of a large number of compounds containing only single bonds and of simple mono-olefins, *bond energies* for C—H, C—C, C—O, C=C, and so on can be calculated.

Calculation of the heat of formation of 1,4-pentadiene (10) by summing the energies of the C—H, C—C, and C=C bonds gives a value identical with the experimental (measured) value.

$CH_2=CH—CH_2—CH=CH_2$ (10) $\qquad$ $CH_3CH=CH—CH=CH_2$ (11)

The isomeric compound, 1,3-pentadiene (11), however, gives a different result. It has been found that 1,3-pentadiene (11) is about 3 kcal/mole *more stable* than 1,4-pentadiene (10). Similar measurements on isomeric dienes and polyenes show that when the double bonds alternate with single bonds, as in (11), added stability, not expressed in simple summation of bond energies, is conferred upon the compound. Double bonds in such a relationship are called *conjugated* double bonds. Conjugation of double bonds is a stabilizing factor because interaction of the electrons of the adjacent C=C bonds permits a degree of delocalization of the electrons over the C=C—C=C system. In the system C=C—CH_2—C=C no such interaction can occur, for the electrons of the double bonds are insulated from each other by the intervening —CH_2— group.*

---

* The structure of the carbon-carbon double bond is described in Section 10-3.

Benzene is a hydrocarbon of the composition C_6H_6. Experimental evidence shows that

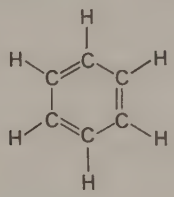
(*a*) it is a symmetrical six-membered ring;

(*b*) all of the carbon-carbon bond distances are identical (there are not three C—C bonds and three C═C bonds);

(*c*) the C—C—C and C—C—H bond angles are all 120°, suggesting that each carbon atom is sp^2 in bonding type;

(*d*) all of the C—H bonds are identical. Only one compound is known for each mono-substituted benzene, C_6H_5X.

The structure of benzene was first written (by Kekulé) as (12), conventionally written as (13):



(12)

(13)

(14)

If we now use this Kekulé structure to *calculate* the heat of formation of benzene by summing the empirical bond energies of six C—H, three C—C, and three C═C bonds, we obtain the value 1287 kcal/mole. The calorimetrically *measured* energy of the heat of formation of benzene is 1323 kcal/mole. Thus, benzene is actually 36 kcal/mole more stable than it would be if it had structure (12).

It should be mentioned that the calculated and experimental values for the heat of formation of 1,4-cyclohexadiene (14) are in excellent agreement. This shows that the disparity found in the values for benzene is not due simply to the fact that the compound is cyclic or that the double bonds are present in a ring.

What, then, is the structure of benzene? The thermochemical evidence is that benzene does not possess the simple Lewis structure (13), yet physical and chemical evidence shows that it is a symmetrical six-membered cyclic compound. The answer is simply that we cannot write a single satisfactory structure for benzene by using conventional valence-bond notation. An improved representation is

(15)

It should be apparent that (15), which shows that benzene is a resonance hybrid, resembles the structure (5) written for the $CH_3CH_2OCH_2^+$ ion. Neither of the indi-

vidual contributing structures is real; the actual structure of the compound (benzene) or ion ($CH_3CH_2OCH_2^+$) is intermediate between them.

The term "resonance" has the unfortunate connotation of movement, or of a relationship between two real entities. Used with a proper appreciation of its true meaning, it is a convenient and generally employed term. But it is more realistic to speak of "delocalization energy." That is, the "resonance energy" of benzene is a measure of the energy that would be required to constrain the six π electrons* to the discrete locations shown in the Kekulé formula.

From time to time attempts have been made to introduce new kinds of symbolism to avoid the inconvenience or ambiguity of writing more than one structure to represent a single compound. For example, benzene is sometimes written as (16) or (17). All of these—(15), (16), and (17)—mean the same thing; it must be kept clearly in mind that they are only representations—they are symbols for *one* compound, benzene.

(16)

(17)

Further comment on representation of the structures of resonance hybrids will be found in Section 9-10.

Exercise 4

The allyl carbonium ion, commonly written simply as $CH_2{=}CH{-}CH_2^+$, is in fact a resonance hybrid. Write the other contributing structure and explain briefly the nature of the charge delocalization.

9-4 Resonance and isomerism

We cannot speak of (8*a*) and (8*b*) as isomers of nitromethane, since neither structure alone represents a substance. Rather, they are *contributing structures* of the hybrid, which *is* nitromethane. In other words, (8*a*) and (8*b*) are symbolic approximations, each of which is, in a sense, a "correction" of the other. Since they involve identical

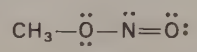
* The disposition of the π electrons in the carbon-carbon double bond is described in Section 10-3.

kinds of bonds, the true nature of the nitro ($—NO_2$) group is that of a perfectly symmetrical group with two identical N—O bonds.

Exercise 5

Do the "bookkeeping" for the electrons in the structures written for nitromethane, and show why the formal positive and negative charges that are shown must be a part of the structures (8*a*), (8*b*), and (8*d*).

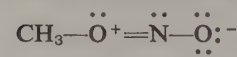
Now we can write another structure with the same empirical composition as nitromethane:



(18)

This is *another compound*, methyl nitrite (the methyl ester of nitrous acid). It is clear that nitromethane and methyl nitrite differ in more than just the way the electrons are distributed; the structural formula for nitromethane cannot be converted into that for methyl nitrite simply by rearranging the disposition of the electrons. In nitromethane, carbon is attached to nitrogen; in methyl nitrite there is a carbon-oxygen bond. The two compounds have quite different atomic arrangements; thus they are isomers. It is one of the conditions for resonance that *the resonance hybrid can be represented only by contributing structures in which the atoms occupy the same or nearly the same relative positions*, and which differ only in disposition of the bonds and unshared electrons.

Exercise 6

Write another contributing structure for the compound methyl nitrite. (ANSWER:  ; account for the charges shown by doing the appropriate "bookkeeping.")

9-5 Stability of carbonium ions

In Chapter 7, before resonance had been considered in detail, some discussion was devoted to the stability of carbonium ions as this related to the S_N1 displacement reaction. This discussion should be studied again in the light of our analysis of the nature

of resonance. We have seen that the S_N1 reactivity of α-chloro ethers in nucleophilic displacement reactions is very high; this can be accounted for by the readiness with which dissociation (solvolysis) occurs to form the carbonium ion, and that dissociation is aided by resonance stabilization of the carbonium ion, by participation of the unshared electron pairs on oxygen in the delocalization of the positive charge.

$$\left\{ R{-}O{-}\overset{+}{C}H_2 \longleftrightarrow R{-}\overset{+}{O}{=}CH_2 \right\} \tag{19}$$

It is significant that α-halogen-substituted ketones, such as bromoacetone (20), react *very slowly by S_N1 displacement mechanisms* (although they are highly reactive by the S_N2 route). We conclude from this that it is energetically *disadvantageous* for the ionization (20) → (21) to occur:

$$\underset{(20)}{CH_3{-}\overset{O}{\overset{\|}{C}}{-}CH_2Br} \underset{\text{solvolysis}}{\rightleftharpoons} \underset{(21)}{\left\{ CH_3{-}\overset{O}{\overset{\|}{C}}{-}CH_2{}^{+} \right\} Br^-}$$

Why is the ion (21) a "poor" carbonium ion? If we realize that the normal carbonyl group (C=O) is a resonance hybrid to which one of the contributing structures bears a positive charge on carbon (C=O ↔ C^+—O^-), we can see that the ion (21) would contain like charges on adjacent atoms. Thus, the normal resonance stabilization of the carbonyl group in (20) would be *diminished* in (21), and, consequently, there would be a *loss* of resonance stabilization in the ionization reaction (20) → (21). The situation cannot be improved by postulating a contribution such as

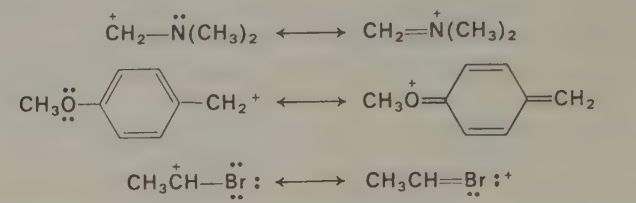
$$\left\{ CH_3{-}\overset{:\ddot{O}}{\overset{\|}{C}}{-}\overset{+}{C}H_2 \longleftrightarrow CH_3{-}\overset{:\ddot{O}^+}{\overset{|}{C}}{=}CH_2 \right\} \tag{22}$$

for this structure would be opposed by the electronegativity difference between oxygen and carbon and could not be a stabilizing factor.

In general, reactions that require passage through an intermediate state in which carbonium (positive) ionic character is created on a carbon atom adjacent to a carbonyl group are slow reactions; they are not aided by resonance. Indeed, the ion $RCOCH_2{}^+$ is energetically *disfavored*, compared with $RCH_2CH_2{}^+$.

In summary, the stability of a carbonium ion depends upon the degree to which the positive charge on carbon can be dispersed by the substituents. The charge delocalization of alkyl carbonium ions such as $(CH_3)_3C^+$ is unique in that it cannot adequately be represented by ordinary valence-bond formulas, except by those of the type shown in Section 9-7. Many other examples of charge delocalization can, however,

be illustrated by conventional valence-bond structures. The case of $ROCH_2^+$ has been described above. Other examples are



(23)

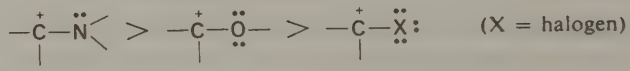
(24)

(25)

It should be borne in mind that the *degree* of such stabilization is not the same in all of these examples, for it depends upon the capacity of the group —X (in the following general expression) to release an electron pair in the manner shown:

(26)

We can make an assessment of the degree of stabilization in (26) by knowing the capacity for —X to yield an electron pair to the electrophilic (electron-deficient) C^+ atom. Since nitrogen is more basic than oxygen, and oxygen more basic than halogen, we may conclude that the order of stabilization of the corresponding three "-onium" ions is



(X = halogen)

9-6 Resonance and bond lengths

If a bond in a compound that is a resonance hybrid of two contributing structures is neither a single nor a double bond, but a hybrid bond, it would be expected to have characteristics different from those of a true single or a true double bond.

Table 9-1
Carbon-carbon single-bond lengths

Substance	*Measured* C—C *bond length* (Å)
ethane	1.54
ethanol	1.55
ethyl mercaptan	1.54
isopropyl bromide	1.54
glycerol	1.54
hexane	1.54
cyclohexane	1.54

One readily measurable characteristic of a bond between two atoms is its length. Measurements of bond lengths can be made by such physical means as X-ray or electron diffraction, and accurate values are available.

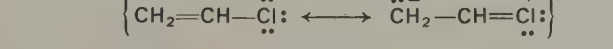
Measurements on many saturated molecules containing carbon-carbon single bonds have shown that the C—C single bond is very close to 1.54 Å in length (Table 9-1).

Similar measurements on substances containing other kinds of bonds have given the values shown in Table 9-2. These values are representative of those that have been obtained by measurements on a great many compounds. With the exception of acetone, each of the compounds in this table can be adequately represented by a single valence-bond formula.

Table 9-2
Typical bond lengths in organic compounds

Substance	*Bond type*	*Bond length* (Å)
ethylene	C=C	1.34 ± 0.02
acetone	C=O	1.22 ± 0.03
dimethyl ether	C—O	1.43 ± 0.03
ethanol	C—O	1.43 ± 0.02
methyl chloride	C—Cl	1.77 ± 0.02
ethylene dichloride	C—Cl	1.78 ± 0.01
methyl bromide	C—Br	1.91 ± 0.06
ethyl bromide	C—Br	1.91 ± 0.02
acetylene	C≡C	1.20 ± 0.01
methylacetylene	C≡C	1.21 ± 0.03

In substances that are resonance hybrids, the measured length of a given bond usually differs from that predicted from any one of the contributing structures. Chloroethylene is found by measurement to have a carbon-chlorine distance of 1.69 Å. This is shorter than the C—Cl bond in such compounds as methyl chloride and ethylene dichloride (1.77 Å), an indication that in chloroethylene the C—Cl bond has some *double-bond character*. The representation of chloroethylene as a resonance hybrid supports this inference:



(27)

Benzene is found to have only one kind of carbon-carbon bond, of length 1.39 Å, intermediate between the C—C single bond (1.54 Å) and the C=C double bond (1.34 Å).

Carbon dioxide possesses a carbon-oxygen bond length of 1.15 Å, suggesting the structure

$$\left\{ \overset{+}{\text{O}} \equiv \text{C} - \overset{-}{\text{O}} \longleftrightarrow \text{O} = \text{C} = \text{O} \longleftrightarrow \overset{-}{\text{O}} - \text{C} \equiv \overset{+}{\text{O}} \right\} \qquad (28)$$

The partial triple-bond character of the C—O bond causes an effective shortening of the bond from the expected (for C=O) 1.22 Å.

Exercise 7

In cyclo-octatetraene, two kinds of carbon-carbon bonds are found: one with a length of 1.50 Å, the other with a length of 1.35 Å. What information does this finding give us about the structure of this compound, in comparison with benzene? The molecule is not planar.

Exercise 8

Biacetyl (2,3-butanedione) is found to have a carbon-oxygen bond length of 1.20 Å, a CH_3—C length of 1.54 Å, and a $\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{O}}{\|}}{\text{C}}$ length (carbon-carbon) of 1.47 Å. From these values, and with the aid of Tables 9-1 and 9-2, write a probable important contributing structure.

CH_3—C bond lengths for a number of acetylenic compounds are given in Table 9-3. The shortening of the bond distance from 1.54 Å (ordinary single bond) to

Table 9-3
Carbon-carbon single-bond lengths in alkynes

Alkyne	*Bond type*	*Bond length* (Å)
$CH_3C{\equiv}CH$	CH_3—C	1.46
$CH_3C{\equiv}CCH_3$	CH_3—C	1.47
$CH_3C{\equiv}CCH_2CH_3$	CH_3—C	1.47, 1.54
$CH_3C{\equiv}C{-}C{\equiv}CCH_3$	CH_3—C	1.47

the observed 1.47 Å indicates that the CH_3—C bond has some double-bond character, and thus that structures such as

$$\left\{ {}^{+}HCH_2{=}C{=}\ddot{C}H^{-} \longleftrightarrow CH_3{-}C{\equiv}CH \right\} \tag{29}$$

contribute. This kind of participation of the σ-bond electrons of the C—H bond in overlap with the π orbitals of the triple bond is known as *hyperconjugation*. Hyperconjugation is also encountered in other situations in which σ-bond electrons can be utilized by an adjacent electron-deficient atom. The resonance stabilization of the *tert*-butyl carbonium ion is a case in point.

9-7 Resonance as a factor in chemical reactions

The addition of HBr to propylene leads by the ionic mechanism to 2-bromopropane, a result that can be accounted for by the two-stage nature of the addition reaction. That the protonation of propylene at the first stage leads to (30) rather than (31) can be accounted for by noting that the secondary carbonium ion (30) is stabilized by the contribution of six additional structures, whereas the primary carbonium ion (31) has only two additional contributing structures:

$$CH_3\overset{+}{C}HCH_3 \longleftrightarrow CH_3CH{=}CH_2\overset{+}{H} \longleftrightarrow \text{5 more} \tag{30}$$

$$CH_3CH_2\overset{+}{C}H_2 \longleftrightarrow CH_3\overset{H^+}{C}H{=}CH_2 \longleftrightarrow \text{1 more} \tag{31}$$

No one of the structures (30) or (31) can be regarded as the significant stabilizing contribution, but since (30) and (31) are of the same kind, and since there are more structures like (30), we can conclude that (30) is a "better" carbonium ion than (31). Thus, the 2-bromo compound is formed.

As we pointed out earlier, stabilizing effects of this kind exert their effect upon reaction rate by influencing the stability of the transition state, and thus the activation energy. An energy diagram for a case comparable to that just described was shown in Figure 9-1. It must be emphasized that although the discussion there, and in this section, has been concerned with the structure and stability of the *intermediate* carbonium ions and not with that of the transition state itself, the stabilization of the latter is subject to the same structural factors that affect the stability of the intermediate to which it leads. Consequently, most discussions of relative stabilities of transition states are based upon the structures of the closely related intermediates. This approach is generally valid and leads to the correct conclusion.

It is very interesting to note that the addition of HBr to $CH_2{=}CHCF_3$ takes

place in the opposite direction to that which Markovnikov's rule (Section 10-12) would predict:

$$CH_2{=}CHCF_3 \xrightarrow{HBr} BrCH_2CH_2CF_3 \qquad \text{not} \quad \overset{\overset{Br}{|}}{CH_3CHCF_3} \tag{32}$$

On the basis of the same arguments we have used to account for the manner of addition of HBr to propylene, we would conclude from this result that the ion (33) must be a more stable product of the protonation of $CH_2{=}CHCF_3$ than the ion (34):

$$\overset{+}{C}H_2CH_2CF_3 \qquad\qquad CH_3\overset{+}{C}HCF_3$$
$$\text{(33)} \qquad\qquad \text{(34)}$$

Why is (33) "better" (more stable) than (34)? Because of its great electronegativity, fluorine has a powerful inductive effect (see Section 23-2), which decreases the electron density on the carbon atom of $-CF_3$, giving it a good deal of positive character. Thus (34), in which the carbonium-carbon atom is adjacent to the electron-deficient carbon atom of the $-CF_3$ group (two adjacent positively-charged atoms), is less stable than (33). Thus Markovnikov's rule is "violated," but for a readily discernible reason.

Exercise 9

How would you expect HI to add to the ion $(CH_3)_3N^+CH{=}CH_2$? Would $(CH_3)_3N^+CH_2CH_2I$ or $(CH_3)_3N^+\overset{\overset{I}{|}}{C}H{-}CH_3$ be formed?

9-8 Conjugate addition to dienes

When chlorine is added to 1,3-butadiene, a mixture of two dichlorobutenes is formed. These are the result of "1,2-addition" (35) and "1,4-addition" (36):

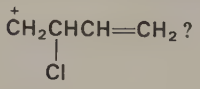
$$CH_2{=}CH{-}CH{=}CH_2 + Cl_2 \longrightarrow \underset{\text{(35)}}{ClCH_2\overset{\overset{Cl}{|}}{C}HCH{=}CH_2} + \underset{\text{(36)}}{ClCH_2CH{=}CHCH_2Cl}$$

This result can be accounted for by invoking considerations of resonance along with the recognized mechanism of halogen addition. The initial attack of chlorine on the diene would lead to the intermediate (37):

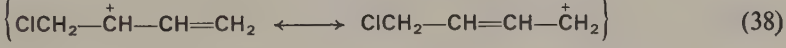
$$CH_2{=}CH{-}CH{=}CH_2 + Cl_2 \longrightarrow \underset{\text{(37)}}{\left\{ClCH_2{-}\overset{+}{C}H{-}CH{=}CH_2\right\}Cl^-}$$

Exercise 10

Why would (37) be formed rather than the alternative

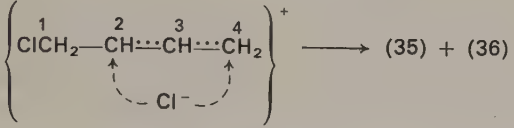


The ion (37) can be seen to be a resonance hybrid, more properly represented by the contributing structures



(38)

Whatever the relative importance of the two structures of (38), it is clear that *the positive charge is delocalized* over the three-carbon system C⋯C⋯C, and thus a chloride ion can attack either at carbon 2 or at carbon 4:



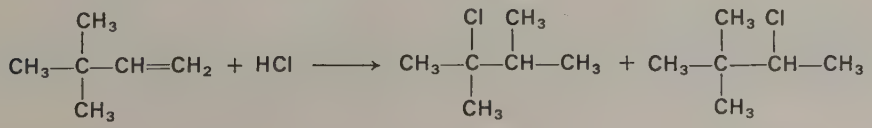
The fact that (35) and (36) are both produced, in varying proportions, is a result of subtle factors that we shall not enter into here, but it is readily explained in terms of the resonance concept. The proportion (35)/(36) depends upon the reaction conditions.

Exercise 11

When HCl is added to 2-methyl-1,3-butadiene (isoprene) the only 1,4-addition product obtained is 1-chloro-3-methyl-2-butene. Can you explain why 1-chloro-2-methyl-2-butene is not formed? HINT: Examine the structures of the protonated intermediates that would give rise to these two compounds.

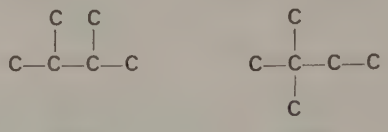
9-9 Carbonium ion rearrangements

When HCl is added to *t*-butylethylene the product is, surprisingly, a mixture of 2-chloro-2,3-dimethylbutane (39), and the compound that would normally be expected, namely, 2-chloro-3,3-dimethylbutane (40):



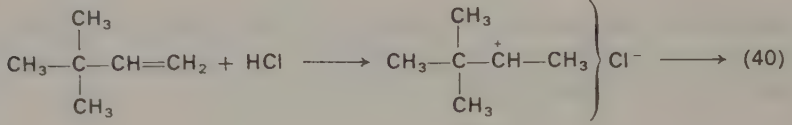
(39) (40)

It is evident that in the formation of (39) a rearrangement of the carbon skeleton has occurred; (39) has the carbon skeleton (41) and (40) has the skeleton (42):



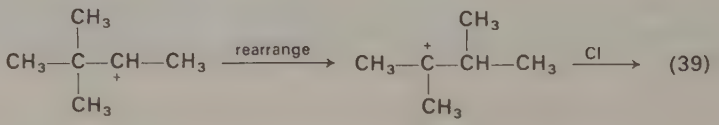
(41) (42)

We may write the first step in the reaction, as usual, as the protonation of the olefin. This would be expected to produce the ion (43), which is the immediate precursor of (40):



(43)

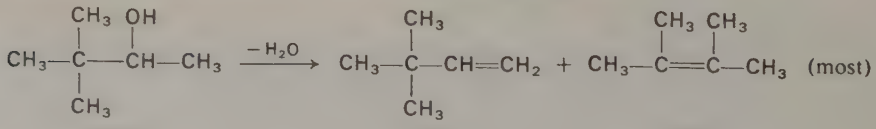
The secondary carbonium ion (43) is, however, less stable than the ion (44), produced by a migration of one of the $—CH_3$ groups to the carbon atom adjacent to it, which bears but six (a sextet) of electrons:



(44)

The *tertiary* carbonium ion (44) is more stable than the *secondary* carbonium ion (43). Thus the gain in resonance energy encourages the rearrangement.

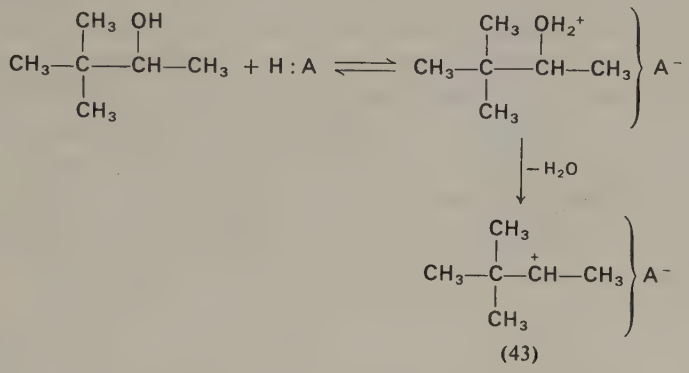
A related rearrangement is observed when an attempt is made to dehydrate the alcohol *t*-butylmethylcarbinol (45). The "normal" dehydration to (46) occurs to a minor extent; the major product is the rearranged olefin (47):



(45) (46) (47)

This rearrangement may be explained in the same way as the rearrangement that occurs upon the addition of HCl to *t*-butylethylene. In the acid-catalyzed dehydration

of (45), the first steps involve the protonation of the alcohol and formation of the carbonium ion (43):



(43)

The loss of a proton from (43), without rearrangement, would give (46). But the secondary carbonium ion, as we have seen in the previous case, rearranges to form the more stable tertiary carbonium ion (44). Loss of a proton from (44) leads to the rearrangement product, the olefin (47).

Exercise 12

What isomeric olefin, of the same carbon skeleton as (47), would you expect to find along with (46) and (47)? This third olefin is actually found as another (minor) product of the acid-catalyzed dehydration of (45).

9-10 Terminology and representation of structures

Most of the structural formulas written by organic chemists are convenient symbolic representations, quite adequate for the communication of ideas under discussion. The usual formulas, containing conventional single, double, and triple bonds, are referred to as *Lewis structures*; they embody the normal concepts of valency and represent atoms C, H, N, O, and the halogens with complete octets of electrons.

We have seen in this chapter that many Lewis formulas are arbitrary; but it is accepted usage, as a concession to convenience, to write a single structure for a compound that is a resonance hybrid. The student should accept as a matter of course that it is only seldom, and for special reasons, that more than one structure is written for compounds that are in fact resonance hybrids. Thus, $CH_3CH_2OCH_2^+$ is

an adequate representation even though we have learned that the compound is the hybrid (*5a* ↔ *5b*).

For the same reason the Kekulé formula for benzene is preferable to (and often superior to) the structure in which a circle is used to show the delocalized π electrons. It will also be noticed that a circle denotes a *symmetrical* delocalization, and therefore is "correct" only for benzene itself or for a symmetrically substituted benzene ring. A single substituent on a benzene ring, by altering the nature of the electron delocalization, would require that a distorted "circle" be used. It is obvious that this could become tedious. We shall use the Kekulé symbol throughout (except that occasionally, in non-benzenoid rings of special kinds, a symbol for symmetrical delocalization may be used).*

Problems

1. Write two permissible electronic structures for each of the following:
   (*a*) methyl vinyl ether $CH_2{=}CH{-}O{-}CH_3 \leftrightarrow \bar{C}H_2{-}CH{=}\overset{+}{O}{-}CH_3$), (*b*) methyl formate, (*c*) boron tribromide, (*d*) acetate ion, (*e*) acetamide, (*f*) acrolein (propenal), (*g*) methyl azide (CH_3N_3), (*h*) nitrate ion, (*i*) nitrous acid, (*j*) acetaldehyde.
2. Guanidine is a strong base, in part because of the high degree of resonance stabilization in the symmetrical guanidinium ion, $\overset{+}{N}H_2{=}C(NH_2)NH_2$. Write the contributing forms of the resonance hybrid, showing all of the unshared electron pairs in the structures.
3. Given the data in Tables 9-1 and 9-2, account for the bond lengths observed in the following compounds:

   (*a*) $HC{\equiv}\overset{a}{C}{-}\overset{b}{C}{\equiv}C{-}CH_3$ C—C (a) 1.38 Å; C—C (b) 1.46 Å

   (*b*) $CH_3{-}\overset{\displaystyle O}{\overset{\|}{\underset{a}{C}}}{-}\underset{b}{O}{-}CH_3$ C—O (a) 1.36 Å; O—C (b) 1.46 Å

   (*c*) CH_3CN C—C 1.49 Å

   (*d*) $CH_2{=}\underset{a}{CH}{-}\underset{b}{CHO}$ C—C (a) 1.36 Å; C—C (b) 1.46 Å

   (*e*) $CH_2{=}\underset{a}{CH}{-}CH{=}CH_2$ C—C (a) 1.46 Å

4. Can you account for the greater acidity of the hydroxyl group of $CH_3{-}\overset{OH}{\overset{|}{C}}{=}CHCOOEt$ than of the hydroxyl group of $CH_3\overset{OH}{\overset{|}{C}}HCH_2COOEt$? (NOTE: Examine these two structures carefully so that the difference between

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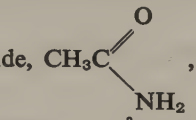
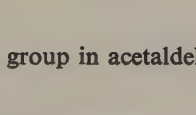
* A useful discussion of this subject will be found in an article by W. Baker, *Proceedings of the Chemical Society, 1959*, p. 75.

them is clear. The first is the enol form of ethyl acetoacetate, the second is ethyl β-hydroxybutyrate.)

5. Nitromethane dissolves in alkali to form a sodium salt, $NaCH_2NO_2$. Write the electronic structure of this salt, indicating the resonance in the anion.

6. State in *words* what is meant by the terms (*a*) resonance hybrid, (*b*) resonance stabilization, (*c*) contributing structures, and (*d*) resonance energy.

7. Make a sketch showing the approximate spatial relationship between the C, O, H, and N atoms in acetamide,  , given the information that the C—N bond distance is about 0.15 Å less than the C—N bond distance in methylamine.

8. The hydrogen atoms of the methyl group in acetaldehyde,  , have a readily recognizable degree of acidic character. This can be attributed to the fact that the ion $(:CH_2CHO)^-$ derived from acetaldehyde is resonance-stabilized. Show this resonance by drawing the electronic structures involved. What prediction can you make regarding the acidity of the methyl-group hydrogen atoms in crotonaldehyde, $CH_3CH{=}CHCHO$?

9. Explain the difference between the effects of resonance stabilization upon reaction rates and upon equilibrium.

10. Which of each of the following pairs would be the more resonance-stabilized? Explain briefly.
    (*a*) $(CH_3)_2NCH_2^+$ or $(CH_3)NCH_2CH_2^+$
    (*b*) $CH_3CH{=}CHCH_2^+$ or $CH_2{=}CHCH_2CH_2^+$
    (*c*) $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2:^-$ or $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2:^-$

10

The carbon-carbon multiple bond. Alkenes and alkynes

Organic chemistry can be presented in a number of ways, no one of which is superior in all respects to the others. One of these is to discuss compounds in terms of the *functional groups* they contain: double bonds, hydroxyl groups, amino groups, carbonyl groups, and so on. Another is to discuss organic compounds as *classes*; alkenes (olefins), alcohols, aldehydes, carboxylic acids, and so on.

In this chapter one of the principal groups of organic compounds, the unsaturated compounds, is considered as a class; but it will be recognized that the chemical behavior of these compounds is characteristic of their principal functional groups: the carbon-carbon double bond (in alkenes) and the triple bond (in alkynes, or acetylenes). The carbon-carbon multiple bond is a ubiquitous structural unit that occurs throughout organic chemistry, even in many compounds that are not classed as alkenes or alkynes. Nevertheless, much of the chemistry of unsaturated alcohols, amines, ketones, and so on is best understood after study of the simpler unsaturated compounds.

Another feature of olefinic (unsaturated) compounds, already alluded to in Chapter 6, is the stereoisomerism of the double bond. *Cis*- and *trans*-stereoisomeric alkenes are usually quite different in chemical behavior. An important aspect of the stereochemistry of unsaturated compounds is the effect of this difference upon

biological properties. Many unsaturated compounds are of great biological importance; among them are vitamin A, the sex-attractants of insects, and many compounds of intermediate metabolism. Most of these are active in only one of the possible geometrically isomeric forms, demonstrating again—as in the case of molecular dissymmetry—the strict spatial requirements for the action of a substrate in a biological system.

10-1 Unsaturated compounds

Organic compounds that contain carbon-carbon double bonds (C=C) or triple bonds (C≡C) are *unsaturated* compounds, so called because they are able to undergo reactions in which *addition* to the double or triple bond takes place. Saturated compounds, which include such hydrocarbons as ethane and the homologous alkanes, as well as cyclic compounds that contain only single bonds, such as cyclohexane, do not undergo addition reactions. The "saturation" of a double bond is ordinarily construed to mean the addition of hydrogen, but addition reactions of many other kinds are known.

The simplest compounds containing the carbon-carbon double bond are hydrocarbons known as *olefins*, or by the IUPAC* term *alkenes*. Acetylenes, or *alkynes*,

Table 10-1
The boiling points of some olefins and their saturated analogues

Olefin	*B.p.* (°C)	*Related nonolefin*	*B.p.* (°C)
$CH_2{=}CH_2$	−103.9	CH_3CH_3	−89.0
$CH_3CH_2CH{=}CH_2$	−6.3	$CH_3CH_2CH_2CH_3$	0.6
$CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$	93	$CH_3(CH_2)_5CH_3$	98
	83		81
	41		51
	45	—	—
$CH_2{=}CHCH_2Br$	71	$CH_3CH_2CH_2Br$	71
$CH_2{=}CHCOOH$	142	CH_3CH_2COOH	141
$CH_3CH{=}CHCH_2OH$	121	$CH_3CH_2CH_2CH_2OH$	118

* International Union of Pure and Applied Chemistry. See Appendix A.

contain the carbon-carbon triple bond. Compounds containing two or more double or triple bonds are named in ways that are illustrated in Sections 10-2 and A-5.

The reactivity of olefins is due chiefly to the chemical properties of the double bond. The lower members of the series, produced in large quantities by the petroleum industry, are valuable raw materials for the industrial synthesis of alcohols, ethers, aldehydes, ketones, polymers and plastics, and organic halogen compounds. The double bond, which is a structural feature of many kinds of organic compounds, is a point of attack upon a molecule; it permits the controlled degradation of the compound by oxidizing agents and the alteration of the structure of the compound by chemical manipulation that makes use of the reactivity of the double bond.

The physical properties of olefinic compounds resemble those of the corresponding saturated compounds. The carbon-carbon double bond has no marked effect upon boiling point, although it does increase water solubility to some degree, probably because the greater electron density at the double bond permits some degree of association with the dipolar water molecules. In Table 10-1 are given the boiling points of a few representative olefinic compounds, along with those of the corresponding saturated hydrocarbons. It is apparent that the double bond has no profound effect upon this property.

10-2 Nomenclature of unsaturated compounds

Most of the simpler olefins and acetylenes bear trivial names. The most suitable names for unsaturated compounds are the IUPAC names, in which the endings *-ene*, for the double bond, and *-yne* for the triple bond, are used. The IUPAC name is based upon the longest chain that bears the multiple bond. Substitution names are also used (see Table 10-2).

It should be noted that when *cis* and *trans* isomers can exist, the designation should be included in the name. Thus, formula 4 is a nonexplicit formula for *cis*-2-butene or *trans*-2-butene.

In writing structural formulas for unsaturated compounds, a number of conventions can be used. These have been described earlier (Section 3-19) and several of them will be used as convenience requires in the discussion to follow.

10-3 The structure of the carbon-carbon double bond

Physical measurements of simple olefinic molecules reveal the following:

1. In ethylene, the four hydrogen and two carbon atoms lie in a single plane, with a C═C—H angle of about 122°, and a H—C—H angle of about 116°. These angles suggest that the two carbon atoms carry sp^2 bonds.

Table 10-2
Names of some unsaturated compounds

Compound	*Name*
1. $CH_2{=}CH_2$	ethylene ethene *
2. $CH_3CH{=}CH_2$	propylene propene *
3. $CH_3CH_2CH{=}CH_2$	1-butene *
4. $CH_3CH{=}CHCH_3$	2-butene *
5. $(CH_3)_2C{=}CH_2$	isobutylene methylpropene *
6. $CH_3CH{=}CHCH_2CH_2CH_3$	2-hexene *
7. $CH_2{=}C(CH_2CH_3)CH_2CH(CH_3)$	2-ethyl-5-methyl-1-hexene *
8. $CH_2{=}CHBr$	vinyl bromide bromoethene *
9. $CH_2{=}CHOCH_3$	methyl vinyl ether
10. $CH_2{=}CHCH_2Cl$	allyl chloride 3-chloro-1-propene *
11. $(CH_3)_2C{=}C(CH_3)_2$	tetramethylethylene
12. $HC{\equiv}CH$	acetylene ethyne *
13. $CH_3C{\equiv}CH$	methylacetylene propyne *
14. $CH_2{=}CH{-}CH{=}CH_2$	1,3-butadiene *
15. $CH_2{=}CH{-}C{\equiv}CH$	vinylacetylene 1-buten-3-yne * (*or* but-1-en-3-yne)
16. $CH_3CH{=}CH{-}CH{=}CH{-}CH{=}CH_2$	1,3,5-heptatriene *

* Systematic (IUPAC) names. The unstarred names are substitution names. See Appendix A.

Other simple olefins show similar though not identical values:

$(CH_3)_2C{=}C(CH_3)$	$CH_3{-}C{-}CH_3$	angle 112°
$CH_3CH{=}CH_2$	$CH_3{-}C{=}C$	angle 125°
$ClCH{=}CH_2$	$Cl{-}C{=}C$	angle 123°

2. The ethylene carbon-carbon distance is 1.34 Å, considerably shorter than the single-bond length of 1.54 Å.

Chemical evidence provides further information:

3. The disposition of the groups attached to the double bond is rigid; that is, there is no "free rotation" about the double bond.

4. The olefinic double bond is a *nucleophilic center*; it is characteristically reactive toward electrophilic reagents such as strong hydrogen (Brønsted-Lowry) acids, halogens, and other electron-deficient centers.

All of these qualities can be accounted for by a model of the double bond of ethylene constructed by joining two sp^2-hybridized carbon atoms with a single (σ) bond, and utilizing the two remaining electrons (one on each carbon) in a second (π) orbital symmetrically disposed above and below the plane of the molecule (Figure 10-1).

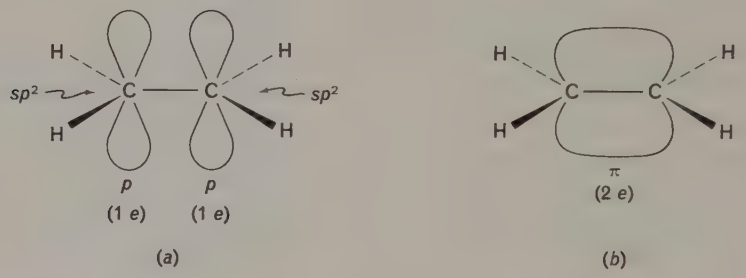


Figure 10-1
(*a*) The ethylene molecule before π-bond formation, each carbon atom with sp^2-hybridized bonds and containing a single unpaired electron. (*b*) Normal ethylene molecule with single electrons paired in a molecular π orbital.

Several things are now apparent: (1) the planar (and trigonal) sp^2 bonds of both carbon atoms must be in one plane to permit effective overlap of the remaining p orbitals, which are at right angles to the sp^2 plane; (2) in order to rotate the $—CH_2$ groups it would be necessary to provide sufficient energy to break the π bond; (3) the electrons of the π bond are more accessible to electrophilic attack than those of an $sp^3—sp^3$ bond, for they lie outside of the region of the axis joining the two carbon atoms; and (4) since the σ bond of ethylene has more s character than an sp^3 (single) bond, the electrons are closer to the carbon nucleus, making the C=C bond of ethylene somewhat shorter than the C—C bond of ethane.

All of these conclusions are in accord with the physical and chemical properties noted above: the ethylene molecule is planar, it is configurationally stable, and it is nucleophilic in character.

It should be noted that the *degree* of nucleophilicity of an olefinic double bond is low, since the electron pair available to an attacking electrophile is not an unshared pair, but is a bonding pair in a stable π orbital. Thus, olefinic compounds react with strongly electrophilic reagents such as strong acids, Lewis acids, or electron-deficient centers in other molecules or ions.

10-4 The stereochemistry of the carbon-carbon double bond. *Cis-trans* isomerism

Since the electronic distribution between the carbon atoms is not cylindrically symmetrical, the carbon atoms are not free to rotate with respect to one another. Thus, if the carbon atoms joined by the double bond hold groups other than hydrogen, as in 2-butene, there are two possible ways in which these substituents can be arranged. These are shown for two representative olefinic compounds in Figure 10-2.

Such *cis-trans isomers* are distinct compounds. They have different chemical properties and different physical properties, such as boiling points, densities, and refractive indices. In order to convert one into the other, sufficient energy must be supplied to the molecule to break one of the bonds of the double bond (that is, to destroy the overlap of one pair of orbitals). It is found that the more stable of the two 2-butenes is the *trans* compound, for in this configuration the mutual interference of the two methyl groups is minimal.

Cis-trans isomerism is commonly encountered among unsaturated compounds; both isomers are known for many such compounds.

Since the electrons of the double bond are not confined to the region close to the

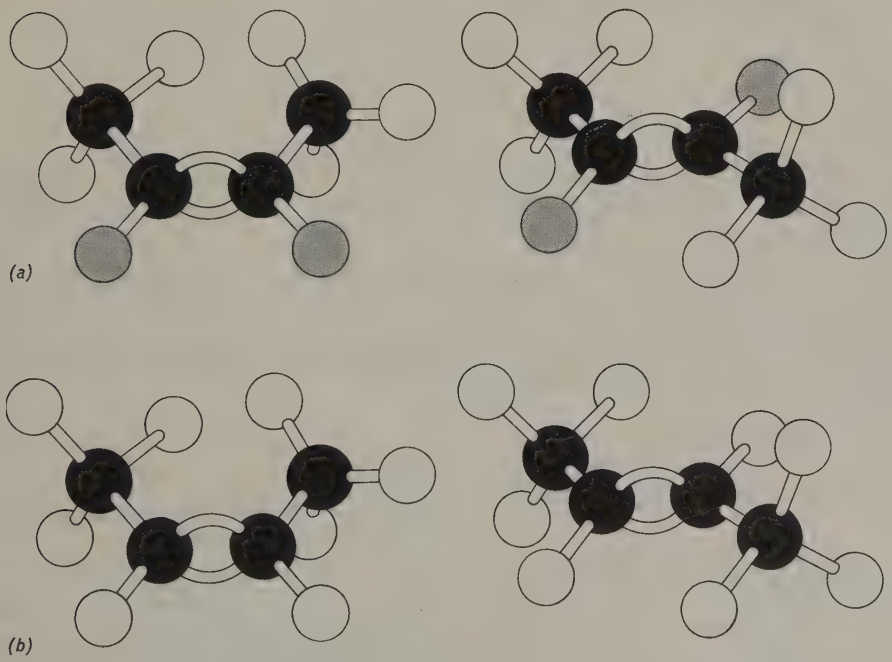
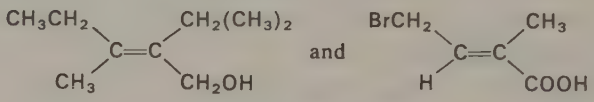


Figure 10-2
Ball-and-stick models of (*a*) *cis*- and *trans*-2,3-dibromo-2-butene ($CH_3CBr{=}CBrCH_3$) and (*b*) *cis*- and *trans*-2-butene ($CH_3CH{=}CHCH_3$).

axis joining the two carbon atoms, the molecule is accessible to attack by electron-seeking reagents. Thus, one of the two pairs of electrons of the double bond is available for combination with the reagent, leaving the two carbon atoms joined by the remaining electron pair, which forms a carbon-carbon single bond in the final addition product.

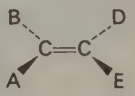
10-5 Nomenclature of *cis-trans* isomers

In many cases the designation of configuration at a double bond by the *cis-trans* system of nomenclature becomes ambiguous; two examples in which the meaning of *cis* or *trans* would not be readily apparent are



A recently proposed method for specifying the configuration of olefinic compounds, called the *EZ system*, is the following:

1. Consider an olefin of the general structure

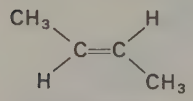


First, assign "priorities" to the atoms or groups A, B, D, and E according to the Cahn-Ingold-Prelog RS system of nomenclature for optically active compounds (this was described in Chapter 6).

2. If B and D, or A and E, have the highest priority, the compound bears the designation Z (German: *zusammen*, together).

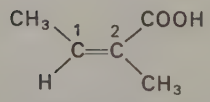
3. If B and E, or A and D, have the highest priority, the compound bears the designation E (German: *entgegen*, opposite).

Some examples follow:



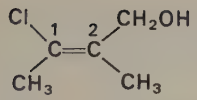
(E)-2-butene

In cases like this, where no ambiguity exists, the term *trans* is usually applied.



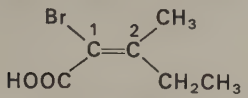
(Z)-2-methyl-2-butenoic acid

at C-1, higher priority is CH_3
at C-2, higher priority is COOH



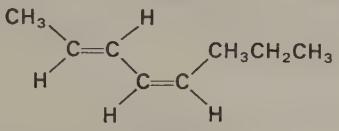
(Z)-2-methyl-3-chloro-2-butene-1-ol

at C-1, higher priority is Cl
at C-2, higher priority is CH_2OH



(E)-2-bromo-3-methyl-2-butenoic acid

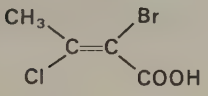
at C-1, higher priority is Br
at C-2, higher priority is CH_2CH_3

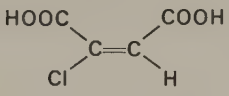


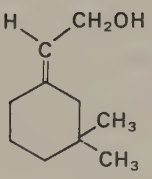
(E,Z)-2,4-heptadiene

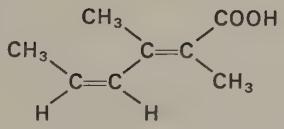
Exercise 1

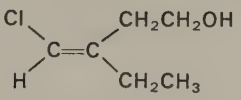
Name the following compounds by the EZ system.

(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*) 

10-6 Methods of preparing olefinic compounds. Introduction of the carbon-carbon double bond

The low-molecular-weight olefins (C_1 to C_4) are produced in large amounts as by-products of the refining of petroleum. In 1972, 2×10^7 tons of ethylene were produced, most of this serving as a starting material for the synthesis of ethanol, ethylene glycol, polythene, and other industrial chemicals.

The preparation of olefinic compounds of more complex structure can be accomplished by a wide variety of methods. The principal reaction that serves as a

means of introducing the double bond is the *elimination* reaction. In the most general terms this can be represented as

$$\underset{\text{(A base)}}{B:^-} + -\overset{|}{\underset{H}{C}}-\overset{|}{\underset{X}{C}}- \longrightarrow -C{=}C- + X^- + HB \qquad (1)$$

Elimination reactions of many kinds are known; they differ in the details of their mechanism, in the stereochemistry of the starting materials and products, and in the nature of the group X in the above expression.

Dehydration of alcohols (X = OH). This is a very general method, with the special advantage that alcohols of a wide variety of structures are readily prepared; for example, by the Grignard reaction (Section 11-12) or by the reduction of carbonyl compounds.

The practical limitations on the production of olefinic compounds by the dehydration of alcohols are:

(*a*) If elimination can occur in more than one way, a mixture of olefinic products may result, the proportions of which are dependent upon the conditions of the reaction:

$$CH_3CH_2\overset{OH}{\overset{|}{C}}HCH_3 \xrightarrow[\Delta]{H_2SO_4} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2 \qquad (2)$$

(*b*) Ethers may be formed as by-products:

$$RCH_2CH_2OH \xrightarrow[\Delta]{H_2SO_4} RCH{=}CH_2 + (RCH_2CH_2)_2O \qquad (3)$$

(*c*) Rearrangement may occur, either as the principal reaction or as a side reaction:

$$(CH_3)_3\overset{OH}{\overset{|}{C}}CHCH_3 \xrightarrow{H_2SO_4} (CH_3)_3\overset{+}{C}CHCH_3 \longrightarrow (CH_3)_2\overset{+}{C}CH(CH_3)_2$$

$$\longrightarrow (CH_3)_2C{=}C(CH_3)_2 + CH_2{=}\overset{CH_3}{\overset{|}{C}}{-}CH(CH_3)_2 \qquad (4)$$

Although the products of the acid-catalyzed dehydration of an alcohol may consist *chiefly* of a single product, the presence of by-products may be undesirable or may necessitate time-consuming purification procedures.

Special methods of dehydration of alcohols that obviate rearrangements are known and are described in a later chapter.

Dehydrohalogenation of alkyl halides (X = halogen). Treatment of alkyl halides with strong alkali (for example, alcoholic KOH) results in the elimination of HX. The ease of removal of HX is greatest with tertiary halides, least with primary halides. Side reactions include nucleophilic substitution to form the corresponding alcohol or ether; these are most prominent in the case of primary halides, and do not occur with tertiary halides.

$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[KOH]{alc.} CH_3CH{=}CHCH_3 \qquad (5)$$

$$CH_3CH_2CH_2CH_2Br \xrightarrow[KOH]{alc.} CH_3CH_2CH{=}CH_2 \qquad (6)$$

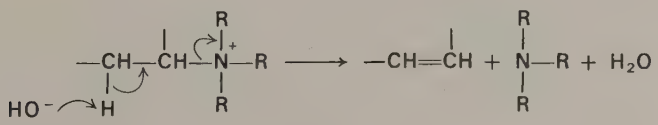
A related reaction is also useful, in which X is the readily displaced sulfonic acid ester grouping.

$$C_6H_5CH_2CH_2OSO_2CH_3 \xrightarrow[KOH]{alc.} C_6H_5CH{=}CH_2 + \overset{+}{K}\overset{-}{O}SO_2CH_3 \qquad (7)$$

The Hofmann elimination reaction ($X = \overset{+}{N}R_3$). Reaction of hot concentrated alkali with a quaternary ammonium salt (Section 16-4) that contains a hydrogen atom in the β position to the $-\overset{+}{N}R_3$ group results in the elimination of the tertiary amine NR_3:

$$OH^- + RCH_2CH_2\overset{+}{N}R_3' \longrightarrow RCH{=}CH_2 + NR_3' + H_2O \qquad (8)$$

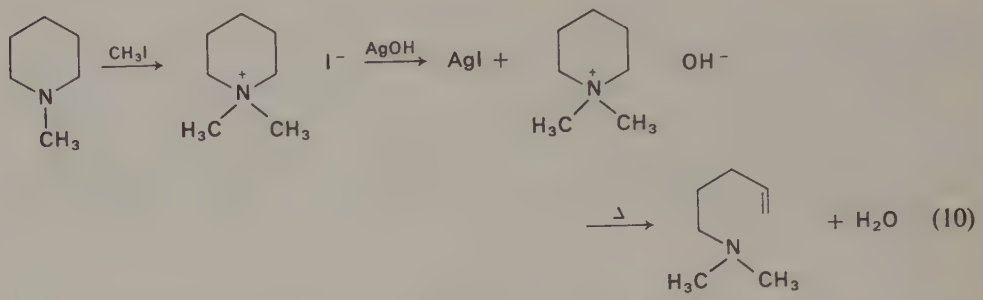
This, the *Hofmann elimination*, is extensively used to degrade amines, for it results in the introduction of a double bond to which subsequent oxidative attack may be directed. Its most frequent application is in proving the structures of the natural amines known as alkaloids. The details of the reaction are shown in the partial formulation



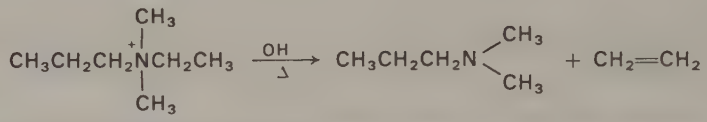
(9)

and a representative example is the following, in which the quaternary ammonium

compound is prepared by alkylation of a tertiary amine. Since the amine is cyclic, the elimination reaction simply opens the ring:

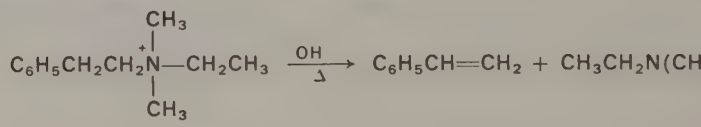


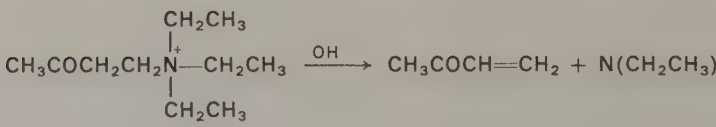
A characteristic feature of the Hofmann elimination is that in most cases the *least substituted* olefin is formed. Application of the reaction to the following compound proceeds as shown:



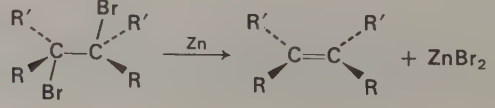
It is clear that this elimination could proceed in two ways: to give ethylene (as shown), or to give propylene. Only the former course is observed.

When the β hydrogen atom is of enhanced acidic character ("activated" by a substituent), the Hofmann "rule" does not apply:





Dehalogenation of 1,2-dihalides. Treatment of a 1,2-dibromoalkane with metallic zinc in a suitable solvent (such as ethanol) results in the removal of the halogen with the formation of a zinc bromide and the olefin:



This method has special uses. A carbon-carbon double bond may be "protected" by the addition of bromine while a reaction is carried out at some other center in the molecule. The double bond may then be regenerated by reaction with zinc. As equation (15) shows, the reaction is stereospecific.

Other methods of olefin synthesis. The synthesis of olefins by means of the Wittig reaction is described in Section 20-4.

The pyrolysis of amine oxides can be used as a method of preparing olefins (Section 16-9).

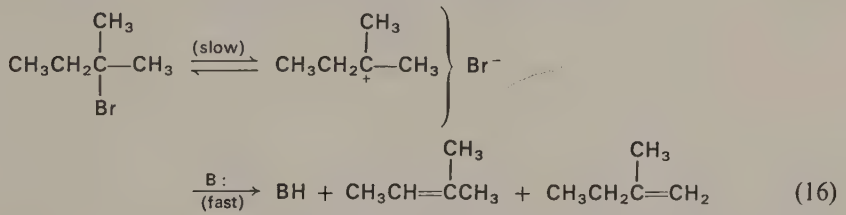
Partial reduction of alkynes is a stereospecific method for the preparation of *cis*-olefins (Section 10-14).

10-7 Mechanisms of β-elimination reactions

Depending upon the structure of the alkyl halide and the experimental conditions, β-elimination reactions may proceed by any of several mechanistic pathways.

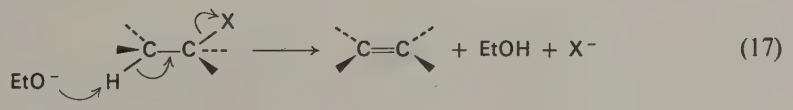
E1 (*unimolecular*) *eliminations* are characteristic of compounds in which the atom or group X can undergo initial ionization to yield a stabilized carbonium ion. Proton removal then follows as a fast reaction.

The E1 mechanism is characteristic of tertiary alkyl halides:



E1 eliminations follow what is known as the *Saytzeff rule*; namely, the formation of the most highly substituted olefin is favored.* Evidence for this mechanism is kinetic: since the rate-determining ionization step does not involve the base, the rate of the overall elimination reaction depends only upon the concentration of the alkyl halide.

E2 (*bimolecular*) *eliminations* occur by the simultaneous attack of the proton-acceptor (the base) and loss of the departing group (X). This concerted process may be represented as follows:



* Acid-catalyzed dehydration of alcohols, an elimination reaction of the E1 type, also leads to the most highly substituted olefin. However, see Section 10-8.

E2 eliminations are favored by increase in the concentration of the base, and are typical of primary and secondary halides.

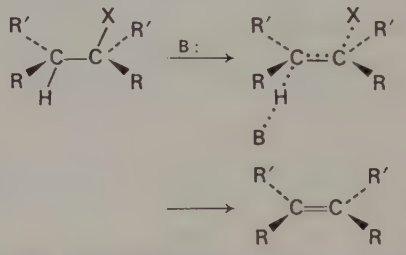
A third mechanism (E1cB) involves a preliminary ionization (removal of the β hydrogen atom by the base) followed by elimination of X^-. This process occurs when the β-carbanion formed is stabilized by structural features. A typical case is that in which the carbanion is adjacent to a carbonyl group:

$$RCOCH_2CH_2X \xrightarrow{OEt^-} \left\{RCO\ddot{C}\bar{H}CH_2X\right\} \longrightarrow RCOCH{=}CH_2 + X^- \qquad (18)$$

Elimination reactions of this kind proceed with exceptional ease. Mild bases (for example, acetate ion) are often effective.

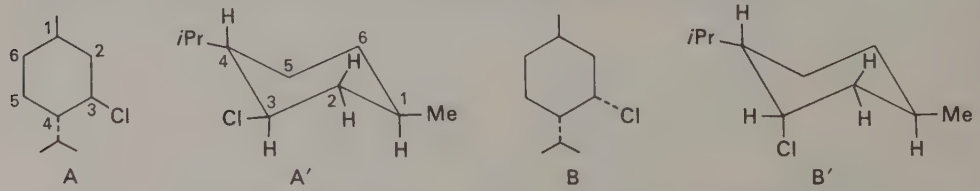
10-8 Stereochemistry of elimination reactions

The E2 elimination takes place most readily when the four atoms H—C—C—X are coplanar or can become coplanar, so that the reaction proceeds through a transition state in which bond-breaking and bond-making take place in a smooth, concerted manner, with maximum opportunity for overlap of the orbitals that will form the olefinic π bond. The reaction can be illustrated by the general expression



(19)

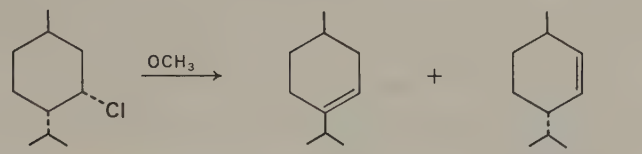
In cyclic systems, the disposition of the groups may have a profound influence on the rate and products of this reaction. Consider the well-known compounds *menthyl chloride* and *neomenthyl chloride*. These are represented both in the conventional way (A and B) and in a way (A′ and B′) that shows the most favored conformation of the molecules (only the relevant hydrogens are shown):



Menthyl chloride
(Cl equatorial)

Neomenthyl chloride
(Cl axial)

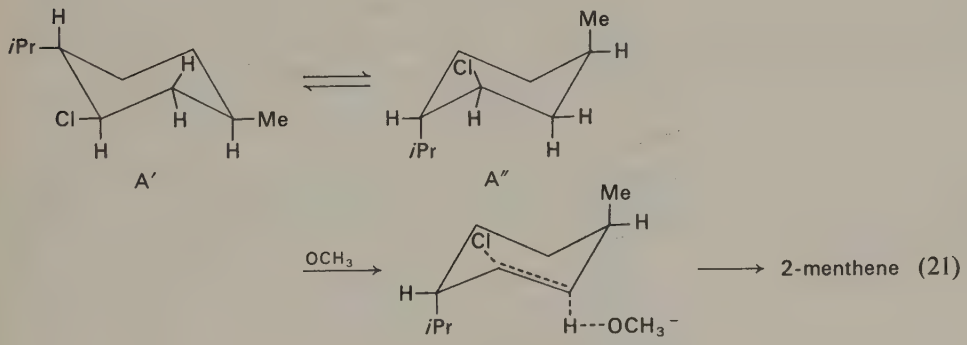
When neomenthyl chloride is treated with methanolic sodium methoxide, a mixture of 2-menthene (25%) and 3-menthene (75%) is formed:



3-menthene (75%) 2-menthene (25%) (20)

It can be seen (in B′) that the chlorine atom is ideally situated in a *trans*-diaxial position to hydrogens at both C-2 and C-4, so that planar transition states are possible for elimination in both directions. As the Saytzeff rule requires, 3-menthene predominates.

For menthyl chloride to react, however, a change from the stable (A′) conformation to a less favored conformation (A″) must first occur in order for the chlorine to assume a position in which *trans*-diaxial elimination can take place; and elimination can occur only between H at C-2 and Cl at C-3:



The result is that menthyl chloride reacts more slowly than neomenthyl chloride, and gives only 2-menthene.

Exercise 2

Addition of bromine to (Z)-stilbene ($C_6H_5CH{=}CHC_6H_5$) gives a dibromide, $C_6H_5CHBrCHBrC_6H_5$. Treatment of the dibromide with alcoholic KOH gives $C_6H_5CH{=}C(Br)C_6H_5$. Write these reactions, showing by appropriate formulations the stereochemistry at all stages. Name the product (bromostilbene) by the EZ system.

Finally, it should be emphasized that elimination reactions are often not exclusively E1 or E2 in mechanism. As an example, consider menthol and neomenthol (which have the same stereochemistry as the chlorides A and B). Although the dehydration of secondary and tertiary alcohols is generally regarded as an E1 elimination, it is found that dehydration of menthol and neomenthol do not give identical products. If a C-3 carbonium ion were a discrete intermediate it would be expected that menthol and neomenthol would give identical olefin (menthene) mixtures, for both would yield the same carbonium ion.

Exercise 3

What would you expect to find as the products of acid-catalyzed dehydration of menthol and neomenthol?

10-9 Reactivity of olefins

One of the characteristic properties of olefins is their reaction with strong acids (HCl, H_2SO_4, HBr) and with halogens (Cl_2, Br_2) to give products in which *addition to the double bond* has occurred. The following are examples of these reactions:

$$\underset{\text{Propylene (propene)}}{CH_3CH{=}CH_2} + HBr \longrightarrow \underset{\text{\textit{iso}propyl bromide}}{CH_3\overset{\displaystyle Br}{\overset{|}{C}}HCH_3} \qquad (22)$$

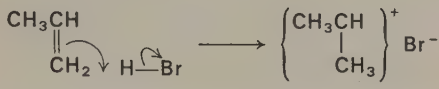
$$\underset{\text{Ethylene}}{CH_2{=}CH_2} + Br_2 \longrightarrow \underset{\text{1,2-dibromoethane}}{BrCH_2CH_2Br} \qquad (23)$$

$$\underset{\text{\textit{iso}butylene (methylpropene)}}{(CH_3)_2C{=}CH_2} + HCl \longrightarrow \underset{\text{\textit{tert}-butyl chloride}}{(CH_3)_2\overset{\displaystyle Cl}{\overset{|}{C}}CH_3} \qquad (24)$$

$$\underset{\text{1-butene}}{CH_2{=}CHCH_2CH_3} + HOCl \longrightarrow \underset{\text{1-chloro-2-butanol}}{ClCH_2\overset{\displaystyle OH}{\overset{|}{C}}HCH_2CH_3} \qquad (25)$$

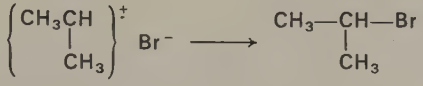
Let us examine these reactions in detail, beginning with the addition of HBr to propylene. Since the overall result is the addition of HBr as H and Br to the double bond, we might start by assuming that HBr is acting in its usual fashion to provide a proton (H^+) and a bromide ion (Br^-). There is excellent evidence that this is indeed the case, and that the reaction is an electrophilic attack of HBr upon the

olefin, in which the latter supplies an electron pair with which the proton coordinates in the first stage of the reaction:*



(26)

The second step is the addition of the bromide ion to the positively charged (carbonium) carbon atom:

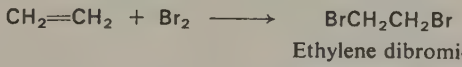


(27)

The behavior of the olefin is thus that of a *nucleophilic*, or *basic*, *substance* since it supplies the electron pair to which the proton is furnished by the acid. As the picture of the olefinic double bond in Figure 10-1 shows, this pair of electrons is outside the region between the two carbon nuclei and is thus accessible to attack by an electrophilic reagent.

10-10 Experimental evidence in support of the hypothesis of stepwise addition

Evidence for the nucleophilic behavior of the olefinic double bond is found in the addition of bromine. Ethylene reacts with bromine to form 1,2-dibromoethane (ethylene dibromide):



Ethylene dibromide

(28)

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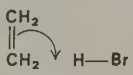
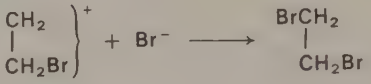
* This way of representing the course of a reaction is a convenient way of summarizing graphically the essential nature of the process. The arrow  indicates that one of the electron pairs of the double bond is being supplied to the attacking reagent. The arrow  indicates that a bromide ion is being expelled (displaced) from the hydrogen bromide molecule as the electron pair of the olefin is being accepted. This is a concerted process, at some stage of which the C—H bond is in the process of forming and the H—Br bond is in the process of breaking. It is to be emphasized that these are conventional representations, and are only devices used to illustrate a sequence of events. The arrows have no general significance beyond that which is ascribed to them in this explanation. Similar methods of representing the course of displacement reactions of other kinds have been used in earlier chapters.

The reaction can be written as a nucleophilic displacement on bromine, with expulsion of bromide ion,

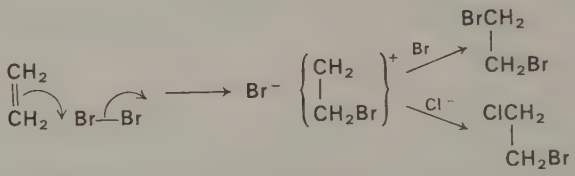
(29)

followed by combination of the bromide ion with the electron-deficient carbon atom:



(30)

The two-step nature of this process has been demonstrated by carrying out the addition of bromine to ethylene in the presence of "foreign" nucleophilic agents. For example, if ethylene is brominated in an aqueous solution of sodium chloride, the intermediate $\{C^+H_2CH_2Br\}$ accepts a chloride ion as well as a bromide ion:



(31)

Bromination of ethylene in aqueous sodium nitrate solution produces both 1,2-dibromoethane and 2-bromoethyl nitrate, $BrCH_2CH_2ONO_2$. This and other experimental evidence shows clearly that in the addition reactions of olefins with strong acids and halogens there is an initial stage in which one electron pair of the double bond coordinates with the attacking reagent, followed by a step in which the positively charged intermediate ion accepts an anion to complete the process.

The stability of the intermediate, positively charged species varies with the nature of the olefin to which addition is taking place. In the case of ethylene, the ion $(CH_2CH_2Br)^+$ can be represented as a very unstable intermediate at a high-energy minimum in the energy diagram for the reaction (Figure 10-3). Examples are known,

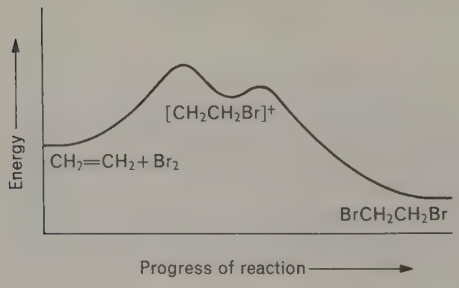
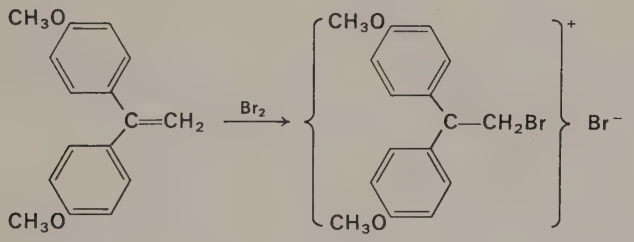


Figure 10-3
Energy diagram for the addition of bromine to ethylene:
$CH_2{=}CH_2 + Br_2 \rightarrow BrCH_2CH_2Br$

however, in which the intermediate is sufficiently stable to be isolated. A specific example of this is the following. The bromination of 1,1-dianisylethylene can be carried out in such a way as to yield the crystalline salt shown in the following equation:



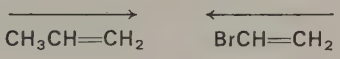
(32)

This, although an unusual example, shows that when the intermediate is stabilized by structural factors it can be isolated as a discrete species. Further reaction of such an ionic intermediate, either to lose a proton or to add Br^-, can often occur as a separate step.

Relative reactivities of olefins in addition reactions vary greatly with the nature of the substituents on the double bond. The energy diagrams for addition reactions with more reactive olefins resemble that in Figure 10-3 but show transition state maxima at lower energies, the faster the reaction.

10-11 Effect of substituents upon the reactivity of olefins

Since the olefin furnishes the electron pair for the first stage of the addition reaction, the presence in the molecule of substituents that increase the availability of electrons will aid the reaction. Alkyl groups are electron-repelling; halogens are electron-attracting:



In propylene, the methyl group increases electron density in the double bond; in vinyl bromide, the halogen atom decreases it. It is found experimentally that propylene adds bromine faster than does ethylene, and vinyl bromide slower. When several alkyl groups are present the reactivity is greater, as the data in Table 10-3 show.

It should be noted that crotonic acid ($CH_3CH{=}CHCOOH$) adds bromine much more slowly than does ethylene. The inductive effect of the —COOH group (see Section 29-8) tends to draw the electrons of the double bond closer to the carbon nuclei and reduces their accessibility to the electrophilic bromine. The effect is similar to that described above for vinyl bromide.

Table 10-3
Rates of addition of bromine to olefins

Olefin	*Relative rate of bromine addition (in CH_2Cl_2 solution, −78°C)*
$(CH_3)_2C{=}C(CH_3)_2$	14.0
$(CH_3)_2C{=}CH_2$	5.5
$CH_3CH{=}CH_2$	2.0
$CH_2{=}CH_2$	1.0
$CH_3CH{=}CHCOOH$	0.3
$BrCH{=}CH_2$	very slow

10-12 Addition of unsymmetrical reagents

The addition of HCl to propylene yields isopropyl chloride (2-chloropropane); no appreciable amount of *n*-propyl chloride is formed:

$$CH_3CH{=}CH_2 + HCl \longrightarrow \underset{\displaystyle Cl}{\underset{|}{CH_3CHCH_3}} \quad \text{not} \quad CH_3CH_2CH_2Cl \tag{33}$$

If the addition proceeds by way of the protonated olefin as an intermediate stage, it is clear from this result that $CH_3C^+HCH_3$, not $CH_3CH_2C^+H_2$, is the structure of the protonated olefin to which chloride ion coordinates in the last stage of the reaction. In general, addition of halogen acids to unsymmetrical olefins gives products in which the halogen atom is found on the most highly substituted carbon atom (the carbon atom having the lowest number of hydrogen atoms):

$$(CH_3)_2C{=}CH_2 + HCl \longrightarrow \underset{\displaystyle Cl}{\underset{|}{(CH_3)_2C}}{-}CH_3 \tag{34}$$

$$CH_3CH_2CH{=}CH_2 + HBr \longrightarrow \underset{\displaystyle CH_3}{\underset{|}{CH_3CH_2CHBr}} \tag{35}$$

$$\underset{\displaystyle CH_3}{\underset{|}{CH_3CH_2C}}{=}CHCH_3 + HBr \longrightarrow \underset{\displaystyle Br}{\underset{|}{CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{-}CH_2CH_3}} \tag{36}$$

Exercise 4

Name the reactants and products in the above equations by the IUPAC system.

This mode of addition of unsymmetrical reagents to olefins has been known for a very long time. The Russian chemist Markovnikov proposed a "rule" that is exemplified by the above addition reactions; it states that ionic addition of unsymmetrical reagents proceeds in such a way as *to place the negative part of the addend on the more highly substituted carbon atom of the double bond.* Now in reagents such as HBr, HCl, HI, and H_2SO_4 it is clear that the respective "negative" addends are Br^-, Cl^-, I^-, and HSO_4^-; but it is not at once apparent whether HOCl will add as HO and Cl or as H and OCl. It has been found experimentally that HOCl adds to propylene as follows:

$$CH_3CH{=}CH_2 + HOCl \longrightarrow \underset{\text{1-chloro-2-propanol}}{CH_3\overset{\overset{OH}{|}}{C}HCH_2Cl} \qquad (37)$$

This result indicates that HOCl supplies Cl^+ to the olefin, the reaction proceeding as follows:

$$CH_3CH{=}CH_2 + HOCl \longrightarrow \{CH_3\overset{+}{C}HCH_2Cl\}OH^- \qquad (38)$$

$$\downarrow$$

$$CH_3\overset{\overset{OH}{|}}{C}HCH_2Cl$$

It is likely that this representation is oversimplified, and that in an acidic medium it is *protonated* HOCl that provides the Cl^+ fragment:

$$CH_3CH{=}CH_2 \quad Cl{-}\overset{+}{O}H_2 \longrightarrow \{CH_3\overset{+}{C}HCH_2Cl\}H_2O \qquad (39)$$

$$\downarrow$$

$$CH_3\overset{\overset{{}^+OH_2}{|}}{C}HCH_2Cl$$

The final product shown is simply the protonated form of the chloro alcohol, which by loss of the proton to any proton acceptor gives 1-chloro-2-propanol.

Markovnikov's rule is often ambiguous, and cannot be used to predict the outcome of some olefin addition reactions. For example, in $CH_3CH_2CH{=}CHCH_3$, both carbon atoms of the double bond possess one hydrogen atom and one alkyl substituent. The observed result of the addition of HI to 2-pentene is

$$CH_3CH_2CH{=}CHCH_3 + HI \longrightarrow CH_3CH_2CH_2\underset{\displaystyle I}{\underset{|}{C}}HCH_3 \quad \text{(largely)} \qquad (40)$$

The most that can be concluded from this result is that of the two carbonium ions $CH_3CH_2C^+HCH_2CH_3$ and $CH_3CH_2CH_2C^+HCH_3$, the second is preferred (more stable).

The addition of HBr to vinyl bromide ($CH_2{=}CHBr$) yields 1,1-dibromoethane, and "obeys" Markovnikov's rule. The reason for this is that of the two protonated species

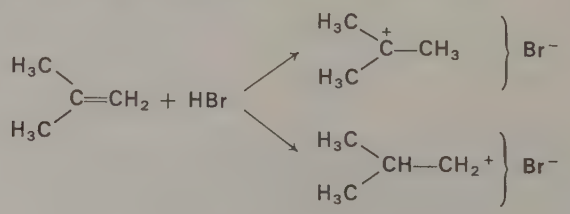
$$Br\overset{+}{C}H{-}CH_3 \quad \text{and} \quad BrCH_2{-}\overset{+}{C}H_2$$

the former is the more stable and is formed through a transition state of lower energy in a step preceding reaction with Br^- to give the final addition product. This course for the reaction will be discussed in the following paragraphs.

When Markovnikov's rule was first stated it was an expression of empirical results. While the rule is still used as a convenient and concise summary of the course of addition to olefins, its theoretical basis can now be described in terms of the details of the addition reaction. Another way of stating the rule is to say that the addition reaction proceeds through a transition state that leads to the more stable of the two possible ionic intermediates. In the case of the simple olefins it is easy to make the decision as to which of the two possible carbonium ions is the more stable. In earlier chapters we have seen the evidence for the conclusion that stability is greatest for tertiary and least for primary alkyl carbonium ions:

$$(CH_3)_3C^+ > (CH_3)_2CH^+ > CH_3CH_2^+ > CH_3^+$$
$$\text{Decreasing stability} \longrightarrow$$

The addition of HBr to isobutylene can be examined from this viewpoint. The initial protonation could take place in either of the two ways:



(41)

It is clear that the protonation will lead to the tertiary carbonium ion rather than the far less stable primary carbonium ion. These two courses can be described by an energy diagram (Figure 10-4) in which the transition state leading to the more stable $(CH_3)_3C^+$ is at a lower energy level than that leading to the primary ion.

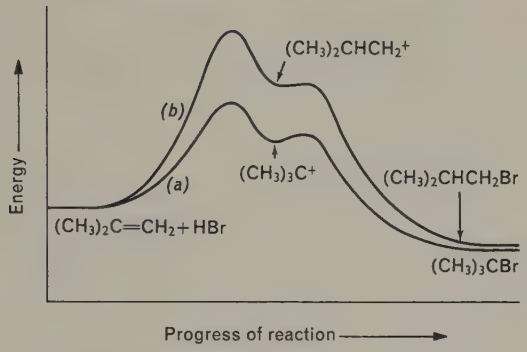


Figure 10-4
Energy diagram for the addition of HBr to isobutylene, $(CH_3)_2C{=}CH_2$. Route (*a*), with lower activation energy, is much the faster of the two possible reactions.

It is clear from this that *t*-butyl bromide is formed because the reaction leading to this product proceeds through the lower energy transition state and thus is much the faster of the two possible reactions. It can be concluded from this that the primary halide is also a product of the reaction in a proportion that depends upon the relative rates of the two rate-determining steps. Since the route via the *t*-butyl carbonium ion is very much faster than the alternative route, the relative amount of *t*-butyl bromide is so great as to make it, for practical purposes, the sole product.

The addition of sulfuric acid to the double bond of an olefin, with the formation of an ester of sulfuric acid,

$$CH_3CH{=}CH_2 + H_2SO_4 \longrightarrow \underset{\displaystyle OSO_2OH}{\overset{\displaystyle |}{CH_3CHCH_3}} \qquad (42)$$

is clearly analogous to the addition of HCl or HBr, and proceeds in the same way:

$$CH_3CH{=}CH_2 + H{-}HSO_4 \longrightarrow \{CH_3\overset{+}{C}HCH_3\}HSO_4^- \longrightarrow \underset{\displaystyle OSO_2OH}{\overset{\displaystyle |}{CH_3CHCH_3}} \qquad (43)$$

The alkyl hydrogen sulfate (in the above example, isopropyl hydrogen sulfate) is hydrolyzed by the addition of water

$$\underset{\displaystyle OSO_2OH}{\overset{\displaystyle |}{CH_3CHCH_3}} + xH_2O \longrightarrow \underset{\displaystyle OH}{\overset{\displaystyle |}{CH_3CHCH_3}} + H_2SO_4(aq) \qquad (44)$$

to form *iso*propyl alcohol. The preparation of alcohols by the hydration of olefins will be discussed in Section 11-5.

Among the byproducts often formed in the hydration of olefins are the dialkyl sulfates corresponding to the alkyl hydrogen sulfates:

$$CH_2{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH_2OSO_2OH + CH_3CH_2OSO_2OCH_2CH_3 \qquad (45)$$

The formation of the dialkyl sulfate is readily accounted for, since the alkyl hydrogen sulfate is a strong acid and can add to the olefin in exactly the same way that sulfuric acid adds:

$$CH_2{=}CH_2 + C_2H_5OSO_2OH \longrightarrow CH_3CH_2OSO_2OC_2H_5 \qquad (46)$$

The dialkyl sulfate can also be hydrolyzed to the alcohol and sulfuric acid.

Exercise 5

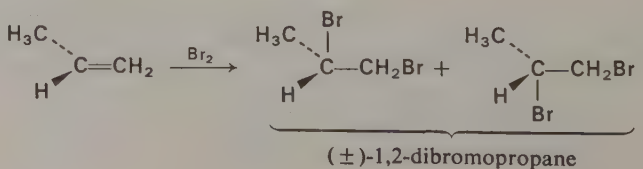
Considering Markovnikov's rule and its mechanistic basis, what would you predict as the product of the addition of HBr to each of the following olefinic compounds?

(*a*) $CH_2{=}CHN^+(CH_3)_3$ (*b*) $CH_2{=}CHCF_3$ (*c*) $CH_3CH{=}CHNO_2$

10-13 The stereochemistry of addition to the carbon-carbon double bond

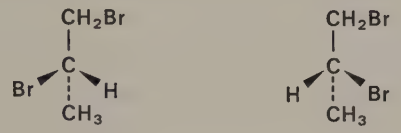
The addition of bromine to propylene gives 1,2-dibromopropane. Since 1,2-dibromopropane contains an asymmetric carbon atom, two possible forms can exist. These differ *only* in their optical properties; one of them rotates the plane of polarized light to the right, the other to the left. They are designated (+)-1,2-dibromopropane and (−)-1,2-dibromopropane. *Both are formed in equal amounts in the addition of bromine to propylene*, and the 1,2-dibromopropane that is the product of the reaction is optically inactive: it has no effect upon plane-polarized light. This optically inactive product is designated (±)-1,2-dibromopropane.

The reason for the formation of both the (+) and the (−) compounds is that bromine can approach the propylene molecule with equal probability from above as from below the plane of the olefin molecule:



(47)

The two dibromides can be redrawn as



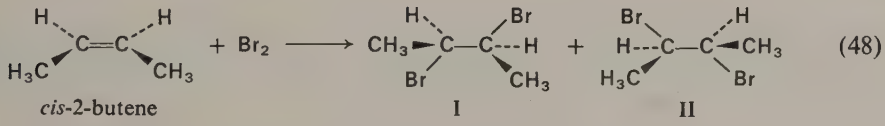
to show their mirror-image relationship.

Exercise 6

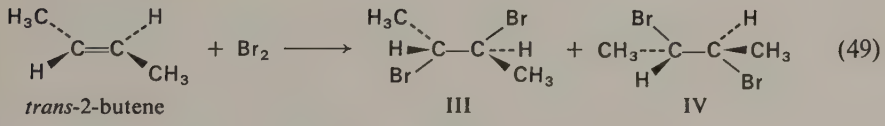
What is the stereochemical result of the addition of bromine to (*a*) isobutylene and (*b*) 1-butene?

The products of reactions in which optically inactive reagents are used are themselves optically inactive; consequently, even though the products may include asymmetric carbon atoms, this is ordinarily not made explicit, and the designation (±) is usually omitted from the name.

The addition of bromine to 2-butene presents a new problem. There are two 2-butenes, the *cis* and the *trans*. The addition of bromine to *cis*-2-butene gives a different dibromide from that obtained from *trans*-2-butene. The experimental fact is that the 2,3-dibromobutanes obtained from the two 2-butenes have the configurations shown in the following equations:



cis-2-butene I II (48)



trans-2-butene III IV (49)

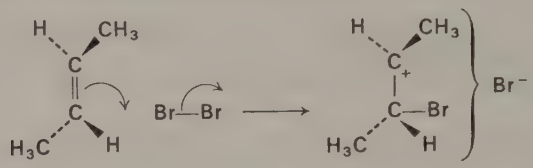
An inspection of the structures I, II, III, and IV discloses the following:

(*a*) I and II are nonidentical mirror images; they are (+) and (−) forms of 2,3-dibromobutane.

(*b*) III and IV are *identical*, and so represent only *one* compound; this is called *meso*-2,3-dibromobutane. *Meso*-2,3-dibromobutane has a plane of symmetry.

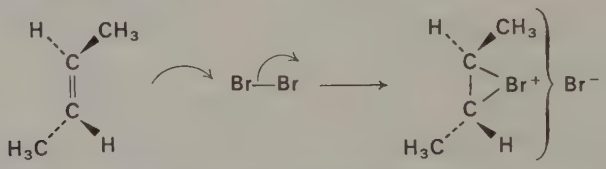
Analysis of the mechanism of addition of these reactions reveals the way in which the products are formed and explains the stereochemical results. Let us examine the reaction of bromine with *trans*-2-butene.

The first stage is the electrophilic attack of bromine upon the double bond (*or* the nucleophilic attack of the olefin upon bromine):

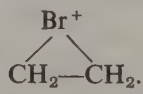


(50)

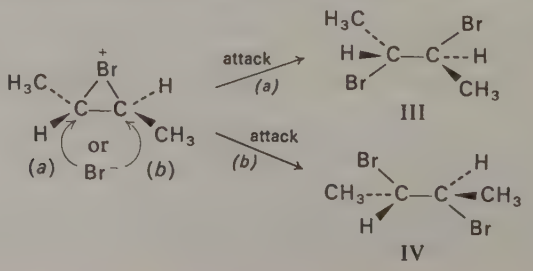
As this step is written here, it is oversimplified; in the formation of the transition state leading to the ionic intermediate, it is probable that the developing carbonium ion remains under the influence of the bromine atom, the unshared valence electrons of which form a bond that utilizes the orbital on the second carbon atom. The resulting ion is called a cyclic bromonium ion. The delocalization of the positive charge contributes to the stabilization of the ion. Thus, another way of describing the initial step is the following:



(51)

It can now be seen that the intermediate shown in Figure 10-3 should be written in the explicit form 

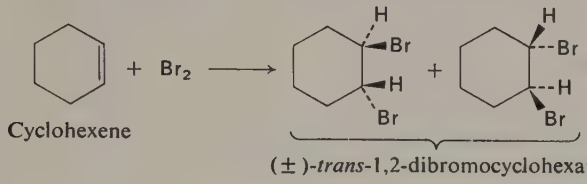
The second step of the addition reaction is the combination of the intermediate "-onium" ion and bromide ion to give the final product. It is clear that the attack of Br^- upon the intermediate is *stereochemically confined to a single course*: the bromide ion displaces the C—Br bond and thus must attack the molecule from the side *opposite* to that occupied by the first bromine atom. The attack of Br^- upon the cyclic bromonium ion can obviously take place at either carbon atom:



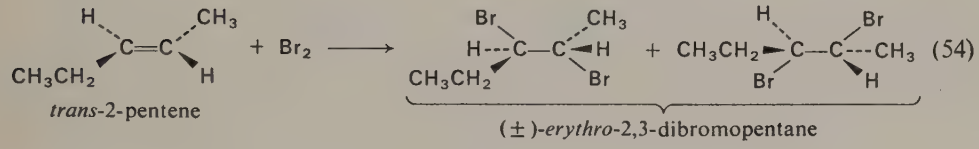
(52)

The products of this step are formulated as III and IV, but, as was pointed out above, these are identical and represent only the one compound, *meso*-2,3-dibromobutane.*

The addition of bromine to the carbon-carbon double bond is thus a *trans* addition: the two bromine atoms become attached to opposite sides of the molecule. It is a *stereospecific* reaction. Some additional examples are the following:



(53)



(54)

Exercise 7

Formulate the stereochemical course of (*a*) the addition of bromine to *cis*-2-pentene, and (*b*) the addition of hypochlorous acid to *cis*-2-butene. Note that there is no *meso* form of 2,3-dibromopentane; there are an *erythro*-[Equation (54)] and a *threo*-2,3-dibromopentane.

The addition of hypochlorous acid, HOCl, to the olefinic double bond is also a *trans* addition.

10-14 *Cis* addition. Hydrogenation of multiple bonds

When an olefin, usually in an inert solvent such as ethanol, is shaken with molecular hydrogen in the presence of a finely divided catalyst, hydrogen adds to the double bond:

(55)

* The student should gain a thorough understanding of the spatial relationships of I, II, and III (=IV) by studying three-dimensional drawings or, better, actual models.

This process, called *catalytic hydrogenation*, is carried out with catalysts that are in most cases finely divided forms of nickel, platinum, or palladium. A special form of nickel, called "Raney nickel," is prepared by the action of sodium hydroxide solution on a nickel-aluminum alloy. The aluminum dissolves (with the formation of sodium aluminate and the evolution of hydrogen), leaving the nickel as a black powder, pyrophoric when dry. Platinum and palladium are used as the oxides (which are reduced in the course of the hydrogenation to the elementary metals), or as the metals supported on charcoal, calcium carbonate, or other inert carriers.

In the hydrogenation of an olefin, the compound is dissolved in a solvent (for example, alcohol, acetic acid, ethyl acetate, water), the catalyst is added, and a positive pressure of hydrogen is applied (after flushing the system to free it of air). The flask is shaken mechanically, and the course of the reaction is followed by measurement

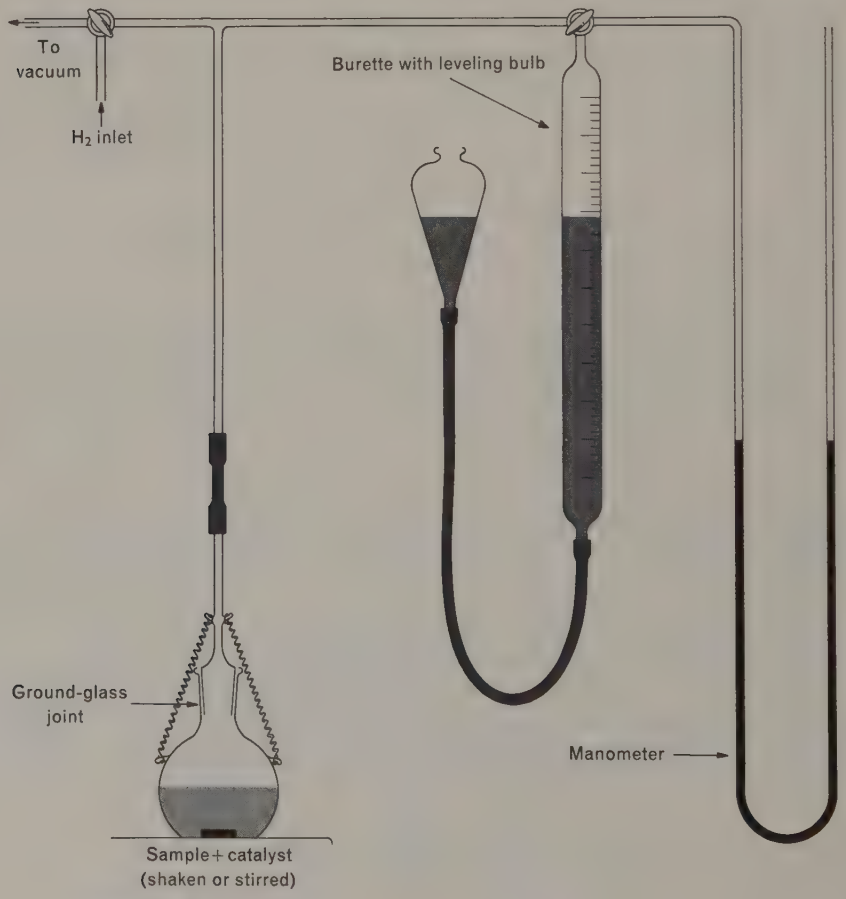
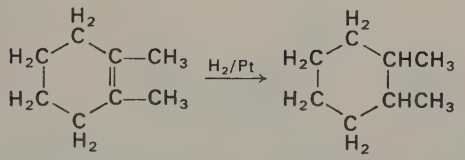


Figure 10-5
A simple apparatus for quantitative catalytic hydrogenation. Uptake of hydrogen by the sample is measured with a calibrated burette.

of the drop in pressure (or volume) of the hydrogen. Most double bonds (C=O, C=N, and C≡N, as well as C=C) are reduced readily, and the reaction is one of the most general and valuable tools of the organic chemist. A simple but useful apparatus for conducting quantitative hydrogenations is shown in Figure 10-5.

The addition of hydrogen to the double bond is a *cis* addition, in contrast to the *trans* additions of halogens and halogen acids.

The course of the addition can be illustrated by the hydrogenation of 1,2-dimethylcyclohexene:



(56)

1,2-dimethylcyclohexene 1,2-dimethylcyclohexane

The 1,2-dimethylcyclohexane formed in this reaction is the *cis* compound. This shows that both hydrogen atoms were added to the same side of the olefin molecule (see Figure 10-6).

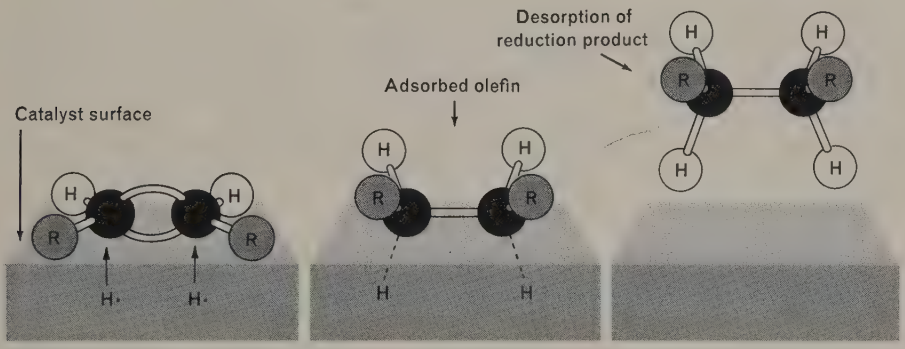


Figure 10-6
Catalytic hydrogenation of an olefin. Note how stereospecificity results from adsorption on the catalytic surface.

Since molecular hydrogen does not add to olefins in the absence of a catalyst, it is believed that the function of the metallic catalyst is to adsorb the hydrogen and, by providing electrons for metal-hydrogen bonds, to dissociate the molecular hydrogen into atoms. It is known that those metals that are effective hydrogenation catalysts have the capacity for absorbing large amounts of hydrogen. The actual hydrogenation process then consists in the adsorption of the unsaturated compound on the surface of the catalyst and the addition of atomic hydrogen to the double or triple bond. It is likely that the transition state involves the formation of hydrogen-carbon bonds as

the substrate collides with the catalyst surface, followed by an exothermic final phase that yields the hydrogenated product.

In Figures 10-6 and 10-7 are shown models of the reaction. Figure 10-7 illustrates the addition of one mole of hydrogen to the triple bond. By the use of special catalysts or by the interruption of the reaction after one mole of hydrogen has been added, an alkyne can be reduced to an alkene. As Figure 10-7 shows, the product is the *cis*-alkene.

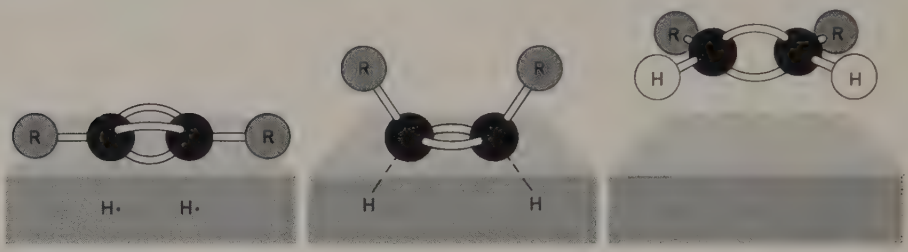


Figure 10-7
Catalytic hydrogenation of an acetylene to an olefin. Note how stereospecificity, with formation of the *cis*-olefin, results from adsorption on the catalytic surface.

The stereospecificity of the catalytic hydrogenation of acetylenic compounds is of great value in the synthesis of olefinic compounds, for one can be confident that the double bond formed is *cis* (or *Z*) in configuration. For example, oleic acid, a naturally occurring fatty acid, is known to have the *cis* configuration at the double bond because it is the product obtained by catalytic hydrogenation of the corresponding acetylenic acid:

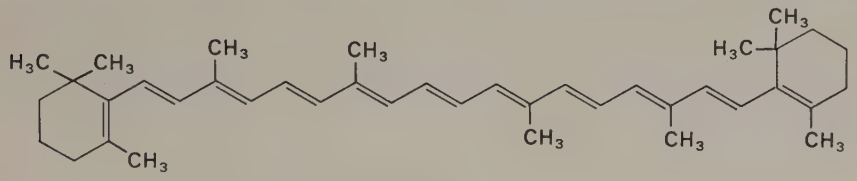
$$\underset{\text{Octadec-9-ynoic acid}}{CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH} \xrightarrow{H_2/Pd} \underset{\substack{\text{Oleic acid}\\ (\textit{cis}\text{-octadec-9-enoic acid})}}{\overset{CH_3(CH_2)_7}{\overset{H}{\diagdown}}C{=}C\overset{(CH_2)_7COOH}{\overset{H}{\diagup}}} \qquad (57)$$

10-15 Analytical application of catalytic hydrogenation

Catalytic hydrogenation of olefins is of practical importance in many ways. It is possible to determine the number of double bonds in a polyolefin (a polyene) by accurate measurement of the amount of hydrogen taken up. It is for this reason that the small-scale hydrogenation apparatus includes a calibrated burette. On larger-scale hydrogenation apparatus a pressure gauge may be calibrated to measure the amount of hydrogen taken up in the course of hydrogenation.

For example, the group of highly unsaturated compounds known as carotenoids, of which carotene and vitamin A are important members, contain long chains of alternating double and single bonds. The first accurate estimate of the number of

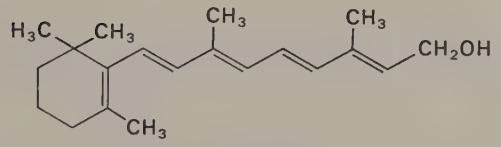
double bonds (eleven) in β-carotene was made by quantitative catalytic hydrogenation:



β-carotene

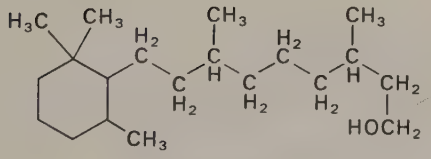
$\downarrow$ Pt/H_2 (11 moles) (58)

$C_{40}H_{78}$ perhydro-β-carotene



Vitamin A_1

$\downarrow$ Pt | H_2 (5 moles) (59)



Perhydrovitamin A_1

10-16 Other applications of catalytic hydrogenation

Industrial applications of catalytic hydrogenation are of considerable economic importance. Many vegetable oils are liquids or low-melting solids containing glycerol esters of unsaturated fatty acids, such as oleic, linoleic, linolenic acids. By bubbling hydrogen through the liquid fat in which finely divided nickel is suspended, the double bonds are hydrogenated. The ultimate product is tristearin:

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$ (Oleic acid)
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ (Linoleic acid)
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$ (Linolenic acid)
} (As esters of glycerol)

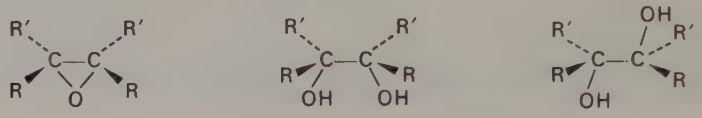
$\downarrow$ H_2/Ni (60)

$CH_3(CH_2)_{16}COOH$ [Stearic acid, as the glycerol ester (tristearin)]

Tristearin is a hard waxy solid; but by stopping the hydrogenation short of completion, intermediate, softer consistencies may be obtained. Hydrogenated oils, such as "Crisco" and "Spry," are widely used as cooking fats. Hydrogenated fats are more stable against the development of rancid flavor than are the more highly unsaturated oils, and are preferable for soap making as well as for some food uses.

10-17 Oxidation of the carbon-carbon double bond

Olefinic compounds can be oxidized at the double bond by a number of oxidizing agents. The products of such reactions include

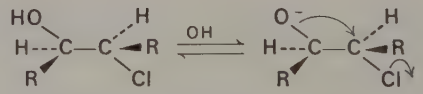


Epoxides 1,2-glycols (61)

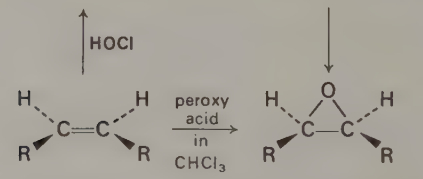
These oxidations and the reagents used in performing them are described in detail in Chapter 36.

10-18 Epoxides from halohydrins

Epoxides can be prepared from chlorohydrins and bromohydrins by an internal nucleophilic displacement reaction that is an intramolecular version of the Williamson ether synthesis (Section 12-7).



(62)

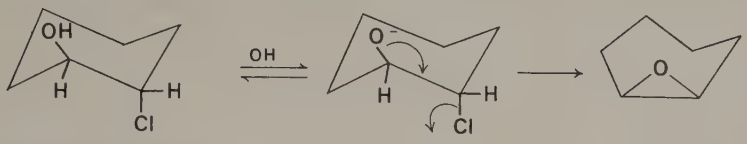


(63)

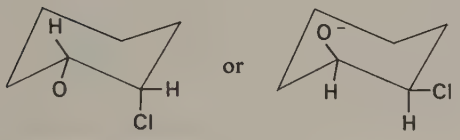
It will be noted that the same oxide is formed by direct (*cis*) epoxidation as by the two-step process involving (1) *trans* addition of HOCl and (2) a displacement reaction with inversion of configuration.

The stereochemical requirements for epoxide formation from a halohydrin should be noted. In order for the nucleophilic attack to take place at the back side of the carbon atom holding the halogen, the OH and Cl must be *trans* disposed. This is

clearly shown in cyclic halohydrins; for example, *cis*- and *trans*-2-chlorocyclohexanol:



trans-2-chlorocyclohexanol Cyclohexene oxide (64)

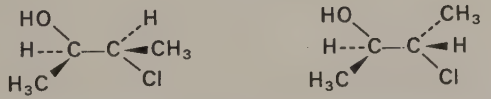


cis-2-chlorocyclohexanol does not give the epoxide (65)

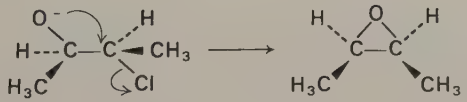
The *cis*-chlorohydrin does not form the oxide because the anionic oxygen cannot reach a position at which it can attack C—Cl at the side opposite to and colinear with the carbon-chloride bond. The difference in the reactivity of these two chlorohydrins is very marked: the *trans* compound consumes hydroxide ion in an almost instantaneous reaction,* whereas the *cis* compound is scarcely affected under the same conditions.

10-19 Steric effects in epoxide ring closure

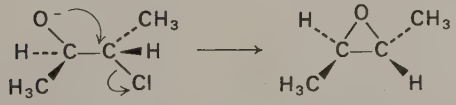
The following two chlorohydrins are formed by the addition of HOCl to *cis*- and *trans*-2-butene, respectively:



An inspection of these discloses that both have the capability of undergoing epoxide formation



(66)



(67)

* It should be noted that the "consumption" of alkali is the disappearance of OH^- and the appearance of Cl^- in the reaction mixture. This change involves a drop in pH and can be monitored by the use of an acid-base indicator such as phenolphthalein.

Experiment shows that the chlorohydrin derived from *trans*-2-butene reacts *more rapidly* than the other isomer. This means that the rate-determining step for the slower reaction, (66), involves a transition state of higher energy than that for the faster reaction, (67). Both of the chlorohydrins react with alkali to give, first, the intermediate ionic species shown on the left side of (66) and (67). This proton exchange is fast, as is typical of acid-base reactions of this kind. The second, rate-determining, step is shown by the curved arrows in the equations. This reaction must occur through a transition state in which the anionic oxygen assumes a position that allows the new O—C bond to form. In the transition state for (66) the two methyl groups are on the same side and repel each other by steric interference caused by their proximity. In the faster reaction, (67), the methyl groups are *trans*-disposed; the lesser degree of crowding in this transition state favors its formation and is reflected in its greater stability, or lower energy.

The energy diagram in Figure 10-8 shows the transition states of the steps leading to the intermediate anions and the transition states of the rate-determining intramolecular displacement steps.

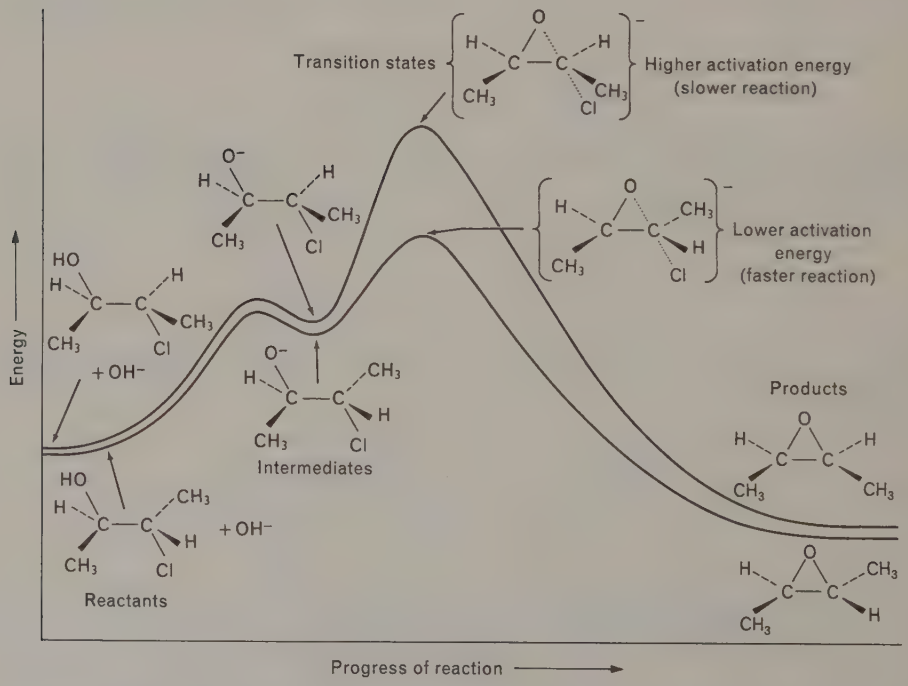
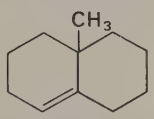


Figure 10-8
Energy diagrams for the epoxide ring closure of the isomeric chlorohydrins derived from *cis*- and *trans*-2-butenes. (Ground-state energies of reactants assumed to be equal.)

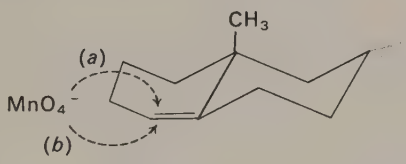
Because the initial reactants, the chlorohydrins, are free to assume their most stable configuration by rotation around the C—C bond, their energies would be expected to differ very little. In the transition state for epoxide ring closure, however, the configurations are *necessarily* those shown in Figure 10-8. Consequently, steric repulsions play an important role in determining the activation energies and thus the rates of the reactions.

Sterically imposed interactions can be important factors in the selection of alternative reaction pathways and in determining the relative rates of two reactions that otherwise appear to be identical. This *stereoselectivity* often causes a reaction that could lead to two possible products to give solely or predominantly a single product.

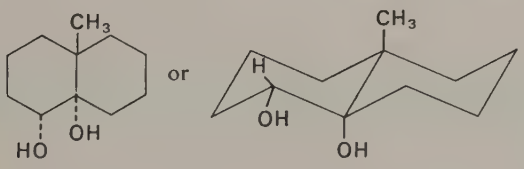
An example of steric selectivity is found in the hydroxylation of the following compound by potassium permanganate:



A three-dimensional drawing of this compound shows the disposition of the methyl group with respect to the double bond:



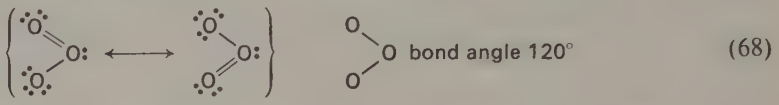
The approach of the bulky MnO_4^- ion by path (*a*) is impeded by the proximity of the methyl group, so that approach by path (*b*) is favored. The product of the reaction is in fact the following glycol:



10-20 Ozonolysis of the carbon-carbon double bond

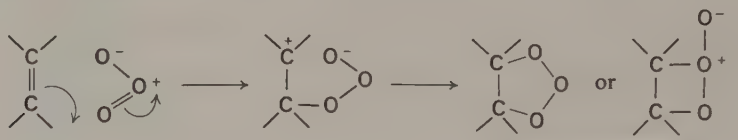
One of the most general reactions of the carbon-carbon double bond is the addition of ozone, with the subsequent transformations of the *ozonide* that is so formed.

Ozone, O_3, is a highly active form of oxygen that is produced by the action upon molecular oxygen of a silent discharge between electrodes at a high potential. Ozone has a structure best represented by the two equivalent contributing structures:



(68)

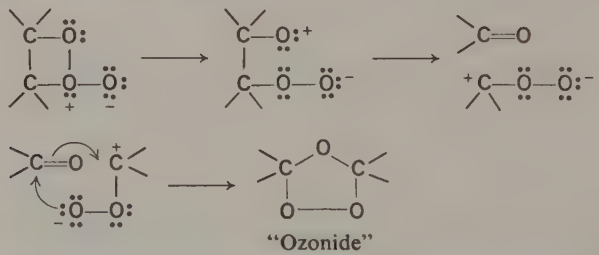
The formal charges on the ozone molecule may be represented as $O{=}\overset{+}{O}{-}\overset{-}{O}$; thus the attack of ozone upon the olefinic double bond may be regarded as an electrophilic attack upon nucleophilic C=C:



"Primary ozonide" (molozonide)

(69)

The structure of the molozonide is still not known with certainty; the reaction proceeds at once to give further products. The instability of the —O⁺—O— bond leads to the following probable sequence of changes:

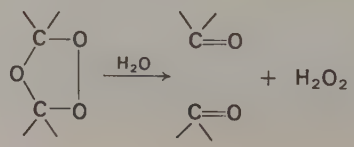


"Ozonide"

(70)

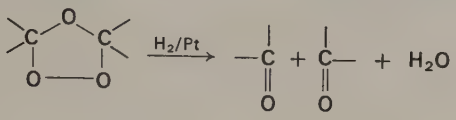
The first isolable product is often the "ozonide"; in most cases the so-called ozonides are of unknown, or at least unproved, structures, and are simply the uncrystallizable residues that remain after removal of the solvent in which the reaction with ozone has been carried out. Ozonides are usually highly unstable, and tend to decompose, often explosively. They are seldom isolated, but are treated further without attempts to purify them. The important thing to notice about ozonides is that *the carbon-carbon bond has been broken.*

Ozonides are treated further in several ways. They may be hydrolyzed directly by boiling with water:



(71)

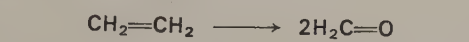
It is more common to carry out the hydrolysis under such conditions that the hydrogen peroxide (or peroxidic intermediates) is reduced in the process. This is done by adding powdered zinc before the hydrolysis is carried out. Another method is to reduce the ozonide catalytically with hydrogen in the presence of platinum:



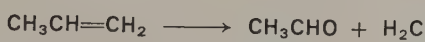
(72)

10-21 The use of ozonolysis in the proof of structure of olefinic compounds

The products of the ozonolysis of compounds containing C=C double bonds are carbonyl compounds, the nature of which depends upon the structure of the particular olefins. The following are examples:

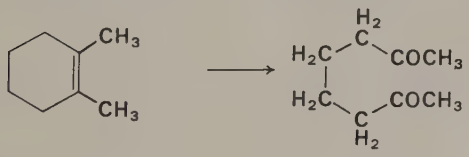


(73)

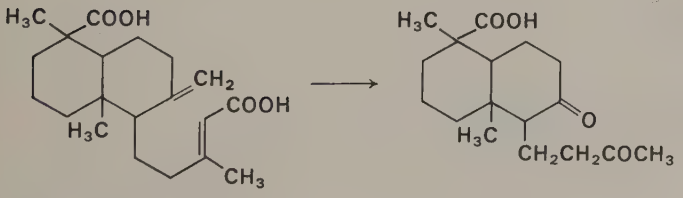


(74)

(75)



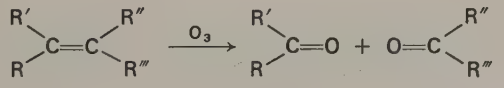
(76)



Agathene dicarboxylic acid

(77)

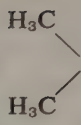
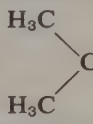
The chief utility of ozonolysis is in the proof of structure. By identifying the products of the ozonolysis, the structure of the olefin can be deduced.



(78)

Example 1

An alcohol, $C_6H_{14}O$, was readily dehydrated to an olefin, C_6H_{12}. Ozonolysis of the olefin gave two products: acetone and a three-carbon aldehyde. Acetone is

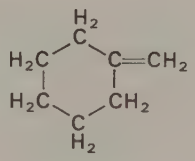
CH_3COCH_3, showing that the olefin contains the grouping  . The three-carbon aldehyde can be only propionaldehyde, CH_3CH_2CHO. Thus, the olefin has the structure  . Further evidence of other kinds would have to be secured to distinguish between the two possibilities for the alcohol.

Exercise 8

What are the two possible structures for the alcohol $C_6H_{14}O$, and how could one distinguish between them?

Example 2

An olefin, C_7H_{12}, was ozonized. Decomposition of the ozonide gave formaldehyde, $H_2C{=}O$, and a ketone, $C_6H_{10}O$. The ketone did not react with ozone, and so contained no carbon-carbon double bond; thus, it must be a cyclic ketone because an open-chain ketone of six carbon atoms (for example, $CH_3COCH_2CH_2CH_2CH_3$) would have the formula $C_6H_{12}O$. One possible structure for the original olefin is



Exercise 9

Write two other possible structures for the olefin in Example 2.

Exercise 10

Ozonolysis of a compound yields three products: acetaldehyde, 2,5-hexanedione, and *iso*butyraldehyde (2-methylpropanal). Write the structure of the original compound.

10-22 Acid-catalyzed reactions of olefinic double bonds

The product of the initial protonation of the carbon-carbon double bond—the protonated olefin, or carbonium ion—can undergo any of several subsequent reactions, depending upon its structure and the reaction conditions.

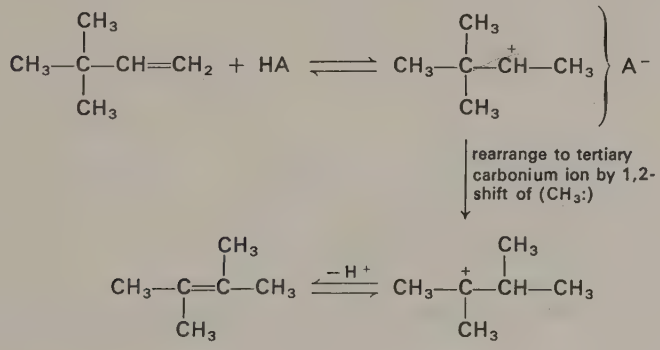
Rearrangement. If the carbonium ion is less stable than one into which it can be transformed by a simple 1,2-shift, rearrangement to the more stable species can ensue. Usually this means that if the initial carbonium ion is a primary one, it may rearrange into a secondary or tertiary carbonium ion. Since protonation is a reversible reaction, the loss of the proton from the rearranged carbonium ion will produce a new olefin. The initial, unrearranged, carbonium ion may also lose a proton in a different way to give a new olefin. After these equilibria have been established, the olefin present in greatest amount in the reaction mixture will be that with the greatest stability. Some examples of these reactions are the following.

Treatment of 1-butene with a strong acid causes it to be transformed into a mixture of 1- and 2-butenes:

$$CH_3CH_2CH{=}CH_2 + HA \rightleftharpoons CH_3CH_2\overset{+}{C}HCH_3\ (+A^-) \rightleftharpoons CH_3CH{=}CHCH_3 + HA \qquad (79)$$

In this reaction the position of the double bond "rearranges" but there is no alteration in the carbon skeleton.

Treatment of 3,3-dimethylbutene with a strong acid (for example, 25% aqueous sulfuric acid) causes a rearrangement to occur; the chief constituent of the final equilibrium mixture is 2,3-dimethyl-2-butene (tetramethylethylene):



(80)

The more highly substituted olefin is the chief product; the alternative deprotonation of the tertiary carbonium ion to give 2,3-dimethyl-1-butene occurs to a lesser extent.

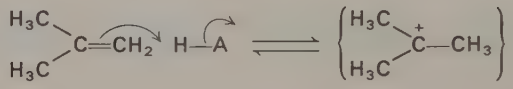
Exercise 11

What new olefins could be formed by the acid-catalyzed isomerization of 3-methyl-1-hexene?

Whenever carbonium ions are formed, whether by loss of H_2O from a protonated alcohol, by protonation of an olefin, or in other ways, the possibility of a rearrangement must be kept in mind.

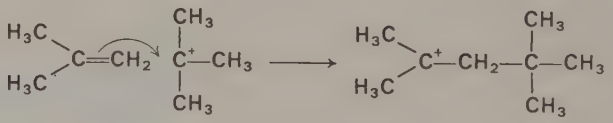
Polymerization. The treatment of olefins with strong acids often gives, besides the products of simple addition of the acid to the double bond, polymerization products consisting of two, three, or more molecules of the olefin. The case of *iso*butylene may be taken as typical, since the polymerization of this olefin to di*iso*butylene, tri*iso*butylene, and so forth, is well known and of industrial importance. The polymerization is best brought about by Lewis-acid catalysts: boron trifluoride can be used, or solid catalysts such as aluminum chloride (on an inert support, such as pumice). Let us examine the process, using the generalized symbol HA for an acid.

The first reaction between the acid and the nucleophilic olefin is the coordination of one of the electron pairs of the double bond with the acid:



(81)

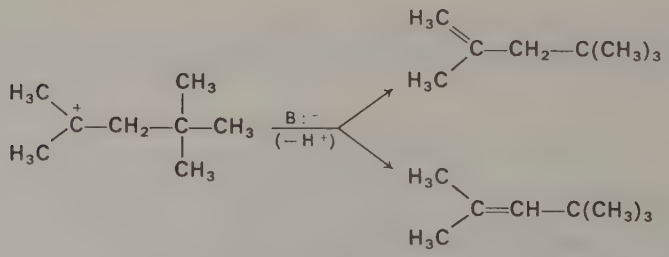
The *tert*-butyl carbonium ion may now do several things: (1) it may lose the proton and revert to the olefin; (2) it may coordinate with the nucleophilic A^-; (3) it may coordinate with another molecule of the nucleophilic olefin to give a new carbonium ion:



(82)

The new carbonium ion may now follow one of the three courses mentioned above:

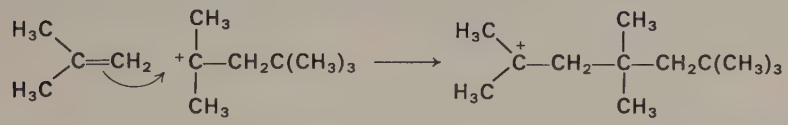
1. Loss of a proton to some nucleophile to form an olefin (di*iso*butylene):



(83)

2. Coordination of a nucleophile with the carbonium carbon atom.

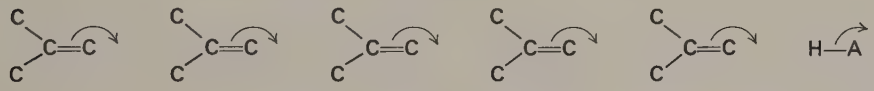
3. Reaction with another olefin molecule:



(84)

"Di*iso*butylene" is the term applied to the mixture of olefins formed in Equation (83); "tri*iso*butylene" can be derived in the same way from the product of Equation (84).

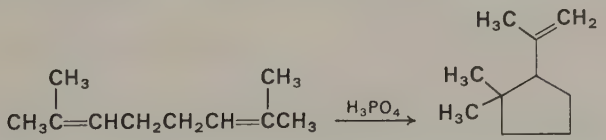
It can be seen that a continuation of the process



could give rise to large *polymeric* molecules containing numerous *monomer* units. When boron trifluoride (plus a trace of water) is used as the catalyst, viscous, high-molecular-weight polymers of the approximate structure $(\text{---}CH_2\text{—}C(CH_3)_2\text{---})_x$ are formed.

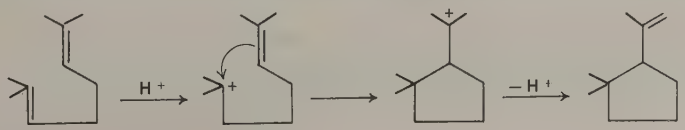
Polymerization is a well-known and industrially important process. However, most industrial polymerizations do not proceed by ionic mechanisms of the sort described for isobutylene, but are "free radical" reactions. The acid-catalyzed polymerization of *iso*butylene is discussed here because it is a good example of the application to a complex process of the principle involved in the simple addition reaction of the double bond, and shows that the fundamental processes involved in the reaction of olefins with acids start with the protonation of the double bond and the generation of the Lewis-acid-like carbonium ion.

Acid-catalyzed ring formation. In reactions (81) through (84) the polymerization is the result of the addition of a carbonium ion to an olefin molecule. If the carbonium ion and the double bond to which it adds are a part of the same molecule, their interaction can lead to ring formation. If the ring so formed is five- or six-membered, this reaction occurs with great ease. A typical example is the following:



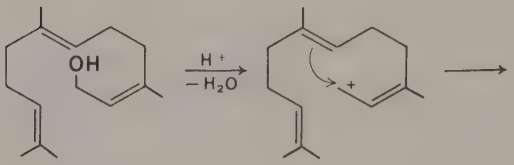
(85)

The course of this cyclization becomes clear when we show the individual stages:

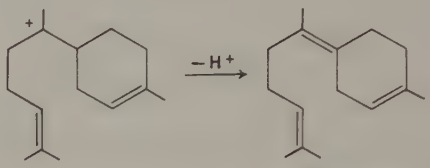


(86)

The more commonly encountered examples of ring closure by intramolecular reaction of a carbonium ion and a double bond are those in which the carbonium ion is generated from an alcohol; for example:



Farnesol (87)



Bisabolene

Farnesol and bisabolene are members of a large class of naturally occurring compounds called *terpenoid* compounds. Ring-closure reactions of the kind shown above are of great importance in the chemistry of compounds of this group and will be dealt with again in a later chapter (Chapter 27).

10-23 The carbon-carbon triple bond. Acetylenes

The alkynes form a homologous series of which acetylene, HC≡CH, is the first member. They are unsaturated compounds, and many of their reactions are similar to those that are characteristic of olefins. They add hydrogen in the presence of a catalyst to give olefins or saturated hydrocarbons:

$$RC{\equiv}CR \xrightarrow[\text{catalyst}]{H_2} \underset{cis}{RCH{=}CHR} \xrightarrow[\text{catalyst}]{H_2} RCH_2CH_2R \qquad (88)$$

Alkynes add halogens; for example, they add bromine to give tetrabromo compounds. In general, electrophilic addition reactions of alkynes are somewhat slower than the corresponding reactions of alkenes.

Alkynes can be prepared by a number of methods. Some of the most general are the following:

1. Double elimination of HX from a 1,1- or 1,2-dihalide:

$$R{-}\underset{Br}{CH}{-}\underset{Br}{CH}{-}R + \text{(alcoholic)KOH} \longrightarrow RC{\equiv}CR + 2KBr + 2H_2O \qquad (89)$$

2. Elimination of HX from a vinyl halide:

$$RCH{=}\underset{Br}{CR} + \text{(alcoholic) KOH} \longrightarrow RC{\equiv}CR + KBr + H_2O \qquad (90)$$

3. Elimination of halogen from a 1,1,2,2-tetrahalide:

$$\begin{array}{l} \text{Br Br} \\ \text{R—C—C—R} \\ \text{Br Br} \end{array} + \text{Zn (in alcohol)} \longrightarrow \text{RC}{\equiv}\text{CR} + 2\text{ZnBr}_2 \qquad (91)$$

4. Alkylation of acetylenes with alkyl halides. This depends upon the ease with which the nucleophilic acetylide anion ($RC{\equiv}C:^-$) can be formed (Section 10-24):

$$\text{RC}{\equiv}\text{CH} + \text{strong base} \rightleftharpoons \text{RC}{\equiv}\text{C}:^- \qquad (92)$$

The formation of the acetylide anion in this equilibrium can be accomplished by strong bases of several kinds. A useful reagent for this purpose is sodamide ($NaNH_2$), in which the anion NH_2^- is the base. Potassium *t*-butoxide is also used. The strongly basic nucleophilic anion $RC{\equiv}C:^-$ reacts in the expected way with alkyl halides and alkyl sulfonates to give alkylated acetylenes:

$$\text{RC}{\equiv}\text{C}:^- + \text{R}'\text{Br} \longrightarrow \text{RC}{\equiv}\text{CR}' + \text{Br}^- \qquad (93)$$

$$\text{RC}{\equiv}\text{C}:^- + \text{R}'\text{OSO}_2\text{R}'' \longrightarrow \text{RC}{\equiv}\text{CR}' + \text{R}''\text{SO}_2\text{O}^- \qquad (94)$$

Secondary halides give poor yields in this alkylation reaction, and tertiary halides cannot be used. The strongly basic character of $RC{\equiv}C:^-$ promotes the dehydrohalogenation (elimination) reaction of the secondary and tertiary halides, and the chief or only products formed are the corresponding olefins and $RC{\equiv}CH$.

10-24 Acidity of acetylenic hydrogen

Although the hydrogen atoms on saturated hydrocarbons (for example, ethane) and olefins (for example, ethylene) have no demonstrable acidity, the $\equiv$CH hydrogen atom of acetylenes is definitely, though weakly, acidic. The anion $RC{\equiv}C:^-$ can be formed by strong bases, and acetylenes form characteristic silver and cuprous salts:

$$\underset{\substack{\text{Silver ammonia} \\ \text{complex}}}{\text{RC}{\equiv}\text{CH} + \text{Ag(NH}_3\text{)}_2^+} + \text{OH}^- \longrightarrow \underset{\text{A silver acetylide}}{\text{RC}{\equiv}\text{C:Ag}} + 2\text{NH}_3 + \text{H}_2\text{O} \qquad (95)$$

Since the silver and cuprous acetylides are insoluble compounds, this reaction serves as a useful diagnostic test for the presence of the grouping $RC{\equiv}CH$. Disubstituted acetylenes, $RC{\equiv}CR'$, which have no replaceable hydrogen atom, do not form such salts.

Acetylenes also react with Grignard reagents (organomagnesium compounds; see Section 11-12 and Chapter 20) to form halomagnesium derivatives:

$$\underset{\substack{\text{Ethylmagnesium} \\ \text{bromide}}}{\text{RC}{\equiv}\text{CH} + \text{C}_2\text{H}_5\text{MgBr}} \longrightarrow \text{RC}{\equiv}\text{CMgBr} + \text{C}_2\text{H}_6 \qquad (96)$$

This, too, is an indication of the acidity of the ≡CH bond, for Grignard reagents react with acids (proton donors) of many kinds in an analogous way:

$$RMgX + HX \longrightarrow RH + MgX_2 \qquad (97)$$

where HX can be HCl, H_2O, ROH, RCOOH, or RNH_2.

The peculiar character of the C—H bond in acetylenes is in sharp contrast to the C—H bond of the olefins and alkanes. It can be accounted for by examining the character of the bonding to carbon in these three classes of compounds. The C—H bond in acetylene is formed with a molecular orbital of the *sp* type, that in olefins with one of the sp^2 type, and that in alkanes with one of the sp^3 type. The great degree of *s* character in the acetylenic C—H bonding orbital requires that the electrons in this bond be in a lower energy state than those in orbitals with a greater degree of *p* character; consequently, the stability of the $RC{\equiv}C:^-$ ion is greater than that of $R_2C{=}CH:^-$, whose stability is greater than that of $R_3C:^-$. The equilibrium in which a proton is added to the carbon anion is a measure of the relative energies of the anion and the protonated compound (that is, $RC{\equiv}C:^-$ and RC≡CH); because of the greater stability of the electron pair in the acetylene anion, the free energy difference between the acetylene (the acid) and its anion (the conjugate base) is smaller than that between the corresponding acid-conjugate pairs of alkenes and alkanes (see Section 5-2). Acetylenes, RC≡CH, have demonstrable acidity (although they are exceedingly weak acids); simple alkenes and alkanes have not.

The different character of the C—H bonds in acetylenes, alkenes, and alkanes is also to be seen in the carbon-hydrogen bond lengths in acetylene (1.063 Å), ethylene (1.086 Å), and ethane (1.102 Å). These figures reflect the character of the bonding orbitals; that of the acetylenic C—H bond, formed with a carbon orbital of the *sp* type, possesses an electron pair that is closer to the carbon nucleus. This reflects a greater electronegativity in carbon atoms with *sp* hybridization, and leads to the expectation that the proton would have enhanced acidity.

A series that shows in a parallel way the effect of bond type upon basicity (and acidity of conjugate acid) is found in nitrogen compounds in which the nitrogen atom possesses *sp*-, sp^2-, and sp^3-hybridized orbitals. The comparisons are made in Table 10-4.

The strongest acids in these two series are, respectively, $CH_3C{\equiv}N{:}H^+$ and $HC{\equiv}C{:}H$; the weakest, $CH_3NH_3^+$ and CH_4.

The synthetic uses of alkynes, both acetylene itself and acetylenes of the type RC≡CH, are many and important. Most of their applications depend upon the formation of a metal acetylide and the subsequent reactions of this with a compound having an electrophilic carbon atom. Some reactions of acetylenes with carbonyl compounds will be described in later chapters (see Chapter 22).

Table 10-4
The effect of bond type upon acidity of conjugate acid in some nitrogen compounds

Compound	*Bond type*	pK_a*	*Corresponding (isoelectronic) carbon compound*
$CH_3\ddot{N}H_2$	sp^3	10.6	$CH_3:^-$
	sp^2	5.3	$CH_2{=}CH:^-$
$CH_3C{\equiv}N:$	sp	−10.1	$HC{\equiv}C:^-$

* pK_a refers to the dissociation constant of the conjugate acid, $\rangle N:H^+$, of the nitrogen-containing compound.

10-25 Acetylene

Acetylene itself is an important industrial chemical, and serves as the starting material for the preparation of many commercially valuable products. Acetylene is prepared by several processes, the most widely used of which is the hydrolysis of calcium carbide:

$$CaO + 3C(coke) \xrightarrow{\text{electric furnace}} CaC_2 + CO \qquad (98)$$

$$CaC_2 + 2H_2O \longrightarrow C_2H_2 + Ca(OH)_2 \qquad (99)$$

Large amounts of acetylene are used for welding and cutting metals. Its combustion with oxygen produces an intensely hot flame, because of the large amount of energy liberated in the reaction and because of the small (compared with, say, ethane) number of molecules of products formed:

$$HC{\equiv}CH + 2\tfrac{1}{2}O_2 \longrightarrow 2CO_2 + H_2O + 317 \text{ kcal/mole} \qquad (100)$$

The acid-catalyzed addition of water to acetylene, a reaction analogous to the hydration of olefins to yield alcohols, yields acetaldehyde by way of an unstable intermediate compound:

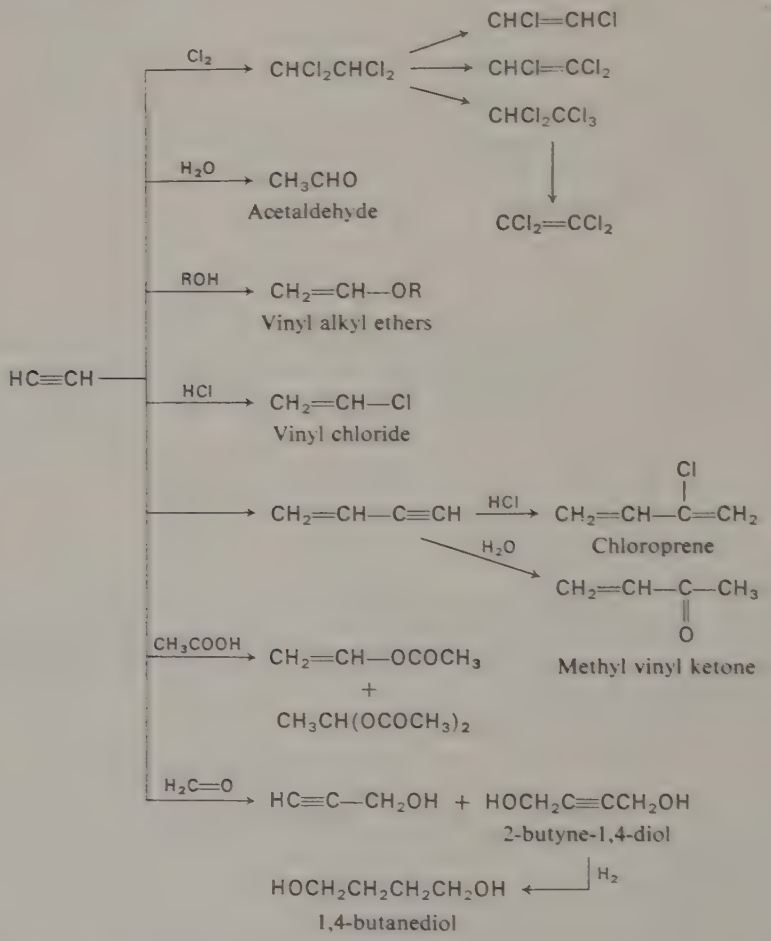
$$HC{\equiv}CH + H_2O \xrightarrow[HgSO_4]{H_2SO_4} \left\{ \begin{matrix} HC{=}CH \\ | \quad | \\ H \quad OH \end{matrix} \right\} \longrightarrow CH_3C(=O)H \qquad (101)$$

Unstable enol form of acetaldehyde

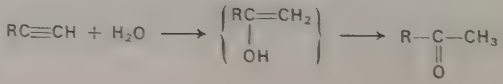
The mercuric salt used as a catalyst probably forms a mercury-acetylene complex that is the actual species to which water is added.*

More than one billion pounds of acetylene, a large proportion of which is used as a raw material for synthesis, is made annually in the United States.

The following summary shows some of the compounds that are produced, and indicates briefly the method of their preparation. Most of the processes involve some kind of an addition to the triple bond. Further transformations of these products give a wide range of useful materials, among which synthetic fibers, rubbers, and plastics are prominent.



* Substituted acetylenes react in an analogous way, addition taking place according to Markovnikov's rule:



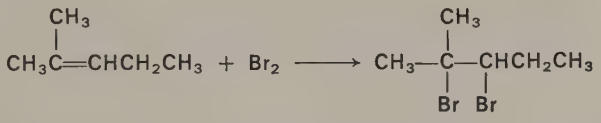
10-26 Some synthetic applications

The chemistry of alcohols and unsaturated compounds that has been discussed to this point includes a great many individual reaction types. In this section we shall apply some of these to actual synthetic procedures.

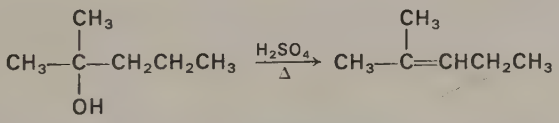
The best general approach to developing the details of a synthesis, which may consist of a series of separate reactions, is to work it out in reverse order by selecting the *immediate* precursor in each step, working from the last step toward the first until the starting materials are reached.

1. Prepare 2,3-dibromo-2-methylpentane, using as the starting material 1-propanol.

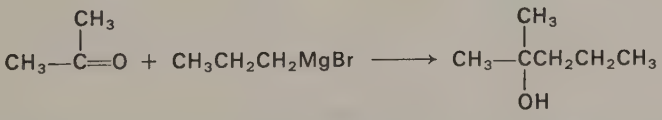
(*a*) The final step could be the addition of bromine to 2-methyl-2-pentene:



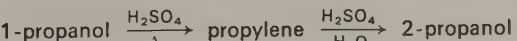
(*b*) 2-methyl-2-pentene can be prepared by dehydration of 2-methyl-2-pentanol:



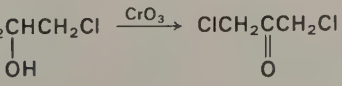
(*c*) 2-methyl-2-pentanol can be prepared by the Grignard reaction:



(*d*) *n*-Propylmagnesium bromide is prepared from 1-bromopropane, which is prepared from 1-propanol by reaction with HBr. Acetone can be prepared by the oxidation of 2-propanol, and 2-propanol can be prepared from 1-propanol as follows:

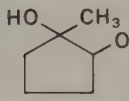


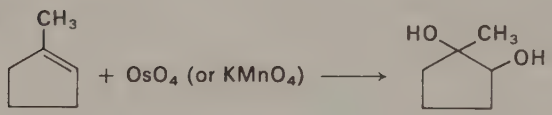
2. Prepare 1,3-dichloro-2-propanone, starting with allyl alcohol.

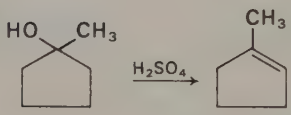
(*a*) 

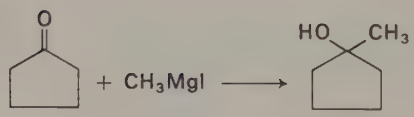
(*b*) $CH_2{=}CHCH_2Cl \xrightarrow{HOCl} ClCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2Cl$

(*c*) $CH_2{=}CHCH_2OH \xrightarrow{\text{conc. HCl}} CH_2{=}CHCH_2Cl$

3. Prepare  starting with cyclopentanone.

(*a*) 

(*b*) 

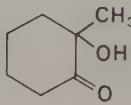
(*c*) 

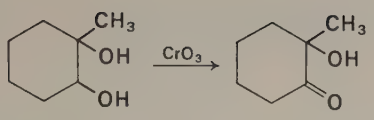
4. Prepare *cis*-9-octadecene [$CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_3$].

The obvious starting material is oleic acid, $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$, the double bond of which is already in the *cis* configuration. The synthetic problem is to convert —COOH into —CH_3. One way of doing this is to make use of the reaction of Grignard reagents with acids [equation (97), Section 10-24]:

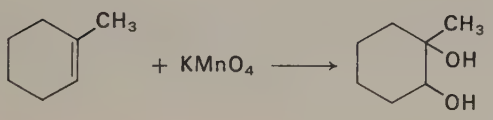
$$RCOOH \xrightarrow{LiAlH_4} RCH_2OH \xrightarrow{PBr_3} RCH_2Br \xrightarrow[\text{Ether}]{Mg} RCH_2MgBr \xrightarrow[H_2O]{HCl} RCH_3$$

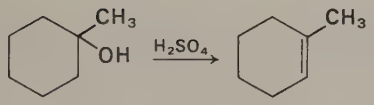
where R = $CH_3(CH_2)_7CH{=}CH(CH_2)_7$—.

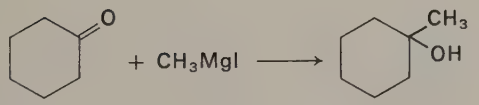
5. Prepare  from cyclohexanone.

(*a*) 

(tertiary alcoholic group not oxidized).

(*b*) 

(*c*) 

(*d*) 

6. Prepare 2-ethoxybutane (ethyl *sec*-butyl ether) from ethanol.

(*a*) $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HO^-K^+ + CH_3CH_2Br \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOCH_2CH_3 + KBr$

(*b*) $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOH + K \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HO^-K^+ + \tfrac{1}{2}H_2$

(*c*) $CH_3CH_2MgBr + CH_3CHO \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HOH$

(*d*) Ethyl bromide and acetaldehyde can be prepared from ethanol by reaction with HBr and oxidation, respectively.

10-27 Molecular configuration and biological activity of olefinic compounds

The relationship between molecular configuration and physiological activity of enantiomeric and diastereomeric drugs has been discussed in Chapter 6. Similar relationships are seen in the physiological action of compounds containing carbon-carbon double bonds: marked differences are observed between the *cis* and *trans* isomers, and between compounds which are isomeric but contain the double bond in different locations on the carbon chain. Some illustrative examples are given in the following sections.

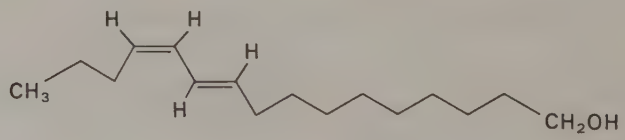
10-28 Insect pheromones

Animals, from arthropods to mammals, employ various devices for the communication of information. Many of these involve the use of specific chemical compounds, often of rather simple structure, that are secreted by the animal for the purposes of sex attraction, defense against predators, aggregation, location of food sources, and so on. Chemical compounds produced by an individual of a species to evoke behavioral responses in another individual of the same species are called *pheromones*.

Among the most widely studied compounds of this kind are those secreted by insects to attract members of the opposite sex for mating purposes. Some of the importance of the study of these compounds lies in their potential value for controlling pests by attracting destructive insects to a location (a trap) at which they can be exterminated.

The sex-attractants of moths, many of whose larvae cause enormous economic losses by damaging food and fiber crops and forests, have been studied intensively for the past two decades, and many of them have been isolated, identified, and synthesized.

The first of these compounds to be intensively studied was the sex-attractant of the silkworm moth, *Bombyx mori*. The practical difficulty of studies of this kind is shown by the fact that 500,000 virgin female moths yielded but 12 mg of the active pheromone, which was called *bombykol*. Bombykol was shown to be hexadeca-*trans*-10-*cis*-12-dien-1-ol:



The activity of bombykol is highly stereospecific. Of the four possible *cis-trans* isomers, the *trans*-10-*cis*-12 compound is 10^{10} times as active in exciting a response

in the male moth as the *cis*-10-*trans*-12 compound. The other isomers are even less active.

Stereoisomeric hexadecadien-1-ols	*Activity (γ/ml needed to excite response in male)*
10-*trans*-12-*cis* (natural pheromone)	10^{-12}
10-*cis*-12-*trans* (synthetic)	10^{-2}
10-*cis*-12-*cis* (synthetic)	1
10-*trans*-12-*trans* (synthetic)	10

It has been estimated that a single female moth contains about 10^{-2} mg of bombykol, and a male responds to 10^{-12} mg. Thus, a single female has sufficient pheromone to excite a response in 10^{10} males.

Table 10-5 lists some sex-attractant pheromones of other kinds of moths. It will be seen that many of these compounds are similar in their general structure; yet each species of moth or butterfly responds to its pheromone with a high degree of specificity.

Table 10-5
Some natural sex-attractant insect pheromones

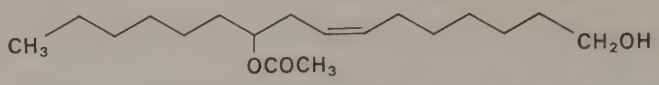
Insect	*Pheromone*
cabbage looper moth	dodeca-*cis*-7-ene-1-ol acetate
false codling moth	dodeca-*trans*-7-ene-1-ol acetate
monarch butterfly	3,7-dimethyl-deca-*trans*-2-*trans*-6-dienoic acid
codling moth	dodeca-*trans*-8-*trans*-10-dien-1-ol

Exercise 12

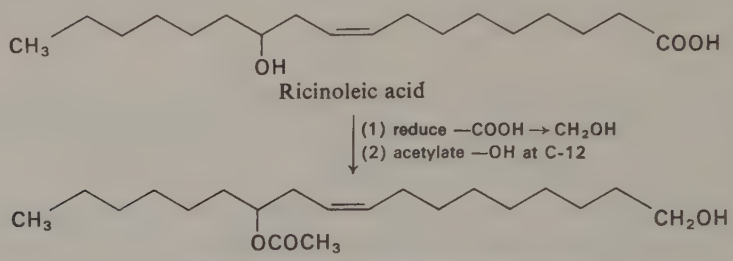
Draw the complete structures of the compounds in Table 10-5.

The practical goals of the use of sex-attractants in insect control may be met in two ways: (1) synthesis in adequate quantity of the natural pheromone; or (2) synthesis of a biologically active, analogous compound. Although the natural pheromones have a high degree of specificity, the specificity is not absolute. A less

active "synthetic pheromone" may still be of practical value if it is economically available in quantity and can be used in larger amounts. For example, the sex-attractant of the gypsy moth is 10-acetoxy-hexadec-*cis*-7-en-1-ol:

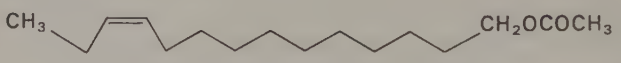
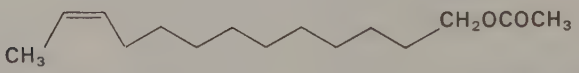
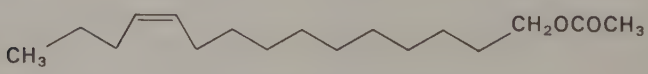
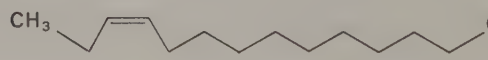


An active analogous compound was prepared from ricinoleic acid, which is commercially available in large quantities as a constituent of castor-bean oil:



Active analogue of gypsy-moth pheromone

The following comparison of a group of related compounds shows that they may act as sex-attractants with various degrees of activity; and that a small change in the molecule may even result in an inhibitor of the natural pheromone:

	Compound	*Activity*
(A)		Natural sex pheromone of the European corn borer
(B)		A weak attractant
(C)		A weaker attractant than *B*
(D)		An inhibitor of *A*
(E)		Inactive

It is clear from observations of this kind and from earlier discussions (Sections 6-17 and 6-18) that biological activity is often strongly dependent upon molecular

size and shape. This is not unexpected, because in most cases the response that is elicited depends ultimately upon an interaction between the active substrate (for example, a drug or a pheromone) and a protein molecule (or enzyme) of the responding organism. Since proteins are complex molecules with specific three-dimensional structures, a "fit" between substrate and protein often can be achieved only when certain specific stereochemical requirements are met. Although in most cases little is yet known about the precise molecular architecture at the "active site," studies of the relationship between substrate structure and biological activity are one means of investigating the stereochemistry of the region of a protein molecule at which the biological response is produced.

Problems

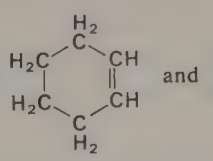
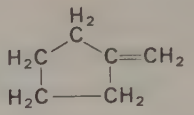
1. Name the following olefins by the IUPAC system:
   (*a*) $CH_2{=}CH_2$
   (*b*) $CH_3CH{=}CH_2$
   (*c*) $CH_3CH_2CH{=}CHCH_2CH_3$
   (*d*) $(CH_3)_2C{=}CH_2$
   (*e*) $BrCH_2CH_2CH{=}CH_2$
   (*f*) $CH_2{=}CH{-}CH{=}CH{-}CH_3$
   (*g*) $CH_2{=}C{=}C{=}CHCH_2CH_3$
   (*h*) $(CH_3)_2C{=}C(CH_3)_2$
   (*i*) $(CH_3)_3CCH{=}CHC(CH_3)_3$

2. Formulate the addition of one molecule of HBr to each of the olefins, except (*g*), in Problem 1.

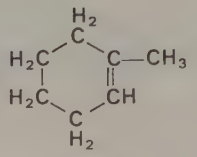
3. Write the structures of the alcohols that would be obtained by the hydration (addition of sulfuric acid, followed by hydrolysis) of the following olefins.
   (*a*) $CH_2{=}CH_2$
   (*b*) $(CH_3)_2C{=}CH_2$
   (*c*) $(CH_3)_3CCH_2CH_2CH{=}CH_2$
   (*d*) $CH_3CH_2CH{=}C(CH_3)_2$
   (*e*) $CH_3CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}CHCH_3$
   (*f*) $CH_3CH_2CH{=}CHCH_2CH_3$

4. By the use of appropriate projection formulas write the structures of all of the products of the following reactions:
   (*a*) *cis*-2-butene + HBr
   (*b*) *cis*-2-pentene + Br_2
   (*c*) *trans*-2-hexene + Cl_2
   (*d*) cyclohexene + Br_2
   (*e*) 1,2-dimethylcyclohexene + H_2 (catalytic reduction)
   (*f*) 1,3-butadiene + $2H_2$ (catalytic reduction)
   (*g*) propene + Br_2
   (*h*) isobutylene + HBr

5. Show how the application of a simple chemical test or analytical procedure will enable one to distinguish between:
   (*a*) propylene and cyclopropane

(*b*)  and 

(*c*) 1-octene and 4-octene

(*d*) 2,4-heptadiene and 

(*e*) dicyclohexyl and 1,11-dodecadiene

6. Write the structures of the olefins from which the following products are obtained on ozonization: (*a*) formaldehyde only; (*b*) acetaldehyde only; (*c*) acetone and formaldehyde; (*d*) methyl ethyl ketone and acetaldehyde; (*e*) 2,6-heptanedione only; (*f*) cyclopentanone and acetone; (*g*) CO_2 and acetaldehyde; (*h*) CH_3COCHO, CH_3CHO, and $(CH_3)_2CO$.

7. Formulate the following reaction series, assigning structures to the compounds designated by letters. Compound *A*, $C_5H_{10}O$, does not react with cold, aqueous $KMnO_4$ and does not add bromine. When *A* is reduced, *B*, $C_5H_{12}O$, is formed. Treatment of *B* with hot 20% sulfuric acid yields *C*, C_5H_{10}. Compound *C* instantly adds bromine and decolorizes aqueous $KMnO_4$. When *C* is dissolved in cold 70% sulfuric acid and the resulting solution diluted with water, compound *D*, $C_5H_{12}O$, is formed. Although *B* can be reoxidized to *A*, a similar oxidation of *D* to a five-carbon-atom compound cannot be accomplished.

8. Starting with isobutyl alcohol as the only organic compound, show how you could prepare (*a*) *tert*-butyl alcohol, (*b*) isopropyl alcohol, (*c*) 1,2-dibromopropane, and (*d*) 2-methylpropane (isobutane).

9. Formulate the transformation of 1-butanol into 2-butanol.

10. How could pure ethylene be prepared from a mixture containing ethylene and ethane?

11. How could cyclohexene be removed from a sample of cyclohexane that contained some of the olefin as an impurity?

12. Vitamin A is a primary alcohol of the composition $C_{20}H_{30}O$. Catalytic hydrogenation affords the fully saturated "perhydro" vitamin A, $C_{20}H_{40}O$. How many rings does vitamin A contain? How many double bonds (assuming no triple bonds) are present?

13. Write the equations showing the course of the acid-catalyzed polymerization of 2-methyl-1-butene (to the trimer).

14. A sample of 19.6 mg of an unsaturated compound absorbed 4.48 ml of hydrogen (measured at 0°C and 760 mm) upon catalytic hydrogenation. What is the minimum molecular weight of the compound?

15. The addition of HBr to the olefin of part (*i*), Problem 1, could give rise to a product other than that formed by simple addition to the double bond. Show the structure of this other product, and write a mechanism for its formation.

16. Show how the following compounds could be synthesized; use the starting material indicated and any other necessary organic or inorganic reagents.
    (*a*) *cis*-2-hexene from propyne
    (*b*) 2-chlorocyclopentanone from cyclopentene
    (*c*) $CH_3COCH_2CH_2CH_2OH$ from $CH_3COCH_2CH_2COOEt$

11

Alcohols. Properties and methods of preparation

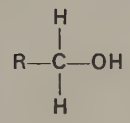
Alcohols are a class of compounds of wide distribution and great economic, social, and physiological importance. This chapter describes some of their properties and uses, and methods for their synthesis. It also introduces one of the most versatile reagents used by the organic chemist: the Grignard reagent. Alcohols are important not only for their practical uses, but also as the starting materials for further syntheses; for example, of alkenes, aldehydes and ketones, esters, and ethers. Thus, the ease and versatility of methods of synthesizing alcohols provides ready access to a wide spectrum of compounds.

In Sections 11-12 to 11-14 are some examples of stereochemical control in the synthesis of alcohols, including an example of the manner in which an enzyme exercises stereochemical control over the course of a biological oxidation-reduction.

11-1 Alcohols and phenols

Compounds containing the hydroxyl group, —OH, attached to a saturated (sp^3) carbon atom are known by the general name *alcohols*. Alcohols are classed as *primary*, *secondary*, or *tertiary*, according to whether the hydroxyl-bearing carbon atom is

attached to two, one, or no hydrogen atoms, respectively. Some typical alcohols of these three classes are the following:

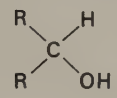
Primary: 

CH_3CH_2OH Ethanol

$CH_2{=}CHCH_2OH$ Allyl alcohol

 Benzyl alcohol

---

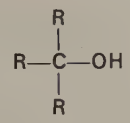
Secondary: 

$(CH_3)_2CHOH$ 2-propanol (isopropyl alcohol)

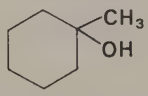
 Cyclohexanol

$CH_2{=}CHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$ 4-penten-2-ol

---

Tertiary: 

$(CH_3)_3C{-}OH$ *t*-butyl alcohol

 1-methylcyclohexanol

$(CH_2{=}CH)_3{-}C{-}OH$ Trivinylmethanol (trivinylcarbinol)

It can be seen from these examples that the groups represented by R in the general formulas can vary over a wide range of types, from simple alkyl groups to unsaturated, aromatic, and cyclic structures.

Compounds in which the hydroxy group is attached directly to an aromatic ring are called *phenols*. Their properties are markedly different from those of the alcohols. Because the principal features of the chemical behavior of phenols involve the aromatic ring and not the hydroxyl grouping itself, their chemistry is more appropriately dealt with separately (Chapter 33). The differences between phenols and alcohols that relate to the —OH group are found chiefly in the greater acidity of phenols and the greater ease of replacement, by breaking of the C—O bond, of the —OH group of alcohols.

11-2 Common alcohols

Many alcohols are familiar materials with wide application to domestic, medical, and industrial purposes.

Methanol ("wood alcohol"), CH_3OH, formerly obtained as a by-product of

the destructive distillation of wood (in the production of charcoal), is now produced by the reduction of carbon monoxide with hydrogen:

$$CO + 2H_2 \xrightarrow[\text{catalyst}]{\text{heat}} CH_3OH \qquad (1)$$

It is used as an anti-freeze, for the production of formaldehyde (by oxidation), and as a raw material for the synthesis of other products. In 1972 the U.S. production of methanol was 6 million pounds.

Methanol is toxic; its ingestion can cause injury to the optic nerve or death. It is metabolized to formaldehyde and formic acid, both of which are more toxic than methanol itself.

Ethanol is produced by yeast fermentation of glucose (an important source; most of the alcohol made in this way is consumed in alcoholic beverages) and by the acid-catalyzed hydration of ethylene.

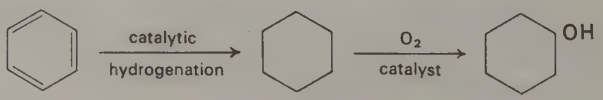
$$CH_2{=}CH_2 + H_2O \xrightarrow{H_2SO_4} CH_3CH_2OH \qquad (2)$$

This is the largest industrial source of ethanol; in 1970 over 1 million tons was produced in the U.S.

Ethanol is a valuable organic chemical with many uses. It is a sedative and an intoxicant when taken orally. It is used medically as an anesthetic and in blocking nerve conduction, and as a solvent and vehicle in compounding medicaments. The intoxicant effect of ethanol ranges from mild exhilaration, through sedation, to stupor and, when consumed in large amounts over a short space of time, death. A blood alcohol concentration of 0.10 percent is reached in an average person after the consumption of about 4 ounces of 90-proof spirits, but metabolism is fairly rapid: in an average adult, consumption of ethanol at a rate of about 15 grams per hour causes no rise in blood alcohol level.

Isopropyl alcohol (2-propanol) is made industrially by the hydration of propylene, which, like ethylene, is an abundant by-product of petroleum refining and processing. Isopropyl alcohol is used as a solvent, as a topical antiseptic (rubbing alcohol), and (in largest part) for the production of acetone.

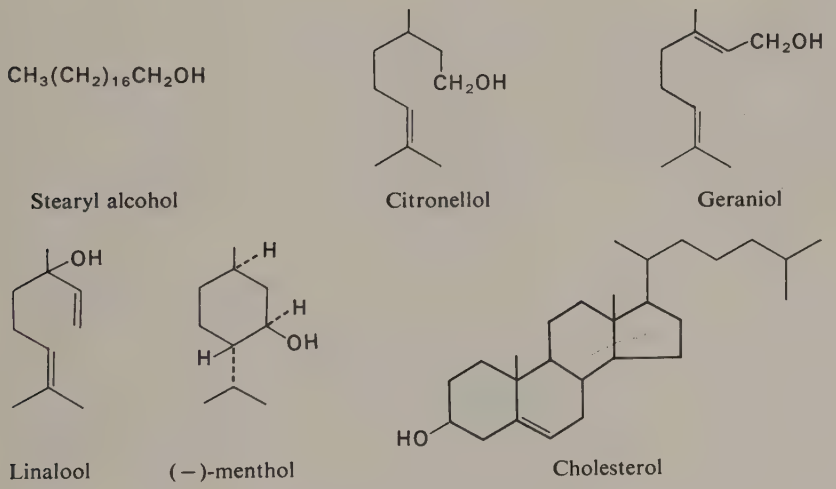
Other alcohols are made industrially by various procedures from low-cost raw materials. The direct oxidation of saturated hydrocarbons is not often practical, for the reaction is not selective and a mixture of alcohols is formed. An exception is found in cyclohexane, the oxidation of which at any position can give only the one product, cyclohexanol:



(3)

Cyclohexanol is an important industrial chemical, being used as a raw material in the production of nylon.

Many complex compounds containing alcoholic hydroxyl groups are derived, directly or indirectly, from natural sources. Cholesterol, a secondary alcohol, is a constituent of nerve tissue and is deposited in gallstones. It is the primary precursor for the synthesis in living organisms of the many steroids involved in cellular metabolic processes. Long-chain fatty acids, present in esterified form in natural fats, can be reduced to the corresponding alcohols—for example, in the manufacture of synthetic detergents and emulsifying agents. Nature also affords a great many alcohols of relatively simple structures. Menthol, a secondary alcohol; citronellol, a primary alcohol; and linalool, a tertiary alcohol, are constituents of the fragrant volatile oils of many plants.



Stearyl alcohol | Citronellol | Geraniol

Linalool | (−)-menthol | Cholesterol

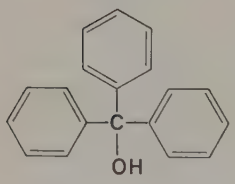
Exercise 1

(*a*) The stereochemistry of natural menthol is shown in the above formula. How many stereoisomers can exist? Show their configurations. (*b*) Does (−)-menthol have the R or S configuration at the >CHOH center?

11-3 Nomenclature of alcohols

Alcohols are usually named in any of three general ways: (1) by trivial (common) names; (2) by systematic (IUPAC) names; and (3) by a system known as the carbinol system. These are discussed in Appendix A. Some alcohols are listed in Table 11-1 along with names that are applied to them.

Table 11-1
Names of some representative alcohols

Compound	*Name*
CH_3OH	methanol* methyl alcohol
CH_3CH_2OH	ethanol* ethyl alcohol
$CH_3CH_2CH_2CH_2OH$	1-butanol* *n*-butyl alcohol†
$CH_3CH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2CH_3$	3-pentanol* diethylcarbinol
$CH_3-\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}-OH$	*t*-butyl alcohol trimethylcarbinol 2-methyl-2-propanol*
$CH_3-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}OH$	4-methyl-2-pentanol* methylisobutylcarbinol
$CH_2=CHCH_2OH$	allyl alcohol vinylcarbinol 2-propen-1-ol*
$CH_2=CH-\underset{\displaystyle OH}{\underset{\vert}{CH}}-CH=CH_2$	divinylcarbinol 1,4-pentadien-3-ol*
	triphenylcarbinol triphenylmethanol
$CH_3-\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}-CH_2OH$	neopentyl alcohol *t*-butylcarbinol 2,2-dimethyl-1-propanol*
$CH_3CH_2CH_2CH_2CH_2CH_2OH$	1-hexanol* *n*-hexyl alcohol
$CH_3\underset{\displaystyle Cl}{\underset{\vert}{CH}}-\underset{\displaystyle Cl}{\underset{\vert}{C}}-CH_2OH$	2,2,3-trichloro-1-butanol*
$CH_3\diagdown\diagup CHOH\diagdown CH_3$	isopropyl alcohol‡ 2-propanol*
$BrCH_2CH_2OH$	β-bromoethyl alcohol 2-bromoethanol*

Footnotes for this table on facing page.

Exercise 2

Draw the structures of the following compounds; indicate stereochemistry where R or S is specified: (*a*) 4-pentanol, (*b*) 2-methyl-4-bromo-1-pentanol, (*c*) triisobutylmethanol, (*d*) (R)-2-hexanol, (*e*) (R)-propane-1,2-diol, (*f*) propane-1,2,3-triol, (*g*) 3-hexen-1-ol, (*h*) optically active cyclohexane-1,2,3-triol, (*i*) *cis*-3-chlorocyclohexanol.

Some advice can be given regarding the naming of organic compounds: (*a*) Use a name that is clear, unambiguous, and as simple as is consistent with ready comprehensibility. Do not use systematic names for complicated molecules for which trivial names are familiar and generally recognized; and do not use trivial names when these are recognized only by specialists in a restricted area. (*b*) Learn the rules, but do not become their slave. Allyl alcohol, $CH_2{=}CHCH_2OH$, is indeed 2-propen-1-ol, but it would hardly ever be so called. (*c*) Although there are many rules for the *construction* of names, there are few for the *selection* of names. Maintain a perceptive attitude and observe how compounds are actually named in books and journals. Facility in proper nomenclature is gained not by memorizing rules but by acquiring experience and judgment.

11-4 Synthesis of alcohols

The introduction of the hydroxyl group into the molecule of an organic compound can be accomplished in many ways, most of them involving alteration of existing functional groups. The principal synthetic methods include:

(*a*) addition of the elements of water to a carbon-carbon double bond (hydration of olefins);
(*b*) addition of boron hydride to a carbon-carbon double bond followed by oxidation of the intermediate alkylborane;
(*c*) hydrolysis of alkyl halides;
(*d*) saponification of esters;
(*e*) reduction of aldehydes, ketones, and carboxylic acid derivatives.

11-5 Hydration of olefins

The principal industrial source of the lower alcohols ethanol, isopropyl alcohol, 2-butanol, and *t*-butyl alcohol is the acid-catalyzed hydration of olefins. Ethylene,

* IUPAC names.

† Prefixes *n*- (normal), *i*- (iso), *sec*- (secondary), *t*- or *tert*- (tertiary) are italicized. Occasionally the prefix "iso" is used as a part of a name, as in "isopropyl," where it is not italicized.

‡ It is improper to use names that combine different conventions of nomenclature. Thus, such names as "isopropanol," "*t*-butanol," and "*n*-hexanol" should not be used.

propylene, and butenes are abundant and inexpensive by-products of the petroleum industry and constitute the principal commercial raw materials for production of the corresponding alcohols. Alcohol can be produced by passing the olefin into concentrated sulfuric acid, followed by the steps described below. This process has been superseded in modern industrial practice by a direct hydration, in which a mixture of the olefin and water vapor is passed over a heated catalyst.

The hydration of an olefin to form an alcohol is the reverse of the dehydration of an alcohol to form an olefin, and both reactions may be viewed as proceeding through an intermediate carbonium ion, formed in the *dehydration reaction* by dissociation of H_2O from the protonated alcohol, or in the *hydration reaction* by protonation of the double bond:

$$\begin{array}{l} RCHCH_2R' + H^+ \rightleftharpoons RCHCH_2R' \rightleftharpoons \overset{+}{R}CHCH_2R + H_2O \\ \quad | \qquad\qquad\quad | \qquad\qquad\quad \Big\uparrow\Big\downarrow \\ \quad OH \qquad\quad {}^+OH_2 \qquad\qquad\quad RCH{=}CHR' + H^+ \end{array} \tag{4}$$

At elevated temperature, the olefin volatilizes from the reaction mixture; at lower temperature the alcohol (or its sulfate; see below) accumulates.

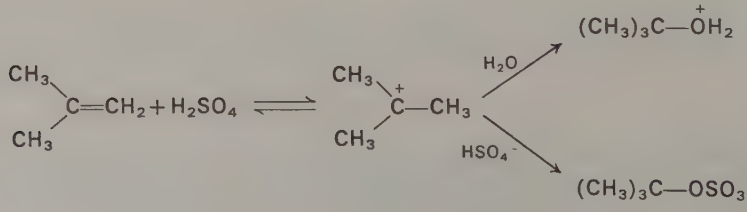
When 90–95% sulfuric acid is used, the protonation of the double bond is followed by addition of the bisulfate ion to form the mono- and diethyl esters of sulfuric acid; this reaction can be employed in the hydration of ethylene:

$$CH_2{=}CH_2 + H_2SO_4 \rightleftharpoons CH_3\overset{+}{C}H_2 \Big\} \; HS\bar{O}_4 \rightleftharpoons CH_3CH_2OSO_2OH \tag{5}$$

$$CH_2{=}CH_2 + EtOSO_2OH \rightleftharpoons CH_3\overset{+}{C}H_2 \Big\} \; \bar{O}SO_2OEt \rightleftharpoons EtOSO_2OEt \tag{6}$$

Hydrolysis of the resulting mixture of ethyl hydrogen sulfate and diethyl sulfate yields ethanol and sulfuric acid, from which the ethanol is recovered by distillation. The aqueous sulfuric acid is concentrated to 90% and recycled.

Propylene and the butenes react in the same manner, but because of the greater ease of protonation of the alkyl-substituted double bond a less concentrated sulfuric acid can be used, and direct hydration to the alcohol occurs along with formation of the sulfuric ester:



(7)

Whether the composition of the olefin/sulfuric-acid mixture is largely alcohol or the sulfuric ester, final hydrolysis by dilution of the solution with water yields the alcohol.

The addition of water (as H and OH) proceeds in such a manner as to form the alcohol with the hydroxyl group attached to the more highly substituted carbon atom:

$$CH_3CH{=}CH_2 \xrightarrow[H_2SO_4]{H_2O} CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \qquad (8)$$

$$CH_3CH_2CH{=}CH_2 \xrightarrow[H_2SO_4]{H_2O} CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \qquad (9)$$

$$(CH_3)_2C{=}CH_2 \xrightarrow[H_2SO_4]{H_2O} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}CH_3 \qquad (10)$$

Alcohol formation by the hydration of olefins, while an important industrial process, is not generally useful in the laboratory. Further details of the addition of hydrogen acids to olefins were discussed in Chapter 10.

11-6 Hydroboration of olefins

The addition of diborane, B_2H_6, to olefins leads to the formation of alkylboranes. The reaction proceeds as if the hypothetical borane, BH_3, added to the carbon-carbon double bond, the electrophilic boron becoming attached to the less-substituted carbon atom. For example, the addition of diborane (represented as BH_3) to 2-methyl-1-butene proceeds as follows; addition continues until all three hydrogens of BH_3 have been utilized:

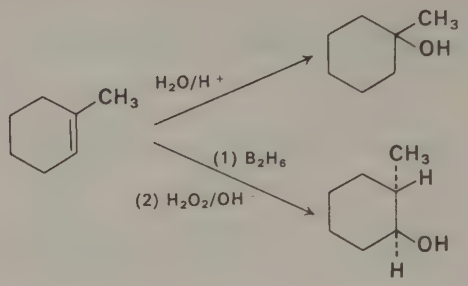
$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2 + BH_3 \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}{-}CH_2{-}BH_2 \longrightarrow (CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2)_3B \qquad (11)$$

The trialkylborane need not be isolated, but may be transformed into an alcohol by oxidation with hydrogen peroxide (alkaline):

$$(CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2)_3B \xrightarrow[OH]{H_2O_2} 3CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH + B(OH)_3 \qquad (12)$$

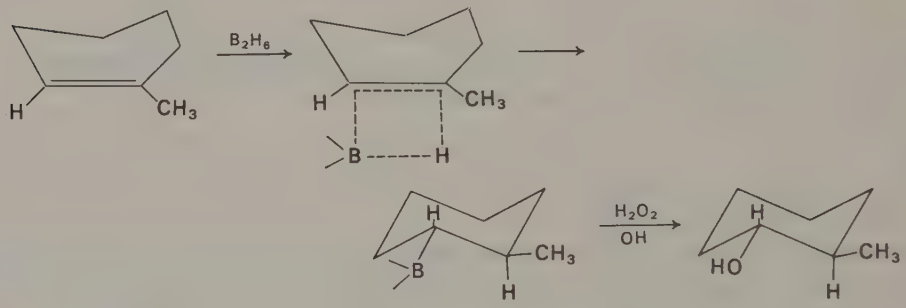
Two aspects of the overall reaction are noteworthy: (1) the addition of diborane and subsequent oxidation accomplishes the addition of water to the double bond in a manner *opposite* to that in acid-catalyzed olefin hydration; and (2) the addition is

stereospecific, the alcohol being that formed by the overall *cis*-addition of H and OH to the double bond.



(13)

In a formulation that shows the conformational relationships, the reaction can be represented as follows:



(14)

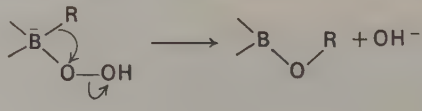
It is also important to note that in the change

(15)

the configuration of the carbon atom at the B—R bond of R_3B and at the O—R bond of ROH is the same; there is neither inversion nor a mixed inversion-retention of configuration. This can be accounted for by considering the mechanism of the oxidation reaction. Because the boron atom in R_3B is electrophilic (with a vacant orbital), it can accept the nucleophilic HOO^- anion:

(16)

Rearrangement of this intermediate, with expulsion of hydroxide ion, proceeds with concerted migration of the R group to oxygen:



(17)

In this concerted migration (of R:) and expulsion (of $:OH^-$) reaction, the R group does not exist as a free, independent entity and retains partial bonding to B and O until the transfer is completed, thus retaining its configuration. Final hydrolysis of the $B(OR)_3$ intermediate occurs by breaking of the B—O bonds, leaving the O—C bonds intact, again with retention of the configuration at carbon.

By the use of deuterated (B_2D_6) or tritiated ($B_2{}^3H_6$) diborane, isotopically labeled compounds can be prepared:

$$RCH{=}CH_2 \xrightarrow[(2)\ H_2O_2/OH^-]{(1)\ B_2D_6} \underset{\displaystyle D}{\overset{\displaystyle |}{RCHCH_2OH}} \qquad (18)$$

A corollary to the above discussion is the decomposition of alkylboranes with acids to bring about an overall addition of hydrogen to the double bond of the starting olefin:

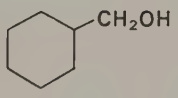
$$R{-}B\!\!\left\langle \right. + H^+(H_2O) \longrightarrow RH + HO{-}B\!\!\left\langle \right. \qquad (19)$$

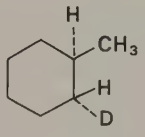
With appropriate reagents B_2D_6 and a deutero acid (for example, DCl), selectively deuterated compounds can be prepared.

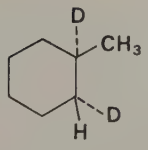
Exercise 3

Using the hydroboration method, with any necessary olefin as a starting material, show how you could prepare:

(*a*) $(CH_3)_2CHCH_2OH$

(*b*) 

(*c*) 

(*d*) 

(*e*) $CH_3CH_2CH_2D$

11-7 Hydrolysis of alkyl halides

The nature of this reaction has been dealt with in Chapter 7. Its application to the preparation of alcohols is limited in practice because alkyl halides are not generally accessible except as products derived *from* alcohols. Direct halogenation of saturated hydrocarbons (alkanes) is unselective, and the formation of polyhalogenated products is not easily avoided.

The halogenation-hydrolysis route to alcohols has some limited industrial applications. Allyl alcohol is produced by chlorination of propylene and hydrolysis of the resulting allyl chloride:

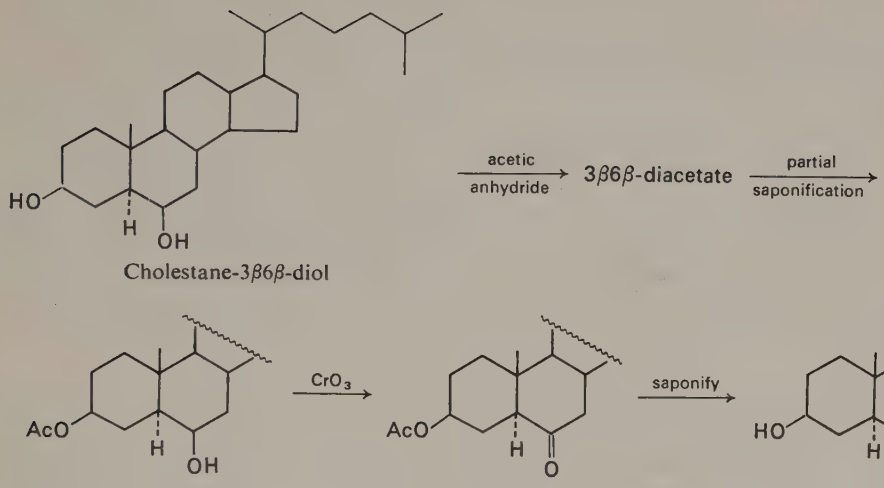
$$\begin{aligned} CH_2{=}CHCH_3 + Cl_2 &\xrightarrow{500^\circ} CH_2{=}CHCH_2Cl \\ CH_2{=}CHCH_2Cl &\xrightarrow[OH^-]{H_2O} CH_2{=}CHCH_2OH \end{aligned} \qquad (20)$$

Chlorination of a pentane fraction (a mixture of C_5 isomers) from petroleum yields a mixture of chlorinated pentanes from which a mixture of $C_5H_{11}Cl$ isomers can be separated by fractional distillation. Hydrolysis of this fraction yields a mixture of five-carbon alcohols (Pentasol). Some Pentasol is fractionally distilled to produce isoamyl alcohol (3-methyl-1-butanol) and 2-pentanol, but most of it is used as the mixture of isomers, chiefly as a solvent.

11-8 Saponification of esters

The only alcohol prepared in important amounts by the saponification of esters is the trihydroxy compound glycerol (propane-1,2,3-triol), which occurs in fats and oils as its tri-esters with long-chain aliphatic acids. Saponification of fats and oils yields glycerol and the sodium salts of the "fatty" acids, used as soaps and detergents. The saponification reaction is discussed at length in Chapter 23.

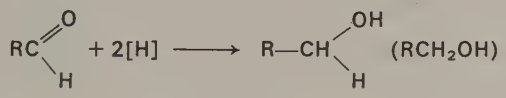
Although saponification of esters is a preparative route to alcohols, it is not generally used as a synthetic method, for esters themselves are usually prepared from alcohols. The reaction is of value, however, for the *regeneration* of an alcohol from an ester. Esterification of a hydroxyl group is in many cases an effective way to "protect" it during a series of chemical transformations in which the hydroxyl group must be preserved. This device can be employed to advantage when, for steric reasons, one of the two hydroxyl groups can be esterified, or one of two ester groupings may be saponified, permitting the free hydroxyl group to be oxidized (see Section 23-9). Many examples of this are found in the chemistry of steroids. The following is illustrative:



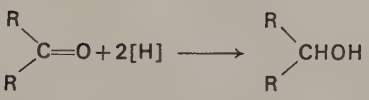
Cholestane-3β6β-diol (21)

11-9 Reduction of carbonyl compounds

A general and widely used method for the preparation of primary and secondary alcohols is by the reduction of the carbonyl group of an aldehyde, ketone, or carboxylic acid derivative. The general expression for the reaction is



(22)



(23)

The symbol 2[H] in the above equations is a formal designation of the addition of hydrogen to the carbon-oxygen double bond. Many procedures and reagents are used to bring about this addition.

Catalytic reduction is performed by shaking a solution of the carbonyl compound in an atmosphere of hydrogen, in the presence of a catalyst. The catalysts commonly used are platinum, palladium, and nickel, but for certain purposes catalysts containing copper and chromium also find use.

Catalytic reduction of aldehydes and ketones is not widely used in laboratory practice, in part because the reaction is unselective, so that other reducible groups in the molecule are also hydrogenated. However, because of its inherently low cost and its applicability to large-scale operation, it finds some industrial application.

Catalytic reduction of acid derivatives is an important industrial process. Fats

and oils, which are esters of long-chain aliphatic acids and glycerol, are reduced at high pressure and elevated temperature to yield long-chain aliphatic alcohols, used in the manufacture of synthetic detergents (Section 23-7).

$$\begin{array}{l} CH_2OCO(CH_2)_xCH_3 \\ | \\ CHOCO(CH_2)_yCH_3 \\ | \\ CH_2OCO(CH_2)_zCH_3 \end{array} \xrightarrow[300°,\ 200\ atm]{H_2,\ CuCrO_3} \begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + \begin{array}{l} CH_3(CH_2)_xCH_2OH \\ CH_3(CH_2)_yCH_2OH \\ CH_3(CH_2)_zCH_2OH \end{array} \qquad (24)$$

Numbers x, y, and z may vary from 10 to 16, and are usually not the same; "pure" fats and oils, in which $x = y = z$, are seldom encountered in natural sources.

11-10 Reduction by metal hydrides

The most frequently used method for reducing aldehydes, ketones, and acid derivatives to the corresponding alcohols is reduction with metal hydrides. Lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, both commercially available, are most widely employed.

Lithium aluminum hydride is very reactive with water and acids; it is used in non-hydroxylic solvents, usually diethyl ether or tetrahydrofuran. Sodium borohydride is a less active reducing agent, and can be used in neutral or slightly alkaline alcoholic solution (methanol or ethanol).

Lithium aluminum hydride (LAH) reduces aldehydes, ketones, carboxylic acids, and acid derivatives to alcohols, and nitriles to amines, smoothly and in good yields. The immediate products of the reaction are alkoxyaluminum salts, which are converted to the alcohols by aqueous acid; the complete expression for the reduction of an aldehyde is the following:

$$RCHO + LiAlH_4 \longrightarrow [(RCH_2O)_4Al]^-Li^+ \xrightarrow[H^+]{H_2O} RCH_2OH + \text{Li and Al salts} \qquad (25)$$

Other reductions proceed to the final products shown in the following:

$$R_2C{=}O \xrightarrow{LAH} R_2CHOH \qquad (26)$$

$$RCOOH \xrightarrow{LAH} RCH_2OH \qquad (27)$$

$$RCOOR' \xrightarrow{LAH} RCH_2OH \qquad (28)$$

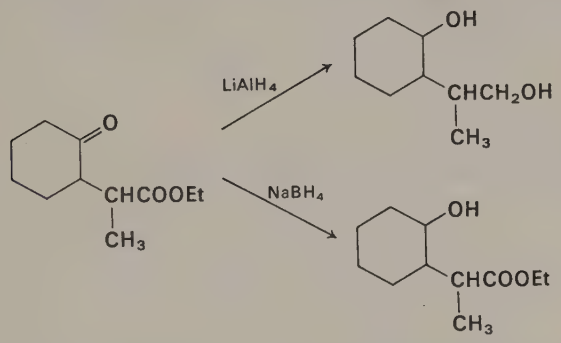
$$RCN \xrightarrow{LAH} RCH_2NH_2 \qquad (29)$$

Treatment of lithium aluminum hydride with *t*-butyl alcohol causes replacement of one or more (depending upon the proportions of reagents used) of the hydrogens of $LiAlH_4$ by the alkoxy grouping:

$$LiAlH_4 + 3t\text{-}BuOH \longrightarrow LiAlH(Ot\text{-}Bu)_3 + 3H_2 \qquad (30)$$

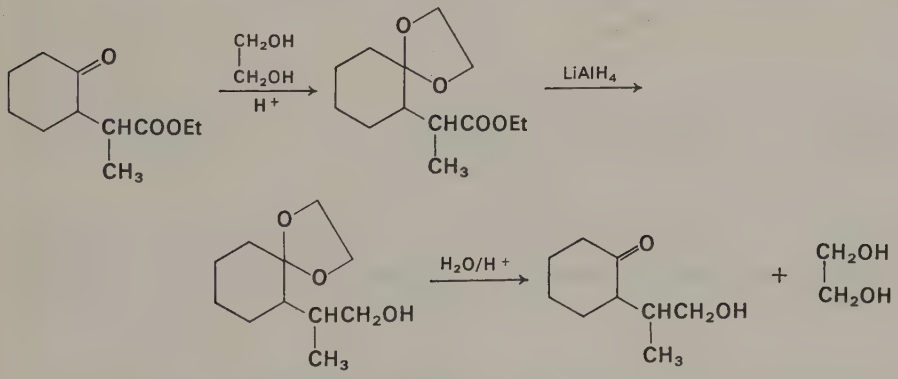
This modified reagent (and others prepared from alcohols other than *t*-BuOH) possesses the reducing power of its remaining hydrogen atom, but with much decreased activity. It can reduce reactive carbonyl compounds (for example, acid halides) but reacts only slowly with most aldehydes and ketones. Its applications will be described in a later chapter.

Sodium borohydride is a much less active reducing agent than LAH. It reduces aldehydes and ketones, but reduces esters slowly or not at all. It is therefore suitable for selective reduction of carbonyl groupings. An example is the following:



(31)

The following example illustrates the use of cyclic acetal formation (Section 12-10) to "protect" a carbonyl group during a metal hydride reduction reaction:



(32)

Chosen judiciously in conjunction with selective protection of reducible functional groups, the metal hydrides are of great versatility and value as reducing agents.

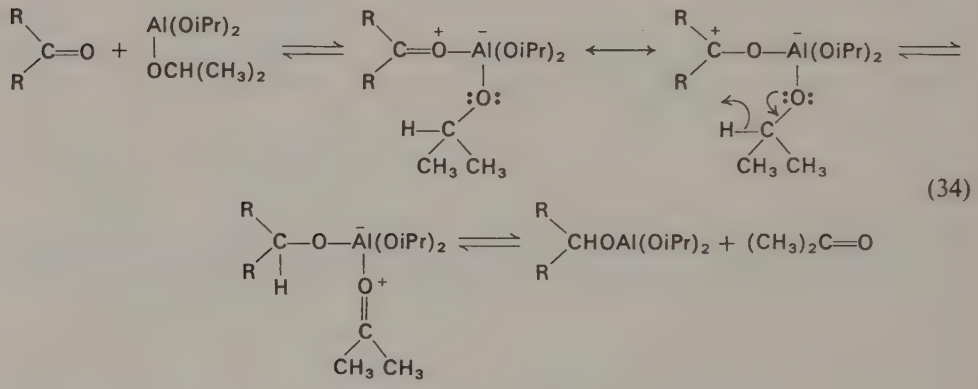
11-11 Reduction by metal alkoxides

The transfer of hydrogen between a ketone and a secondary alcohol

$$R_2C{=}O + R'_2CHOH \rightleftharpoons R_2CHOH + R'_2C{=}O \qquad (33)$$

can be catalyzed by alkoxides of aluminum or magnesium. Because the equation shown represents an equilibrium reaction, complete reduction of $R_2C{=}O$ is accomplished by using a large excess of R'_2CHOH or by removing the ketone (for example, by distillation) $R'_2C{=}O$ as it is formed. In practice, the secondary alcohol used is usually the inexpensive isopropyl alcohol. The catalyst is aluminum isopropoxide, $Al(OCH(CH_3)_2)_3$, which is easily prepared from metallic aluminum and the alcohol.

The role of the metal alkoxide in this reaction is to form a coordination complex with the oxygen atom of $R_2C{=}O$ (recall that AlX_3 is a Lewis acid with a vacant orbital). The following represents the course of the hydrogen-transfer reaction within the coordination complex (only one of the isopropyl groups of $Al(OiPr)_3$ is shown in detail):



(34)

At the completion of three such hydrogen-transfer steps the "new" alcohol, R_2CHOH, is present as the aluminum alkoxide, $Al(OCHR_2)_3$. This is easily hydrolyzed by aqueous acid to form the alcohol and aluminum salts.

This procedure is known as the *Meerwein-Ponndorf-Verley reduction*. It has the advantage that it is specific for the carbonyl group; other reducible structures (for example, carbon-carbon double bonds) are not affected.

11-12 Preparation of alcohols with Grignard reagents

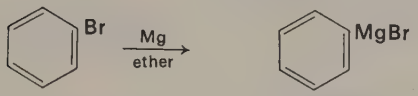
The most general and versatile method for the preparation of alcohols is the addition of organometallic compounds (Grignard reagents and organolithium compounds) to aldehydes, ketones, or esters. The formation and structure of Grignard reagents (organomagnesium compounds) are dealt with in detail in Chapter 20, in which the addition is described. They will be represented here by the generalized formula RMgX, where R is methyl, phenyl, and so on, and X is a halogen, usually Br, Cl, or I.

The preparation of several typical Grignard reagents is shown in these examples;

the ether (ethyl ether or tetrahydrofuran, THF) shown as a part of each equation is an important participant in the reaction (see Chapter 20).

$$CH_3I \xrightarrow[\text{ether}]{Mg} CH_3MgI \qquad (35)$$

Methylmagnesium iodide



(36)

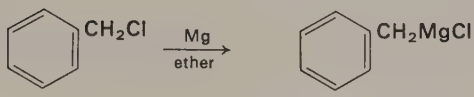
Phenylmagnesium bromide

$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[\text{ether}]{Mg} CH_3CH_2\underset{\displaystyle MgBr}{\underset{|}{C}}HCH_3 \qquad (37)$$

sec-butylmagnesium bromide

$$CH_2{=}CHCl \xrightarrow[THF]{Mg} CH_2{=}CHMgCl \qquad (38)$$

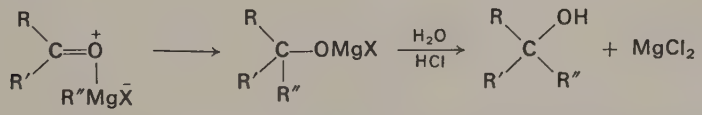
Vinylmagnesium chloride



(39)

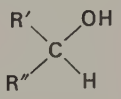
Benzylmagnesium chloride

The reaction of a Grignard reagent with the carbonyl group of an aldehyde or ketone is usually simple and straightforward; it can be expressed in the following generalized terms:

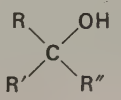


(40)

(*a*) If R = R′ = H (formaldehyde), the product is a *primary* alcohol, $R''CH_2OH$.
(*b*) If R = H and R′ = alkyl or aryl (aldehydes), the product is a *secondary* alcohol:

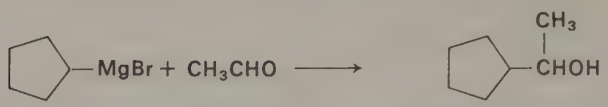


(*c*) If R and R′ are alkyl or aryl (ketones), the product is a *tertiary* alcohol:

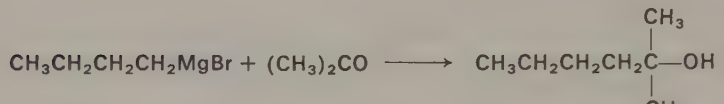


Some specific examples are:*

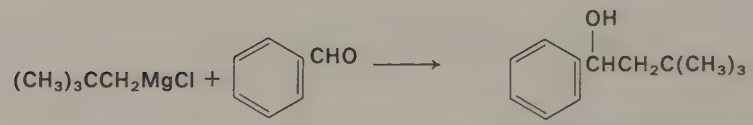
$$(CH_3)_2CHMgBr + HCHO \longrightarrow (CH_3)_2CHCH_2OH \qquad (41)$$



Cyclopentylmagnesium bromide — 1-cyclopentylethanol (cyclopentylmethylcarbinol) (42)

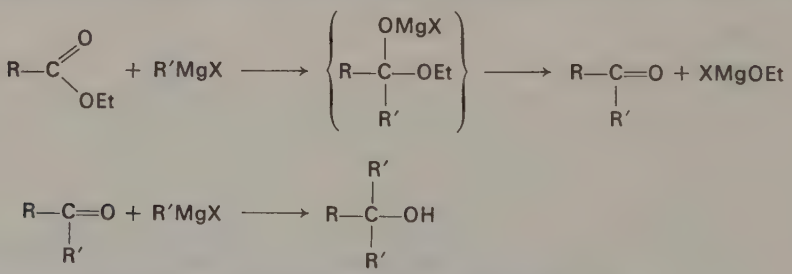


2-methyl-2-hexanol (43)



Neopentylmagnesium chloride — 1-phenyl-3,3-dimethyl-1-butanol (phenylneopentylcarbinol) (44)

Esters react with Grignard reagents to give tertiary alcohols. The reaction has been shown in some closely studied cases to proceed by way of the intermediate ketone, which then reacts with a second molecule of RMgX to yield the tertiary alcohol:



(45)

It should be noted that in the tertiary alcohol prepared in this way, the two added groups (R′ in the foregoing equations) are both derived from R′MgX. There are two variants of this reaction: (*a*) formic esters give secondary alcohols (R_2CHOH from RMgX), and (*b*) diethyl carbonate gives tertiary alcohols in which all three substituents derive from the Grignard reagent. These reactions are illustrated by the following examples:†

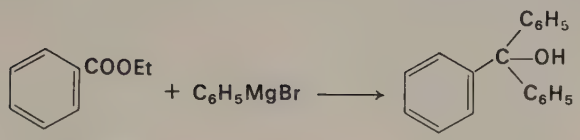
---

* The final step of hydrolysis of the —OMgX addition compound by means of aqueous acid is usually omitted from equations of this kind.

† Since the —OR′ group of the ester RCOOR′ is lost in the reaction, it is immaterial whether a methyl or ethyl (or other) ester is used.

$$CH_3COOEt + C_6H_5MgBr \longrightarrow CH_3-C(C_6H_5)_2-OH \quad (46)$$

Diphenylmethylcarbinol



(47)

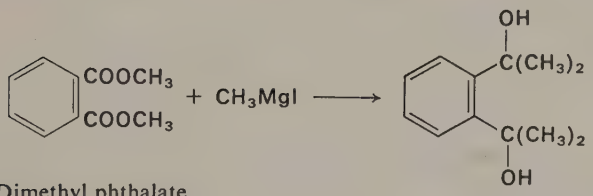
Ethyl benzoate — Triphenylcarbinol

$$HCOOEt + (CH_3)_2CHMgBr \longrightarrow (CH_3)_2CHCH(OH)CH(CH_3)_2 \quad (48)$$

Ethyl formate — 2,4-dimethyl-3-pentanol

$$CO(OEt)_2 + CH_2{=}CHCH_2MgCl \longrightarrow CH_2{=}CHCH_2-C(OH)(CH_2CH{=}CH_2)-CH_2CH{=}CH_2 \quad (49)$$

Diethyl carbonate — Triallylcarbinol



(50)

Dimethyl phthalate

Exercise 4

Formulate the Grignard reactions that would yield the following alcohols: (*a*) $CH_3CH_2CH(OH)CH(CH_3)_2$ (*b*) $CH_3C(OH)(CH_2CH_3)_2$ (three methods)
(*c*) $(CH_3CH_2)_3COH$ (*d*) $(C_6H_5)_2CHOH$ (*e*) $CH_3CH{=}CHCH(OH)CH_2CH{=}CH_2$.

Exercise 5

Show the results of the reaction of *n*-propylmagnesium chloride with (*a*) acetone, (*b*) acetophenone, (*c*) methyl propionate, (*d*) ethyl 4-butenoate, (*e*) diethyl carbonate, (*f*) ethyl formate, and (*g*) diethyl succinate.

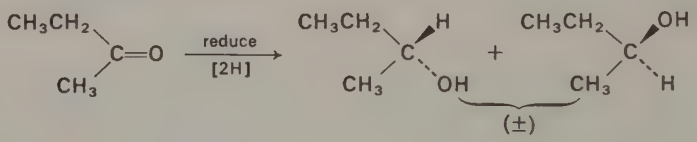
Exercise 6

What compound would be produced if the product formed in the reaction between diethyl succinate and CH_3MgI were heated with aqueous sulfuric acid? (NOTE: The final product has the composition $C_8H_{16}O$ and contains no hydroxyl group or carbon-carbon double bond.)

11-13 Stereochemical control of the reduction of carbonyl compounds

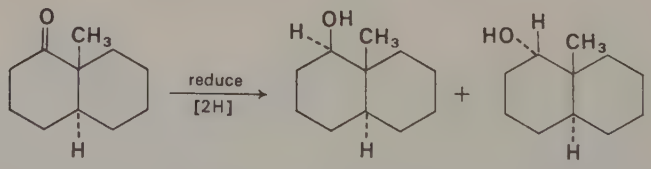
Reduction, by any means that involves only symmetrical reagents, of an aldehyde or ketone that lacks any elements of dissymmetry yields a product that is optically inactive.

For example, the 2-butanol that is formed by reduction of 2-butanone by a metal hydride or by catalytic hydrogenation is the optically inactive, racemic alcohol:



(51)

Because 2-butanone has a planar sp^2 carbonyl carbon atom, attack of the reducing agent *is equally probable at either face* of the planar molecule, and thus the enantiomers are formed in equal amounts. On the other hand, in the reduction



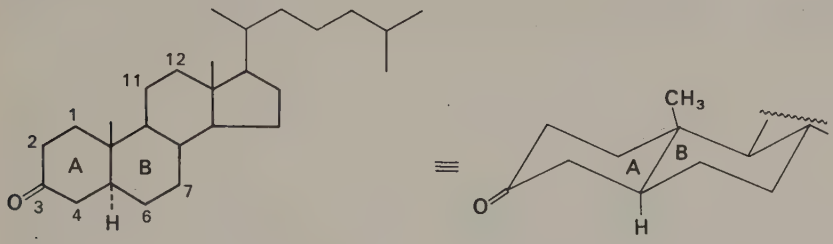
(52)

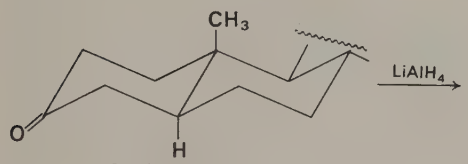
the two alcohols are formed in unequal amounts; the proportion depends upon the method of reduction. It can be seen that the starting ketone is optically active.

When structural factors in the carbonyl compound favor reaction at one face of the C=O group, a preponderance of one of the two possible *epimers* may be formed.

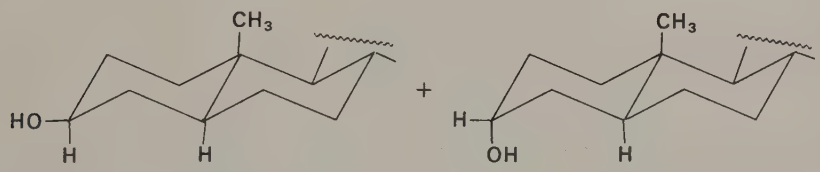
There is no simple rule for predicting with certainty which of a pair of epimers will be formed in greater amount in metal hydride reductions. In general, in epimers formed from cyclic ketones, the *equatorial* alcohol (Section 27-4) will predominate, although the "rule" must be applied with circumspection. The following examples

are drawn from the extensively studied field of steroid chemistry. In these equations only the A and B rings of the steroids are shown, because other parts of the structure (C and D rings) are not near the center at which reduction occurs and so have relatively little effect.





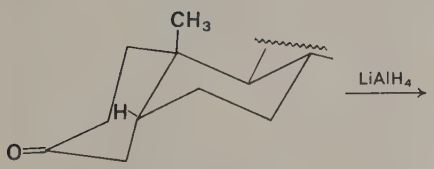
Cholestan-3-one



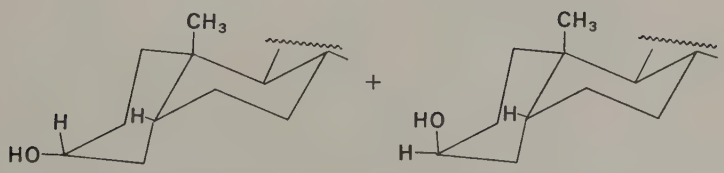
(53)

3β-ol (91%)
(OH equatorial)

3α-ol (4%)
(OH axial)



Coprostan-3-one



(54)

3α-ol (96%)
(OH equatorial)

3β-ol (4%)
(OH axial)

Exercise 7

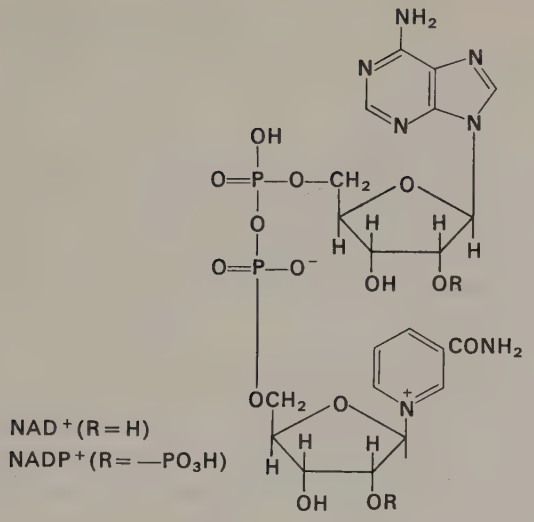
Using for guidance the results shown in the above equations, predict the result of $LiAlH_4$ reduction of (*a*) cholestan-1-one, (*b*) cholestan-11-one, and (*c*) (R)-2-methylcyclohexanone.

Since the stereochemical results of carbonyl-group reduction, as shown in the above equations, are influenced by the steric interactions between the metal hydride and the groups in the environment of the carbonyl group, it could be expected that a larger, more bulky reducing agent would be more influenced by steric effects and would show a greater stereochemical selectivity. This is found to be the case. The somewhat more space-filling sodium borohydride shows a greater selectivity than lithium aluminum hydride, and the bulky lithium tri-*t*-butoxyaluminum hydride, $LiHAl(OtBu)_3$, surpasses $NaBH_4$ in selectivity.

Catalytic reduction depends upon adsorption of the carbonyl compound to the surface of the catalyst, and thus could be expected to show a high degree of stereoselectivity, with both hydrogen atoms attaching to the less-hindered side of the molecule. This is often found to be the case, and in the absence of contrary evidence may be cautiously assumed; but it is by no means an inviolable rule. The stereochemistry of the catalytic hydrogenation is found to be dependent upon the catalyst used, the solvent used, and the acidity or basicity of the reaction medium. No simple generalizations can be made, except that in a basic medium the thermodynamically more stable equatorial alcohol is likely to be the predominant product.

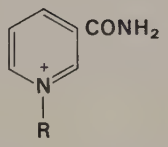
11-14 Steric control in biological reductions

The reversible reduction of carbonyl groups in cellular metabolism is an important biochemical process. Several reactions of this class are shown in the equations below; in all of them hydrogen is reversibly accepted and provided by the oxidized and reduced forms of enzyme prosthetic groups (coenzymes) known as nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$). The structures of these are shown below; the active hydrogen-transferring portion of the molecule is the pyridine ring, emphasized in an abbreviated representation.



$NAD^+ (R = H)$
$NADP^+ (R = —PO_3H)$

Abbreviated representation:



Some examples of these hydrogen-transfer (oxidation-reduction) reactions are the following:

$$CH_3CH_2OH + NAD^+ \rightleftharpoons CH_3CHO + NADH + H^+ \quad (55)$$

$$\underset{\text{Malic acid}}{\begin{matrix}CHOHCOOH\\ |\\ CH_2COOH\end{matrix}} + NAD^+ \rightleftharpoons \underset{\text{Oxaloacetic acid}}{\begin{matrix}O{=}CCOOH\\ |\\ CH_2COOH\end{matrix}} + NADH + H^+ \quad (56)$$

$$\underset{\text{Lactic acid}}{CH_3CHOHCOOH} + NAD^+ \rightleftharpoons \underset{\text{Pyruvic acid}}{CH_3COCOOH} + NADH + H^+ \quad (57)$$

$$\underset{\alpha\text{-glycerophosphate}}{\begin{matrix}CH_2OPO_3H\\ |\\ CHOH\\ |\\ CH_2OH\end{matrix}} + NAD^+ \rightleftharpoons \underset{\text{Phosphodihydroxy acetone}}{\begin{matrix}CH_2OPO_3H\\ |\\ CO\\ |\\ CH_2OH\end{matrix}} + NADH + H^+ \quad (58)$$

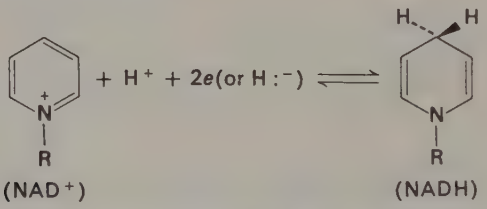
$$\underset{\beta\text{-hydroxybutyric acid}}{\begin{matrix}OH\\ |\\ CH_3CHCH_2COOH\end{matrix}} + NAD^+ \rightleftharpoons \underset{\beta\text{-ketobutyric acid}}{CH_3COCH_2COOH} + NADH + H^+ \quad (59)$$

All of these reactions can be expressed by the partial equation

$$\text{>CHOH} + \text{NAD}^+ \rightleftharpoons \text{>C=O} + \text{NADH} + \text{H}^+ \qquad (60)$$

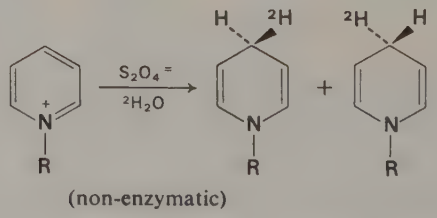
It should be noted that the —CHOH— group of all of them (except ethanol) is an asymmetric center, and that malic acid, lactic acid, glyceryl-1-phosphate and β-hydroxybutyric acid can be (and in nature are) optically active. It is important to emphasize here that enzyme-catalyzed reduction and oxidation by nicotinamide coenzymes is always stereospecific: reduction of oxaloacetic acid gives only one of the two enantiomeric malic acids; reduction of β-ketobutyric acid gives only one of the two enantiomeric β-hydroxybutyric acids; and so on. The asymmetry of these reductions is the consequence of the asymmetrical environment (the enzyme) in which hydrogen transfer occurs.

The role of the nicotinamide derivative is as an acceptor and donator of hydrogen. The oxidized (NAD^+) and reduced (NADH) forms of the coenzyme are represented as follows, where the ribose-diphospho-ribose-adenine portion is represented by R, and the $—CONH_2$ group is omitted:



(61)

That position 4 of the pyridine ring is indeed the site of reduction has been proved by experiments with deuterium(^2H)-labeled reagents.* The reduction of NAD^+ to NADH can also be accomplished by inorganic reagents such as sodium borohydride or sodium dithionite ($Na_2S_2O_4$). If such a reduction is carried out with NaB^2H_4 or with $Na_2S_2O_4$ in ^2H_2O the resulting NAD^2H is a diastereomeric mixture of the two 4-deutero compounds:



(62)

When this NAD^2H is used as the coenzyme to reduce, say, acetaldehyde, it is found that only a part of the deuterium (in simplest terms, half of it) is transferred, to yield

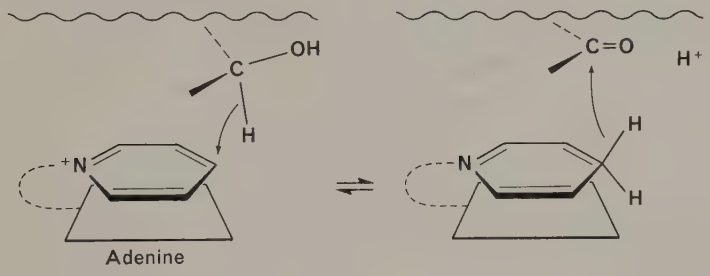
* Note that the D in NAD^+ does not represent deuterium, but is an abbreviation of "dinucleotide."

ethanol-1-^{2}H (1-deuteroethanol) and ethanol:

$$NAD^2H + CH_3CHO \rightleftharpoons NAD^+ + NAD(4\text{-}^2H)^+ + CH_3CH^2HOH + CH_3CH_2OH \quad (63)$$

In another experiment, NAD^+ was reduced enzymatically by $CH_3C^2H_2OH$, giving NAD^2H. When this was used to reduce CH_3CHO, it was found that *all* of the deuterium was transferred to yield *non-deuterated NAD*$^+$ and CH_3CH^2HOH (1-deuteroethanol). The enzymatically reduced NAD^2H was also allowed to reduce pyruvic acid: all the lactic acid was found to be deuterated, and no deuterium remained in the NAD^+.

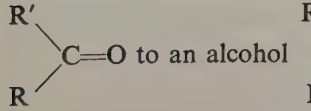
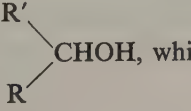
The conclusions from these experiments are (*a*) that there is a direct transfer of hydrogen from the reduced coenzyme to the substrate, and (*b*) that the transfer of hydrogen to and from the NAD molecule in the enzymatic reaction takes place from the same side of the pyridine ring. Additional studies have led to the proposal that in the active enzyme, the NAD molecule is arranged so that the adenine ring and the pyridine ring lie one on top of the other in a sandwich-like disposition. It is apparent that with such an arrangement a substrate providing hydrogen to NAD^+, or accepting hydrogen from NADH, can do so only from one face of the pyridine ring. Thus, the H that reduces NAD^+ is the same one that NADH provides to a hydrogen acceptor (an oxidant):



(64)

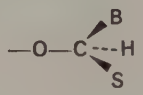
Stereochemical specificity with respect to the substrate molecules (keto compound, alcohol) requires additionally that they must be oriented in a specific manner in the substrate-enzyme complex. Here the protein plays an essential role, by providing an asymmetric environment into which the substrate, for example lactic acid, can "fit" in only one attitude.

11-15 Stereochemical induction in reduction

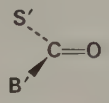
An optically active reducing agent could be expected to reduce a carbonyl compound  to an alcohol  , which would contain a preponderance of one

of the enantiomers and thus show optical activity. This has been achieved in practice, the reducing agent being an aluminum alkoxide in which the alkoxy groups are asymmetric and of the same chirality. Such an agent could be, for example, Al(O-*sec*-butyl)$_3$ in which the *sec*-butyl groups are all R or all S in configuration.

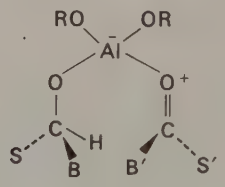
This can be illustrated schematically in the following way. Let the asymmetry of the chiral alkoxy group be represented as



where S is a small group (for example, CH_3) and B is a bulky group (for example, CH_2CH_3 or larger), and the ketone to be reduced similarly represented as

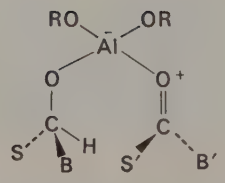


It will be seen that in the transition state for hydrogen transfer, the orientation



(65)

will be less favored than



(66)

because of steric interference between the two larger groups B and B′ in the former complex. Since one of the two complexes is favored, this imposes a chiral orientation upon the transition state and leads to asymmetric reduction. It should be noted that this reaction is seldom entirely stereospecific, for the unfavorable orientation is not absolutely barred.

Problems

1. Using as starting materials any compounds of three carbon atoms or less, show how the following compounds could be prepared: (*a*) 3-pentanol, (*b*) 3-methyl-1-butanol, (*c*) triethylmethanol (triethylcarbinol), (*d*) 2-methyl-2-butanol, (*e*) 3-methyl-2-butanol.

2. Write the structures of the olefins that, on hydration, would yield the following alcohols: (*a*) 2-propanol, (*b*) *t*-butyl alcohol, (*c*) 2-butanol, (*d*) 2-methyl-2-butanol, (*e*) 1-methyl-1-cyclohexanol.

3. What alcohols would be obtained if each of the olefins used in Problem 2 were subjected to hydroboration, followed by hydrogen peroxide oxidation?

4. Write the reactions showing the final products formed in the reduction of the following compounds by lithium aluminum hydride (intermediate organometallic compounds need not be shown): (*a*) acetaldehyde, (*b*) isopropyl propionate, (*c*) 2-butanone, (*d*) methyl acetate.

5. Show the steps involved in the reduction of 3-pentanone to 3-pentanol by means of aluminum isopropoxide in (excess) isopropyl alcohol.

6. Write the equations (showing final products only) for the reaction of isobutylmagnesium bromide with (*a*) acetone, (*b*) formaldehyde, (*c*) cyclohexanone, (*d*) diethyl ketone, (*e*) benzaldehyde, (*f*) ethyl formate, and (*g*) hexane-2,5-dione.

7. Starting with 2-methylpropene (isobutylene), describe how you could prepare (*a*) $(CH_3)_2CDCH_2OH$, (*b*) $(CH_3)_2CHCH_2D$, (*c*) $(CH_3)_2CDCH_3$, and (*d*) $(CH_3)_2CDCH_2D$ (D = ^2H).

8. Starting with ethyl acetate as the only organic compound, show how you could prepare triethylmethanol.

12

The hydroxyl group. Reactions of alcohols

The theory of acids and bases discussed earlier (Chapter 4) finds expression in much of the material in this chapter. The hydroxyl group, which is characteristic of the alcohols, possesses nonbonding (unshared) electrons on oxygen, and an ionizable proton. A great part of the chemistry of alcohols depends upon the nucleophilic properties of the hydroxyl group and of the alkoxide ions formed by removal of the proton. The nucleophilic character of the hydroxyl group itself is expressed in several of the principal reactions of alcohols. The hydroxyl group can be protonated as the initial step in the dehydration of alcohols to form olefins. It can act as the nucleophile in reaction with electrophilic centers such as those in carboxylic acids (to form esters), aldehydes (to form hemiacetals and acetals), and protonated olefins (to form ethers). The mechanisms of these reactions are described here in detail.

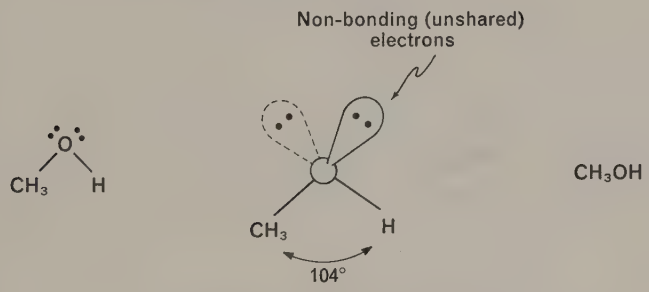
The conjugate bases of alcohols (the alkoxide ions) are excellent proton acceptors and find many uses as the reagents in base-catalyzed reactions. They are excellent nucleophiles as well, as shown by the Williamson ether synthesis and other nucleophilic displacement reactions (described in Chapter 7) and they have many uses in organic synthesis.

The last sections of this chapter describe a class of compounds whose chief importance lies in their practical uses. Esters of alcohols with inorganic acids of sulfur and phosphorus are valuable in medicine, agriculture, and industry, and as reagents in organic synthesis.

12-1 The hydroxyl group

The important chemistry of alcohols is chiefly that of the hydroxyl group and the carbon-oxygen bond. Although we can describe and interpret many of the reactions of alcohols in terms of a generalized formula, R—OH, in their chemical behavior differences exist that depend upon whether they are primary, secondary, or tertiary; whether the group R in ROH is saturated or unsaturated; and, when R is unsaturated, the location of the —OH group with respect to the double bond.

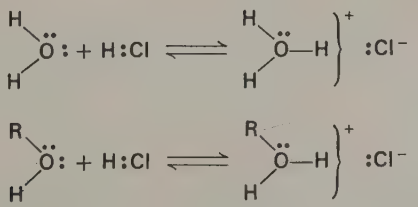
The hydroxyl group consists of a hydrogen atom and an oxygen atom bonded together; in alcohols, the oxygen atom is also bonded to a carbon atom, thus utilizing two of the six oxygen electrons in two covalent bonds and leaving four electrons as two non-bonding (unshared) pairs. The C—O—H angle in methanol is about 104°, slightly less than the tetrahedral bond angle of 109°, indicating that the four orbitals of oxygen are approximately sp^3 in character. It is not usually necessary to represent the structure of an alcohol by drawing it in a way that shows its angular form; a simple linear formula is ordinarily adequate. Whether the unshared electrons are explicitly shown depends upon whether it is desired to direct attention to their involvement in the reaction under discussion.



Formal Representations of Methanol

12-2 Alcohols as weak organic bases

The —OH group of alcohols is qualitatively comparable to the —OH group of water. Just as water is weakly basic, capable of being protonated, so are alcohols:



An alkyloxonium salt

Indeed, we shall see that many of the characteristic reactions of alcohols depend upon an initial protonation.

Since alcohols are very weak bases, their protonated forms are very strong acids (pK_a of *n*-alkyl-OH_2^+ is about -4, indicating that it is about 10^9 times as strong an acid as acetic acid).

12-3 Effect of protonation upon the C—O bond

Because of the difference in electronegativity between carbon and oxygen, the C—O bond is dissymmetric, with oxygen the negative end of a dipole. When the hydroxyl group is protonated, the resulting positive charge on oxygen increases the dissymmetry in the C—O bond, rendering the carbon atom more electron-deficient and thus susceptible to attack by a nucleophilic agent.

When methanol is dissolved in concentrated aqueous HBr, the following unexceptional proton-transfer equilibria are established:

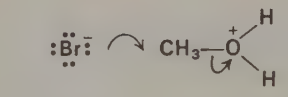
$$H_2O + HBr \rightleftharpoons H_3O^+ + Br^- \tag{3}$$

$$CH_3OH + HBr \rightleftharpoons CH_3OH_2^+ + Br^- \tag{4}$$

$$CH_3OH + H_3O^+ \rightleftharpoons CH_3OH_2^+ + H_2O \tag{5}$$

The solution initially contains the $CH_3OH_2^+$, H_3O^+, and Br^- ions as well as the unprotonated and undissociated CH_3OH, H_2O, and HBr.

Two reactions are now observed to take place: the nucleophilic attack upon the carbon atom of the methyl group of $CH_3OH_2^+$ by the neutral CH_3OH and by the Br^- ion:



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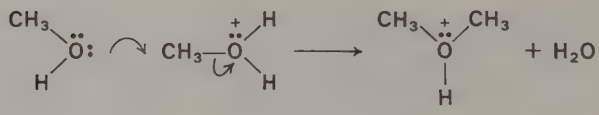

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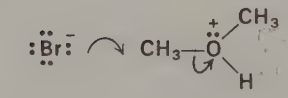
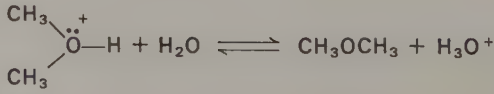


(8)

and the proton exchange:



(9)

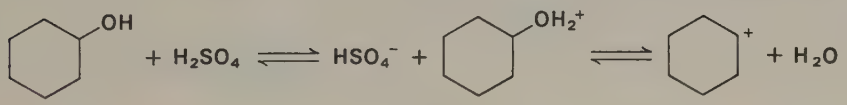
These reactions do not occur instantaneously, but proceed in time to yield methyl bromide and dimethyl ether as products. When a large excess of HBr is used, the principal product of the reaction is methyl bromide.

That the reaction is dependent upon protonation of the hydroxyl group is shown by the fact that methanol is quite unaffected by treatment with a concentrated solution of sodium bromide in the absence of strong acid.

12-4 Dehydration of alcohols

When ethanol and higher alcohols are heated with concentrated sulfuric or phosphoric acid, the conjugate bases (HSO_4^- and $H_2PO_4^-$) of which are poor nucleophiles, the protonated alcohol may dissociate into water and the carbonium ion, which can lose a proton to form the olefin:

$$\mathrm{RCH_2CH(R)-OH \overset{HA}{\rightleftharpoons} RCH_2CH(R)OH_2^+ \overset{-H_2O}{\rightleftharpoons} RCH_2\overset{+}{C}HR \overset{-H^+}{\rightleftharpoons} RCH{=}CHR} \qquad (10)$$



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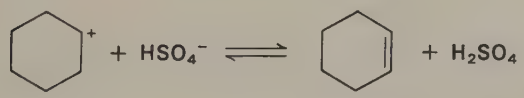


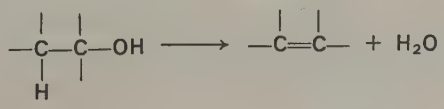
Cyclohexene

$$\mathrm{CH_3CH(CH_3)OH \xrightarrow[\Delta]{H_2SO_4} CH_3CH{=}CH_2} \qquad (12)$$

$$\mathrm{CH_3CH_2C(CH_3)_2OH \xrightarrow[\Delta]{H_2SO_4} CH_3CH{=}C(CH_3)_2} \qquad (13)$$

The ease of dehydration of an alcohol is related to the stability of the intermediate carbonium ion. The ease of dehydration (as expressed by the temperature and concentration of sulfuric or phosphoric acid required) is greatest with tertiary alcohols, least with primary alcohols.

Alcohol dehydration is classed as an *elimination reaction*, for the overall reaction consists of the removal of H and OH:

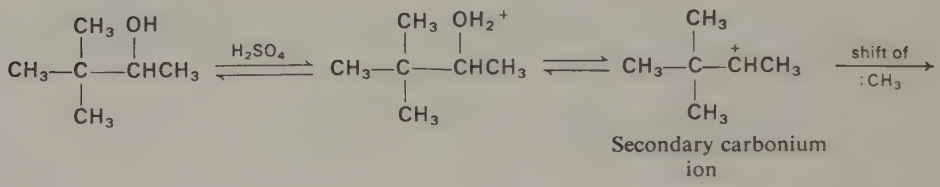


(14)

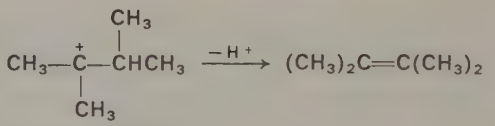
For most alcohols, the mechanism of the reaction is defined as E1 (elimination, unimolecular), for the rate-determining step is the dissociation of the protonated alcohol. Further discussion of elimination reactions was presented in Chapter 10.

12-5 Evidence for the mechanism of alcohol dehydration

The intermediacy of the carbonium ion in alcohol dehydration has been inferred from the relative rates of dehydration of tertiary, secondary, and primary alcohols. It can be convincingly demonstrated by the observation that molecular rearrangements occur when certain alcohols are dehydrated. If the initially formed carbonium ion can be transformed into a more stable isomer by a 1,2-shift of an adjacent group, a change in the carbon skeleton will result:



Secondary carbonium ion



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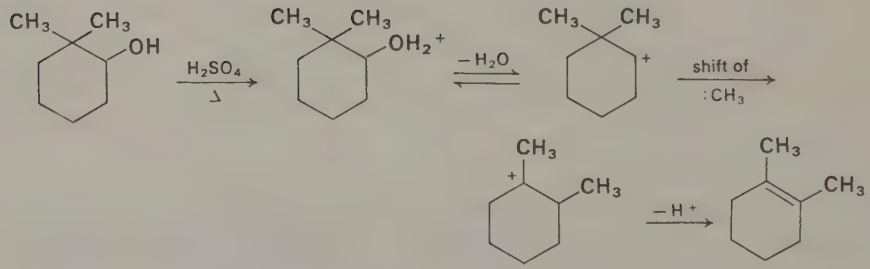
Tertiary carbonium ion



(16)

The course of such reactions, in which the increased stability of the tertiary carbonium ion leads to the formation of the rearranged product, can be illustrated by the energy profile for the acid-catalyzed dehydration of 3,3-dimethyl-2-butanol (Figure 12-1).

It is prudent to assume in experimental work that when such rearrangements are structurally possible and energetically probable, they will occur, at least to some degree. For this reason, preparative routes to olefins by the dehydration of alcohols

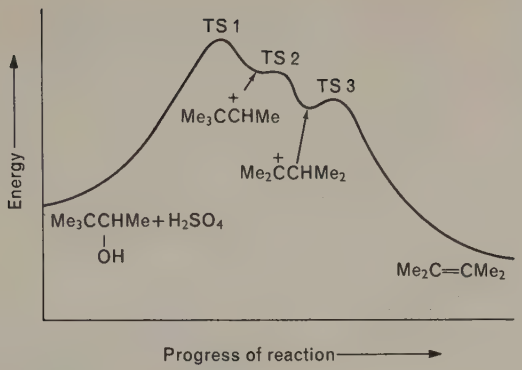
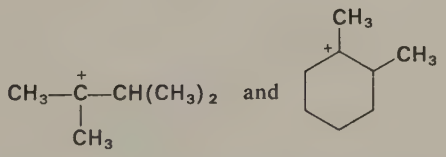


Figure 12-1
Energy profile of the dehydration of 3,3-dimethyl-2-butanol, showing the carbonium-ion intermediates.

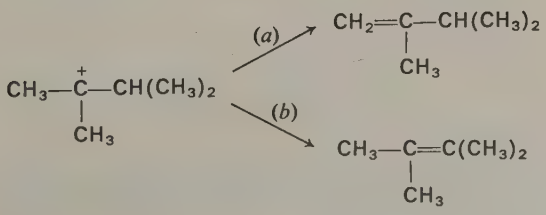
must be chosen with care, with the recognition that mixtures of products may sometimes occur, and that "expected" products may be contaminated with isomeric compounds that are difficult to remove.

12-6 Direction of elimination

The carbonium ion intermediates



described in the foregoing section can form olefinic products by proton abstraction in more than one way:



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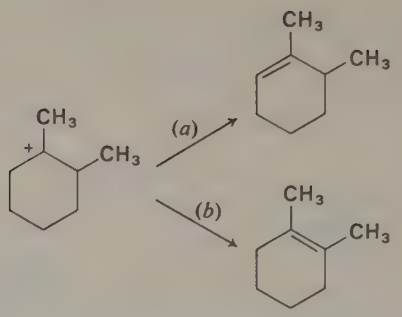


(18)

In each case route (*b*) is predominant, producing *the more highly substituted olefin.* This was early recognized as the usual consequence of alcohol dehydration, and was expressed as *Saytzev's rule.* The rule does not, of course, explain *why* alcohol dehydration, or proton abstraction from a carbonium intermediate, proceeds as it does; this must be explained in terms of the energetics of the reaction.

Taking $(CH_3)_2C^+—CH_2CH_3$ for consideration, it can first of all be said that since both olefinic products arise from the same intermediate, but clearly at different rates of proton abstraction, they proceed through transition states (TS) of different energy. The slower reaction, leading to the less-substituted olefin, passes through the higher-energy TS (2*a*, Figure 12-2); the faster reaction, leading to trimethylethylene, passes through the lower energy TS (2*b*).

Although the exact details of TS structure cannot always be formulated, we can assume that the structure of a TS resembles that of the product to which it leads. We can assume, therefore, that trimethylethylene possesses structural features that render it more stable than its isomer. The reason why alkyl substituents on a double bond increase stability can be stated in more than one way. A satisfactory explanation is

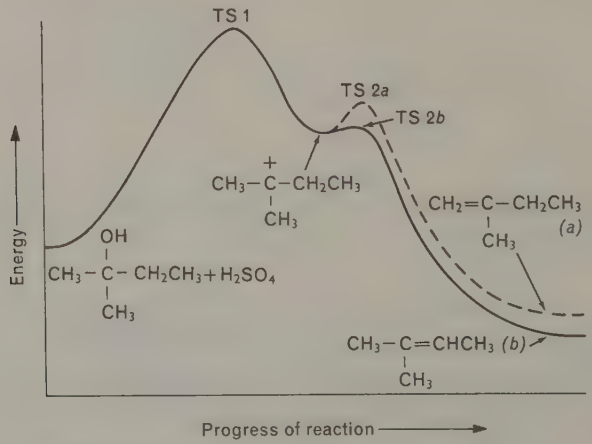
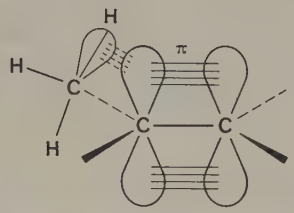


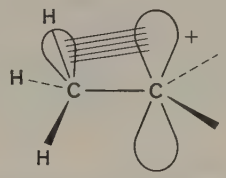
Figure 12-2
Energy profile for the dehydration of 2-methyl-2-butanol to give the olefins 2-methyl-1-butene (*a*) and 2-methyl-2-butene (*b*).

that the π electrons of the carbon-carbon double bonds are delocalized to some extent by participation of these electrons in the C—H bonds of the attached alkyl groups:



(19)

A similar explanation has been offered to account for the stabilization of carbonium ions by attached alkyl groups (Chapter 7):



(20)

It can be seen that the greater the number of alkyl groups (for example, $—CH_3$) attached to the double-bound carbon atoms, the greater the opportunity for such charge delocalization.

Saytzev's rule, then, is really a statement regarding the relative stability of olefins, and expresses the consequences of the difference between the energy levels of transition states through which the reaction passes.

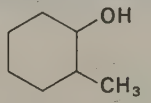
Exercise 1

What are the structures of the two olefins that would be formed by the acid-catalyzed dehydration of $CH_3—\underset{\displaystyle CH_3}{\overset{\displaystyle HO}{\overset{|}{\underset{|}{C}}}}—\overset{\displaystyle CH_3}{\overset{|}{CH}}—C(CH_3)_3$? Which would you expect to be the predominant product? (NOTE: In this case the "Saytzev product" is *not* the principal olefin formed. Why?)

Exercise 2

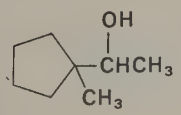
Show the product or products that would be formed upon heating the following alcohols with sulfuric or phosphoric acid.

(*a*) $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$

(*b*) 

(*c*) $(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3$

(*d*) $(CH_3)_3\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2CH_3$

(*e*) 

Exercise 3

When 1-butanol is dehydrated, the product may vary in composition from nearly pure 1-butene to mixtures of this and 2-butenes (*cis* and *trans*). Greater amounts of the 2-butenes are formed the longer the time of contact with the acid catalyst. Explain.

12-7 Alcohols as weak acids. Alkoxides

The familiar reaction of metallic sodium or potassium with water to form hydrogen and the metal hydroxide finds its exact parallel in the reaction of alcohols with these metals:

$$2H_2O + 2Na \longrightarrow 2(Na^+OH^-) + H_2 \qquad (21)$$

$$(CH_3)_3COH + K \longrightarrow (CH_3)_3O^-K^+ + \tfrac{1}{2}H_2 \qquad (22)$$

Potassium *t*-butoxide

$$CH_3CH_2OH + Na \longrightarrow CH_3CH_2O^-Na^+ + \tfrac{1}{2}H_2 \qquad (23)$$

Sodium ethoxide

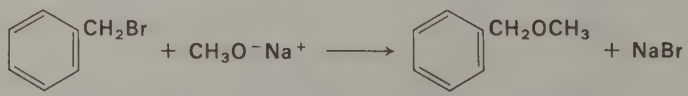
$$3(CH_3)_2CHOH + Al \longrightarrow ((CH_3)_2CHO)_3Al + \tfrac{3}{2}H_2 \qquad (24)$$

Aluminum isopropoxide

$$2CH_3OH + Mg \longrightarrow (CH_3O)_2Mg + H_2 \qquad (25)$$

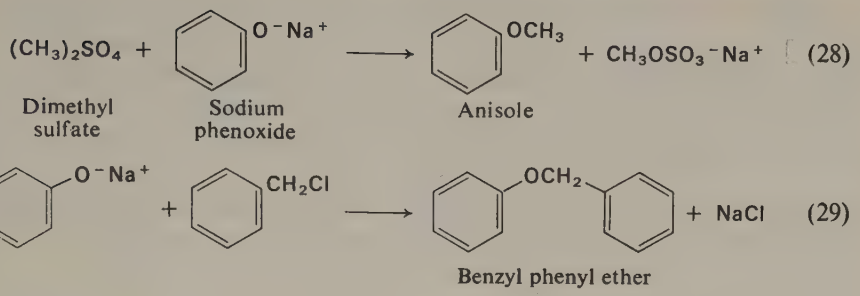
Magnesium methoxide

Since alcohols are very weak acids (pK_a of ROH about 15 to 18) their conjugate bases are very strong bases and effective nucleophiles. They engage in nucleophilic displacement reactions with primary alkyl halides, or sulfonic acid esters of primary alcohols, to yield *ethers*. This reaction, known as the *Williamson synthesis* of ethers, is illustrated by the following examples:



(26)

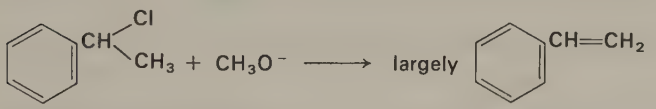
$$(CH_3)_2CHO^-Na^+ + CH_3CH_2I \longrightarrow (CH_3)_2CHOCH_2CH_3 + NaI \qquad (27)$$



The Williamson synthesis is less satisfactory with secondary alkyl halides, and ethyl isopropyl ether is obtained in lower yield from reaction of isopropyl iodide and sodium ethoxide than by reaction (27). The strongly basic alkoxide brings about elimination of HBr (an E2 reaction) in competition with ether formation (an S_N2 reaction). Tertiary alkyl halides give no ethers under these conditions; elimination (E1) is the exclusive result:

$$(CH_3)_2CHBr + CH_3O^- \longrightarrow (CH_3)_2CHOCH_3 + CH_3CH{=}CH_2 \qquad (30)$$

$$(CH_3)_3CCl + CH_3CH_2O^- \longrightarrow CH_2{=}C(CH_3)_2 \qquad (31)$$



The most important property of sodium and potassium alkoxides in organic synthesis is their strongly basic character and the fact that they are easily prepared and used in alcoholic solutions. Sodium methoxide is prepared simply by adding the desired amount of metallic sodium to methanol. The excess methanol may be removed by distillation, leaving the dry sodium methoxide; or the solution of the sodium alkoxide in methanol may be used.

Sodium methoxide, sodium ethoxide, and potassium *t*-butoxide have a wide and varied range of usefulness in organic chemistry. Their principal uses are in the deprotonation of very weak organic acids to form reactive and nucleophilic anions. Some examples of these proton-transfer reactions are (33)–(36); their many applications in organic syntheses will be encountered in succeeding chapters.

$$CH_3COCH_3 + CH_3O^- \rightleftharpoons CH_3COCH_2{:}^- + CH_3OH \qquad (33)$$

$$CH_2(COOEt)_2 + EtO^- \rightleftharpoons {:}CH(COOEt)_2 + EtOH \qquad (34)$$

$$CH_3C{\equiv}CH + t\text{-}BuO^- \rightleftharpoons CH_3C{\equiv}C{:}^- + t\text{-}BuOH \qquad (35)$$

$$CH_3COOCH_3 + CH_3O^- \rightleftharpoons {:}CH_2COOCH_3 + CH_3OH \qquad (36)$$

It should be carefully noted that these are proton-transfer equilibria, and in most cases lie largely to the left-hand side as they are written. The formation of the new anions (which are all written arbitrarily as carbon anions in these examples) can be demonstrated by the subsequent reactions in which they take part. Except for $CH_3C{\equiv}C:^-$ these anions are all resonance-stabilized enolate anions with the charge delocalized over the $-\overset{|}{C}-\overset{|}{C}=O$ system, as described in Chapter 9. Their behavior is not pertinent to the present discussion and will be dealt with later.

12-8 Alcohols as nucleophiles. Ether formation

Diethyl ether is prepared by the reaction of concentrated sulfuric acid and ethanol at about 140°. The equilibria involved in this reaction are complicated in detail but simple in principle. At low temperatures, diethyl sulfate is formed and can be isolated by vacuum distillation:

$$CH_3CH_2OH + H_2SO_4 \rightleftharpoons CH_3CH_2\overset{+}{O}H_2 + HSO_4^- \quad (37)$$

$$CH_3CH_2\overset{+}{O}H_2 + HSO_4^- \rightleftharpoons CH_3CH_2OSO_3H + H_2O \quad (38)$$

$$CH_3CH_2OSO_3H + CH_3CH_2OH \rightleftharpoons CH_3CH_2OSO_2OCH_2CH_3 + H_2O \quad (39)$$

At higher temperatures, unprotonated ethanol attacks protonated ethanol or an ethyl sulfate to give diethyl ether:

$$CH_3CH_2OH + CH_3CH_2\overset{+}{O}H_2 \longrightarrow CH_3CH_2OCH_2CH_3 + H_3O^+ \quad (40)$$

$$CH_3CH_2OH + CH_3CH_2OSO_3H \longrightarrow CH_3CH_2OCH_2CH_3 + H_2SO_4 \quad (41)$$

At still higher temperatures, ethylene is the product.

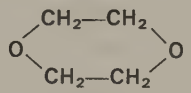
The formation of ethers by treating alcohols with mineral acids is not a useful general method because of the various alternative courses for the reaction. Secondary and tertiary alcohols are chiefly dehydrated to olefins. Exceptions to this are found in certain of the lower primary alkyl ethers (di-*n*-propyl, di-*n*-butyl) which can be prepared in this way. When dehydration is not possible, ether formation can be the principal result, but in most circumstances ethers are most readily prepared in other ways—for example, by the Williamson method.

Cyclic ethers can, however, be prepared by reacting suitably constituted glycols (dihydroxy compounds) with acid. 1,4-Dioxane, an important industrial solvent, is made by the reaction of ethylene glycol (ethane-1,2-diol) with sulfuric acid. In quite

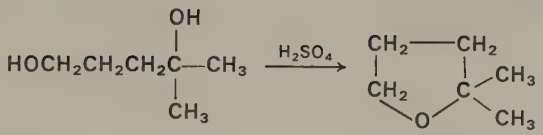
analogous ways, 1,4-diols are readily cyclized by treatment with strong acids (44):

$$HOCH_2CH_2OH + H_2SO_4 \rightleftharpoons HOCH_2CH_2\overset{+}{O}H_2 + HSO_4^- \qquad (42)$$

$$HOCH_2CH_2\overset{+}{O}H_2 + HOCH_2CH_2OH \longrightarrow \begin{matrix} HOCH_2CH_2 \\ \\ HOCH_2CH_2 \end{matrix}\!\!>\overset{+}{O}H + H_2O \xrightarrow[\text{steps}]{\text{similar}}$$



1,4-dioxane (43)



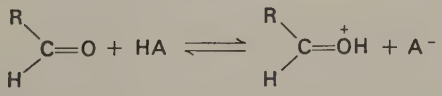
(44)

Exercise 4

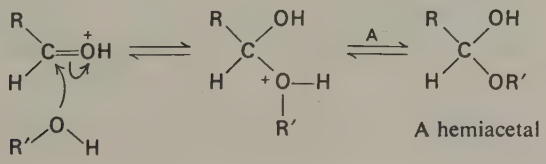
In the acid-catalyzed cyclization of 2-methylpentane-2,5-diol (above), there are two main routes that could lead to the final product (2,2-dimethyltetrahydrofuran). What are they, and which is the more likely course of the reaction?

12-9 Alcohols as nucleophiles. Hemiacetal formation

Alcohols react with aldehydes and ketones by addition to the carbonyl group, a reaction in which the nucleophilic hydroxyl group attacks the electrophilic carbon atom of the carbonyl group. In the presence of a catalytic amount of a strong acid, the reaction involves attack upon the *protonated* carbonyl group, leading to the equilibria



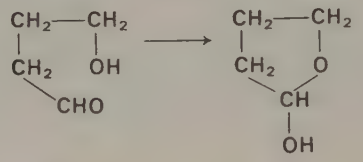
(45)



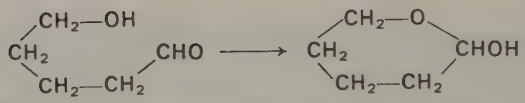
A hemiacetal (46)

Hemiacetals are unstable and upon attempted isolation dissociate to form the aldehyde and alcohol. The equilibrium is usually quite unfavorable to the formation

of the hemiacetal, unless the reaction is *intramolecular* and a five- or six-membered cyclic hemiacetal results. *Intermolecular* hemiacetal formation by the reaction of separate molecules of alcohol and aldehyde necessarily involves the decrease in entropy associated with the ordering of randomly distributed molecules into the specific arrangement necessary for bond formation. When the two reacting structures are already contiguous to each other by being parts of a single molecule, the decrease in entropy of reaction is very much reduced, and the equilibrium constant becomes favorable for hemiacetal formation. When the —OH and —CHO groups are so disposed that a five- or six-membered ring is formed, the most favorable conditions for cyclization obtain (see Chapter 27); such hydroxyaldehydes as 4-hydroxybutanal and 5-hydroxypentanal exist largely in the hemiacetal form:

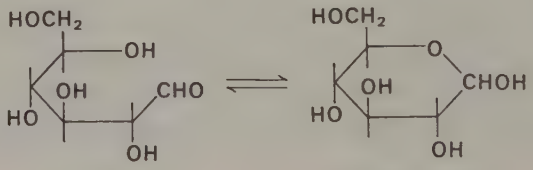


(47)



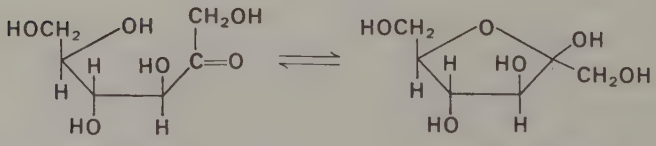
(48)

The most widely known cyclic hemiacetals are the sugars, of which D-glucose is a typical example. D-Glucose exists almost exclusively as the cyclic hemiacetal (pyranose) form. D-Fructose, a keto sugar, is a cyclic *hemiketal*:



D-glucose (aldehydo form) D-glucopyranose

(49)



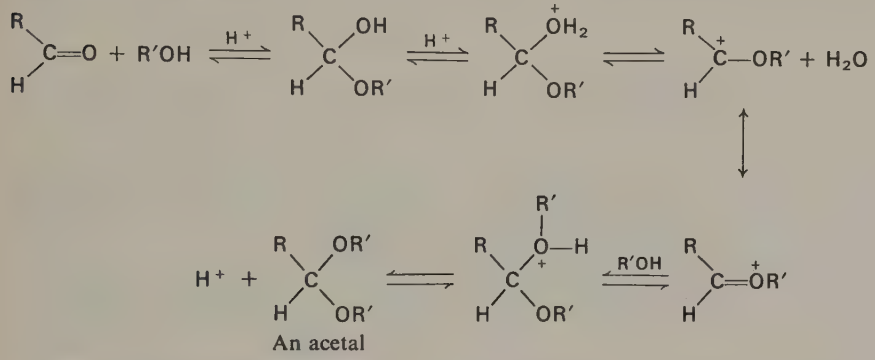
D-fructose (keto form) D-fructofuranose

(50)

It can be anticipated that, when steric considerations permit, a hydroxy aldehyde will always exist largely in the cyclic form.

12-10 Acetals

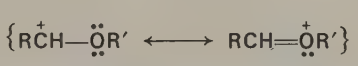
In the presence of excess alcohol and an acid catalyst, hemiacetal formation is only the first stage in a reaction that leads finally to an *acetal*. An acetal is a 1,1-dialkoxy compound; the mechanism of its formation is described in the following equations:



(51)

An acetal

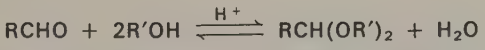
The important feature that contributes to the favorable rate of acetal formation is the stability of the intermediate carbonium ion, $RC^+H—OR'$. This is a resonance hybrid in which the positive charge is delocalized by participation of the adjacent oxygen atom:



(52)

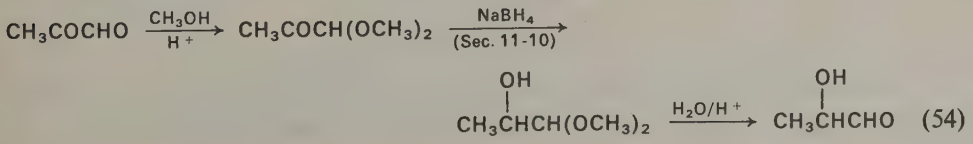
Although the reactions shown for the formation of the acetal are all reversible, complete conversion of the aldehyde to the acetal can be accomplished by using a large excess of the alcohol, and in some cases by adding a mild dehydrating agent (for example, anhydrous sodium sulfate or copper sulfate) to remove the water that is a product of the reaction.

Acetals are quite stable to the action of alkali, but are readily hydrolyzed in aqueous acid, as indicated in the following equation which summarizes the separate equilibria shown above:



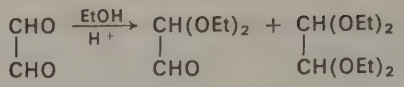
(53)

For these reasons, acetal formation is a valuable synthetic device. An aldehyde group can be "protected" by acetal formation during a chemical transformation of another part of the molecule, then hydrolyzed to reform the aldehyde. One example is the preparation of lactaldehyde:

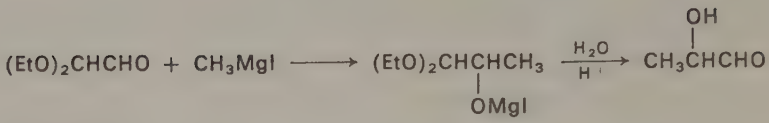


(54)

or



(55)

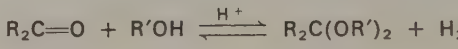


(56)

An attempt to reduce methylglyoxal, CH_3COCHO, directly would result in reduction of the —CHO group rather than, or in addition to, the ketone carbonyl group.

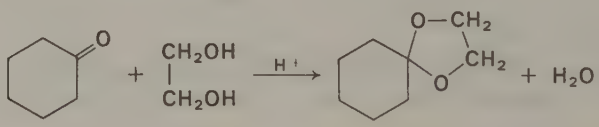
It follows that reactions carried out on a compound containing such a "protected" aldehyde group must be performed in neutral or basic solution, for aqueous acidic conditions would cause the acetal to revert to the aldehyde.

The most common way of protecting a functional group by acetal formation is to form the cyclic ketal by reaction of a ketone with ethylene glycol. The formation of non-cyclic ketals by reaction of a ketone and an alcohol is seldom practicable because of the very unfavorable equilibrium in the reaction, even when an excess of alcohol is used:



(57)

The unfavorable equilibrium can be overcome by applying the principle of intramolecular reaction, discussed above, by which a *cyclic* ketal is prepared. The reaction of cyclohexanone with ethylene glycol, which proceeds readily to give a good yield of the product, illustrates this:



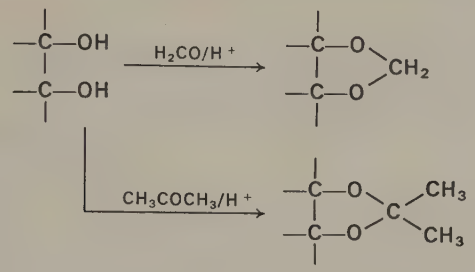
(58)

Exercise 5

Formulate the detailed stepwise course of the acid-catalyzed reaction between cyclohexanone and ethylene glycol to form the cyclic ketal.

As a device for the protection of functional groups, the formation of cyclic ketals and acetals can be employed in two ways: (*a*) With acetone or formaldehyde as the

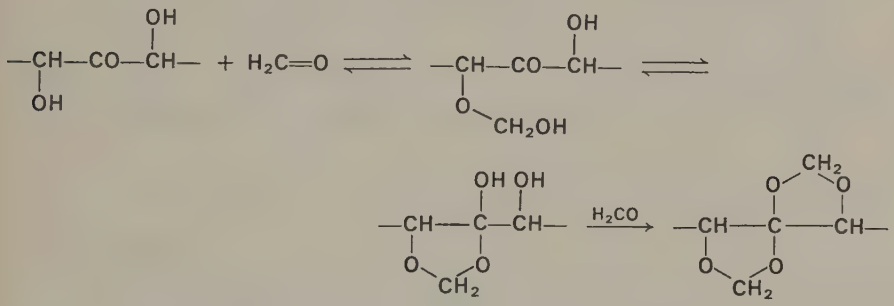
reagent, adjacent hydroxyl groups may be converted into the cyclic acetal or ketal:



(59)

(*b*) With ethylene glycol as the *reagent*, a carbonyl group may be converted into the cyclic acetal or ketal (as described above for cyclohexanone and ethylene glycol).

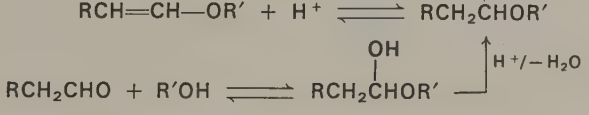
A further extension of this procedure is seen in a reaction of formaldehyde with a compound containing the grouping —CHOHCOCHOH—. The following sequence of steps shows how a bicyclic diacetal is formed:



(60)

12-11 Enol ethers

Enol (or vinyl) ethers, of the general structure RCH=CH—OR′, are closely related to the acetals and hemiacetals, for upon protonation they are converted into the (carbonium ↔ oxonium) ion that is the intermediate in acetal formation:



(61)

(62)

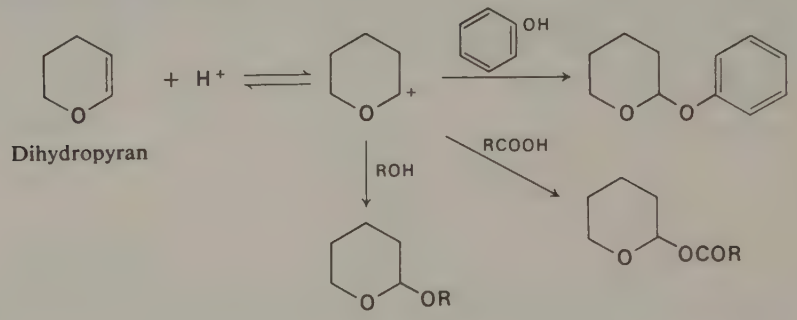
Exercise 6

Why does the protonated species formed from RCH=CHOR′ have the structure $RCH_2\overset{+}{C}HOR'$ rather than $R\overset{+}{C}HCH_2OR'$?

They are, therefore, very readily hydrolyzed by aqueous acid, and are transformed into acetals in the presence of an excess of an alcohol:

$$RCH{=}CHOR' + H^+ \rightleftharpoons RCH_2\overset{+}{C}HOR' \xrightarrow{H_2O} RCH_2CHO + R'OH + H^+ \qquad (63)$$
$$\xrightarrow{R'OH} RCH_2CH(OR')_2 + H^+$$

A commercially available and inexpensive enol ether that finds much use in organic chemistry is dihydropyran. Its acid-catalyzed reaction with compounds containing a hydroxyl group is represented by the general expression above, and by the following examples. It should be noted that although compounds containing hydroxyl groups of several types may be used, the products are in all cases acetals or acetal-like in their structures:



Dihydropyran (64)

12-12 Alcohols as nucleophiles. Esterification

The reaction of alcohols with carboxylic acids and acid derivatives leads to the formation of *esters*. For example, the overall reaction between acetic acid and methanol is

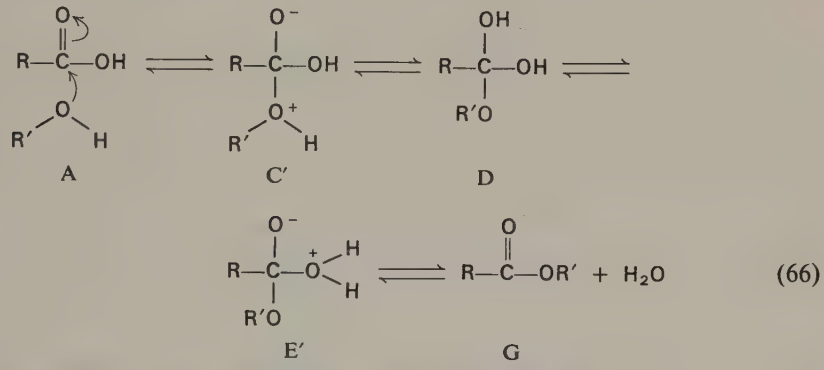
$$CH_3C(=O)OH + CH_3OH \rightleftharpoons CH_3C(=O)OCH_3 + H_2O \qquad (65)$$

Several features of this process are to be noted:

1. This is an equilibrium reaction, and a nearly complete conversion of the acid to the ester can be accomplished by using a large excess of alcohol.
2. In the absence of a catalyst the reaction is slow, requiring many hours to reach final equilibrium.
3. The reaction is greatly accelerated by the use of a strong acid (HCl, H_2SO_4) as a catalyst, although this does not change the position of equilibrium.

4. The oxygen atom of the —OR′ group in the ester RCOOR′ comes from the alcohol R′OH.

These features of the esterification process are accounted for in the mechanism of the reaction, the first step of which is a nucleophilic attack of the alcohol —OH group upon the carbon atom of the —COOH group, followed by the proton-transfer equilibria shown in the following:



(66)

(NOTE: The letters A, C′, and so on refer to the energy diagram, Figure 12-3.)

Exercise 7

If a carboxylic acid, RCOOH, were allowed to react with $H_2{}^{18}O$, would ^{18}O appear in the carbonyl group? Explain by an appropriate formulation.

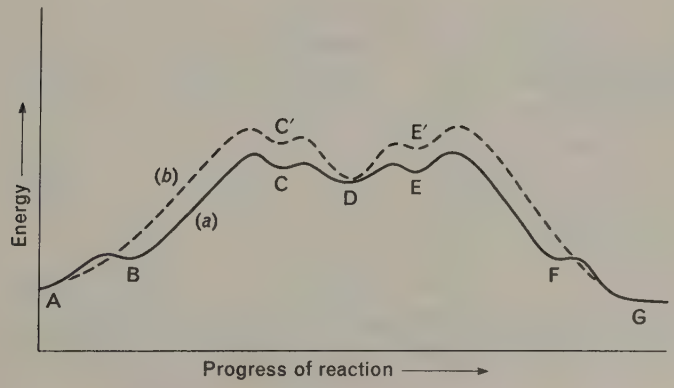
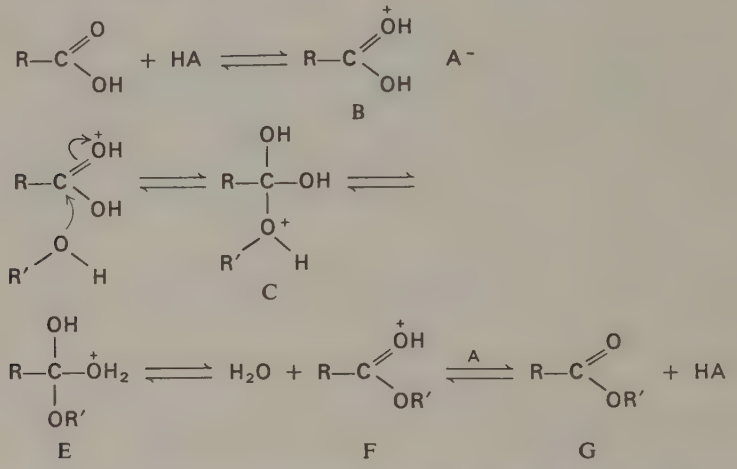


Figure 12-3
An energy diagram for (*a*) an acid-catalyzed and (*b*) an uncatalyzed esterification reaction.

It can be seen from the above equations that the initial attack of the alcohol upon the carboxyl group produces a charge separation in a dipolar transition state. The energy of this process can be lowered by the initial protonation of the carboxylic acid. This renders the carbonyl group of the acid more electrophilic and eliminates charge separation in the first transition state, thus lowering the activation energy for the first (rate-determining) step of the reaction.

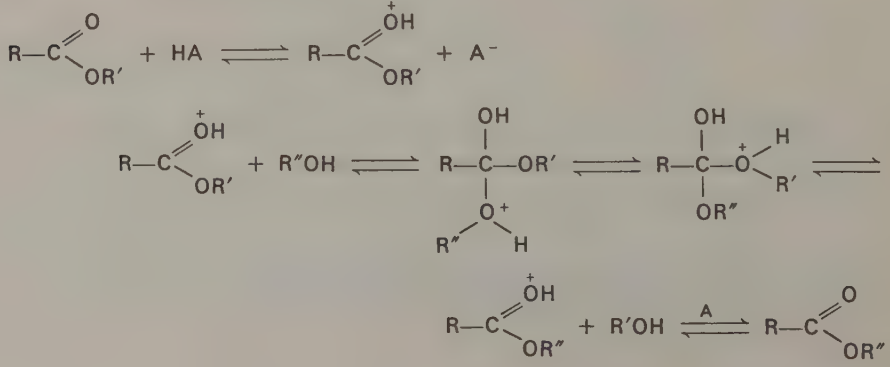


(67)

Figure 12-3 shows a representative energy diagram for an acid-catalyzed and an uncatalyzed esterification reaction. The energy difference between the start (RCOOH + R′OH) and finish (RCOOR′ + H_2O) of the reaction is not great, indicating (as is usual) that the equilibrium constant is not large (for acetic-acid/ethanol, $K_{eq} \cong 4$).

12-13 Acid-catalyzed ester interchange

The reaction of an alcohol with an ester follows a course that is exactly parallel to the esterification reaction. The following expression shows that this, too, is an equilibrium reaction; as such, it can lead to essentially complete ester interchange if the reagent alcohol, R′OH, is in large excess.



(68)

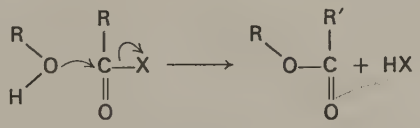
Acid-catalyzed ester interchange is not commonly used as a way of converting one ester into another. Numerous alternative ways are available for converting alcohols into esters; these will be described elsewhere in this book (for example, see Chapter 23).

12-14 Acylation of hydroxyl groups. Preparation of esters with reactive acylating agents

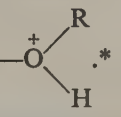
The formation of an ester by the reaction of an alcohol with a carboxylic acid may be described either as the esterification of the acid or the *O*-acylation of the alcohol. Its use is in practice limited to the preparation of esters of low-molecular-weight alcohols, especially methanol and ethanol. The preparative procedure is to dissolve the carboxylic acid in a large excess of the alcohol, add a small amount of mineral acid (HCl, H_2SO_4), and heat the solution until esterification is complete.

For alcohols that are of high molecular weight, or are crystalline solids, or are available in limited amounts, this procedure is either disadvantageous or impossible, and other (related) procedures are employed.

The overall process of acid-catalyzed esterification can be represented by the following expression, in which the intermediate steps are omitted:



(69)

where X is $—OH_2^+$, eventually displaced as a molecule of water. Acid-catalyzed ester interchange follows the same overall course, with X =  .*

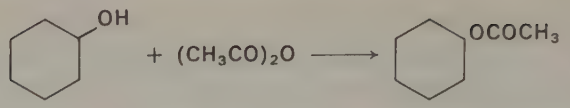
Acid derivatives possessing substituents X that are readily lost as X^- can act in the same way. Indeed, when X = Cl, the reaction proceeds rapidly and to virtual completion because the chloride ion formed is so poor a nucleophile that the reverse reaction is negligible and the equilibrium lies largely to the right. Acid anhydrides (X = —OCOR), although less reactive than acyl halides, are also useful acylating agents.

The reaction between an alcohol and an acyl chloride or anhydride therefore results in rapid and efficient *O*-acylation of the alcohol:

$$(CH_3)_2CHCH_2OH + CH_3COCl \longrightarrow (CH_3)_2CHCH_2OCOCH_3 + HCl \qquad (70)$$

Acetic chloride — Isobutyl acetate

* The fact that in the general expression shown for these cases HX = H_3O^+ or ROH_2^+ means only that usual proton-exchange equilibria obtain; for example, $ROH_2^+ + H_2O \rightleftharpoons ROH + H_3O^+$ or $ROH_2^+ + R'OH \rightleftharpoons ROH + R'OH_2^+$.

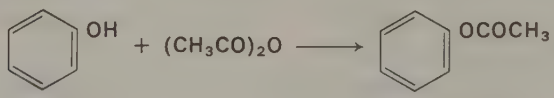


Acetic anhydride Cyclohexyl acetate (71)

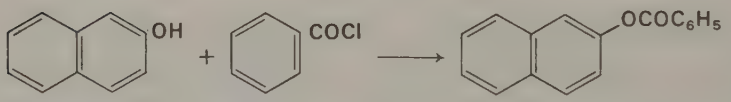
cholesterol + $(CH_3CO)_2O$ ⟶ cholesteryl acetate (3β-acetoxycholest-4-ene) + CH_3COOH (72)

The principal advantage of *O*-acylation with acyl halides and anhydrides is the wide applicability of the method, for these acylating agents are readily available and easily prepared, so that acyl groups of a wide range of structure can be introduced. Many acyl halides and acid anhydrides are commercially available reagents. Acetyl chloride, benzoyl chloride, and acetic anhydride are inexpensive; and other acyl chlorides are readily prepared by the reaction of the carboxylic acid with thionyl chloride ($SOCl_2$) or a halide of phosphorus, such as PCl_3 (Chapter 23).

O-Acylation of phenols is just as readily accomplished:



Phenol Phenyl acetate (73)



β-naphthol Benzoyl chloride β-naphthyl benzoate (74)

Exercise 8

Given the required acyl chlorides and hydroxy compounds, write equations for the preparation of the following: (*a*) menthyl acetate, (*b*) *cis*-1,2-diacetoxycyclohexane, (*c*) cholesteryl benzoate, (*d*) phenyl propionate, (*e*) di-*O*-benzoyl-D(−)-tartaric acid.

Acid chlorides derived from sulfonic acids (RSO_2Cl) react with alcohols in a similar way to give esters of sulfonic acids, RSO_2OR'. These are discussed in the following section.

12-15 Esters of inorganic acids

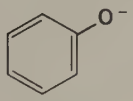
Esters of nitrous, nitric, sulfuric, sulfonic, phosphoric, and pyrophosphoric acids are important compounds in organic chemistry, in industry, in medicine, and in biological chemistry.

Sulfates of long-chain, "fatty" alcohols with twelve or more carbon atoms, such as lauryl hydrogen sulfate, $CH_3(CH_2)_{10}CH_2OSO_3H$, as their sodium salts are in common use as detergents and wetting agents. Like sulfates of other primary alcohols, they can be prepared by direct reaction of alcohols with sulfuric acid (cf. ethyl sulfate), but are more effectively made by the reaction of alcohols with chlorosulfonic acid, $ClSO_3H$:

$$RCH_2OH + ClSO_3H \longrightarrow RCH_2OSO_3H + HCl \qquad (75)$$

Dimethyl sulfate (usually called simply methyl sulfate) is prepared by allowing methanol and sulfuric acid to react, and distilling the mixture under reduced pressure. It is a common laboratory reagent, useful as a methylating agent. It reacts with nucleophilic reagents to transfer a methyl group to the nucleophilic center. Its reaction with three typical nucleophilic agents is shown in the following equations:

$$(CH_3)_3N + CH_3OSO_2OCH_3 \longrightarrow (CH_3)_4\overset{+}{N} + CH_3OSO_2O^- \qquad (76)$$



$$+ CH_3OSO_2OCH_3 \longrightarrow$$

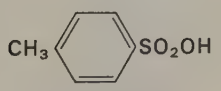
$$+ CH_3OSO_2O^- \qquad (77)$$

$$(CH_3)_2CHO^- + CH_3OSO_2OCH_3 \longrightarrow (CH_3)_2CHOCH_3 + CH_3OSO_2O^- \qquad (78)$$

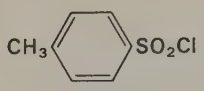
Alkyl sulfonates (RSO_2OR') are esters of the strong acids RSO_2OH, and are useful alkylating agents because of the ease of displacement of the weakly nucleophilic anion, RSO_2O^-. Alkyl sulfonates are readily prepared by the reaction between an alcohol and a sulfonyl chloride. The two sulfonic acids most commonly used in this way are methanesulfonic acid and *p*-toluenesulfonic acid, the chlorides of which are commercially available.*

CH_3SO_2OH
Methanesulfonic acid

CH_3SO_2Cl
Methanesulfonyl chloride



p-toluenesulfonic acid



p-toluenesulfonyl chloride

Since alcohols react with sulfonyl chlorides to give alkyl sulfonates, and the sulfonyloxy anion is easily displaced by nucleophilic attack, the overall process consists in the replacement of —OH of the alcohol by the nucleophilic reagent, as in the following example:

$$ROH + CH_3SO_2Cl \longrightarrow ROSO_2CH_3 + HCl \qquad (79)$$

$$ROSO_2CH_3 + (CH_3)_3N \longrightarrow (CH_3)_3\overset{+}{N}—R\}CH_3SO_2O^- \qquad (80)$$

* Note the nomenclature. For example, CH_3SO_3H is *methane*sulfonic acid, not *methyl*sulfonic acid.

Alkyl nitrites and nitrates are formed by reaction of nitrous and nitric acid with alcohols. Although nitrous acid is unstable, it can be generated in solution by treatment of sodium nitrite with sulfuric acid; in the presence of an alcohol, the nitrous acid ester is formed:

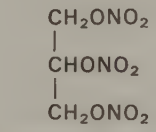
$$NaNO_2 + H_2SO_4 \rightleftharpoons NaHSO_4 + HNO_2\ (HON{=}O)$$

$$HONO + H_2SO_4 \rightleftharpoons H_2\overset{+}{O}NO + HSO_4^- \qquad (81)$$

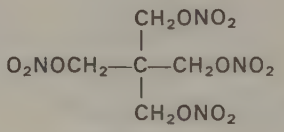
$$H_2\overset{+}{O}NO + CH_3CH_2CH_2CH_2OH \rightleftharpoons \underset{n\text{-butyl nitrite}}{CH_3CH_2CH_2CH_2ONO} + H_2O + H^+$$

Since alkyl nitrites are soluble in organic solvents (for example, ethanol) and react with mineral acids to give nitrous acid, they can be used as a source of nitrous acid in an anhydrous medium.

A number of nitric acid esters are of great importance; two of them are valuable both as explosives and as medicinals. Glyceryl trinitrate ("nitroglycerin") and pentaerythritol tetranitrate (as well as some alkyl nitrites) have a relaxing effect upon the smooth muscle of blood vessels, lowering blood pressure and relieving the symptoms of angina pectoris, a condition associated with diminished blood supply to the heart. Several related alcohol nitrates are also used in therapy for the same purpose:

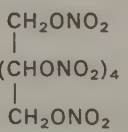


Glyceryl trinitrate
("nitroglycerin")



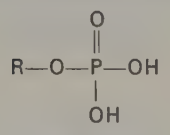
Pentaerythritol
tetranitrate

$C_2H_5C(CH_2ONO_2)_3$
"Propatryl nitrate"

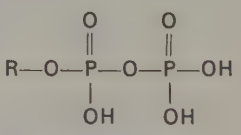


Mannitol
hexanitrate

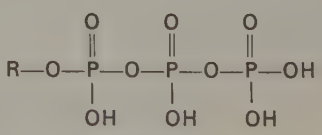
By far the most important inorganic acid esters are those of phosphoric and pyrophosphoric acids:



Phosphates
(orthophosphates)
(R—OP)



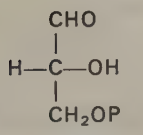
Pyrophosphates
(R—OPP)



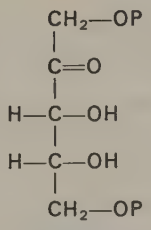
Triphosphates
(R—OPPP)

Phosphates and pyrophosphates play a role in nearly all aspects of cellular metabolism, so that phosphorus is essential to the nutrition of living organisms. Phosphates play fundamental roles in the generation of reactive intermediates (AMP, ATP) of cellular synthesis, in carbohydrate metabolism and photosynthesis, in the formation of the phosphorylated lipids that are important components of cellular membranes, in the synthesis of nucleotides and nucleic acids, in the structure of bones and teeth (inorganic phosphate), and in the structure and function of many specialized biological compounds.

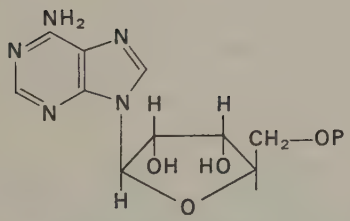
It is impossible to describe here the vast scope of phosphate metabolism in living organisms. Certain aspects of this subject will be encountered in appropriate sections throughout this book; it will suffice here to show the structures of a few phosphate esters of biological importance:*



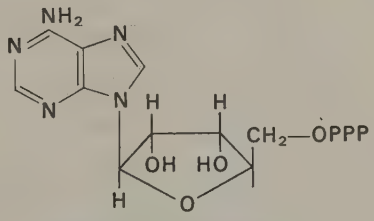
D-glyceraldehyde-3-phosphate



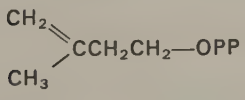
D-ribulose-1,5-diphosphate



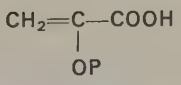
Adenosine monophosphate (AMP)



Adenosine triphosphate (ATP)



Isopentenyl pyrophosphate



Phosphoenol pyruvic acid

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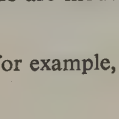
* Since phosphoric acids and their monoesters are moderately strong acids, these compounds exist in physiological systems in ionized form, for example,  .

Problems

1. Show two possible courses for the reaction of sodium methoxide with (*a*) ethyl bromide, (*b*) isopropyl iodide, (*c*) 2-bromo-2-methylpentane, (*d*) $(CH_3CH_2O)_2SO_2$, and (*e*) 3-bromopentane.
2. In each of the reactions in Problem 1, which of the two products would predominate?
3. Write the reactions showing the ester interchange between ethyl acetate and 1-butanol: (*a*) acid-catalyzed (trace of H_2SO_4), (*b*) base-catalyzed (trace of sodium *n*-butoxide).
4. What would be the final result of dissolving acetaldehyde dimethyl acetal in an excess of 1-propanol and adding a small amount of HCl?
5. Write the equations showing the series of steps in the reaction that would ensue upon dissolving $CH_3CH{=}CHOCH_3$ in aqueous HCl.
6. When *t*-butyl alcohol is treated with acetyl chloride (CH_3COCl), *t*-butyl acetate is not the principal product. What is formed, and why?
7. Vinyl acetate ($CH_2{=}CHOCOCH_3$) reacts with ethanol in the presence of a catalytic amount of HCl to give a compound A, with molecular formula $C_6H_{14}O_2$. What is A, and how does the reaction proceed?
8. How would $(CH_3)_3C{-}O{-}CH_2CH_3$ be prepared?
9. What would be formed in the acid-catalyzed reaction between 5-hydroxypentanal and methanol?
10. If (*R*)-2,5-dihydroxypentanal were treated with methanol and a trace of HCl, how many products would be formed? Draw their structures, using projection formulas to show the stereochemistry of the products.

13

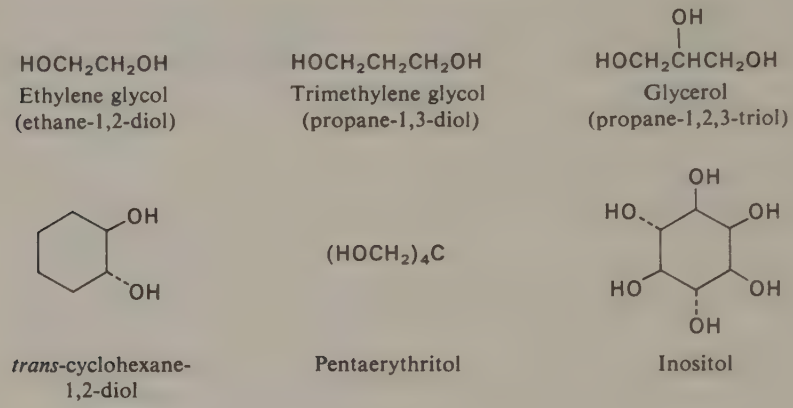
Glycols and polyols

In this chapter we shall examine some of the properties of bifunctional and polyfunctional compounds, in particular those in which the presence of one functional group affects the chemical behavior of another. In the case of diols and polyols two kinds of behavior will be observed: (1) the independent reactivity of the hydroxyl groups (as in ester formation), and (2) reactions in which two or more hydroxyl groups participate.

This chapter is principally an introduction to the chemistry of a large and important class of compounds, the carbohydrates (sugars). The formation of cyclic acetals, the oxidative cleavage of polyhydroxy compounds, and the stereochemical features of polyol (and sugar) chemistry will be central to the understanding of what is to follow, so that it is advantageous to discuss these principles in the terms of simple compounds before applying them, in later chapters, to more complex compounds, sugars and their derivatives. Sections 13-2–13-4, 13-8, and 13-10 have the most immediate bearing upon what is to follow, but the remainder of the chapter provides instructive examples of the application of principles that are presented here.

13-1 Classes of polyols

Compounds containing more than one alcoholic hydroxyl group are designated by the systematic terms *diol*, *triol*, and so on. Dihydroxy compounds are usually called *glycols*. Some polyols bear non-systematic, common names.



13-2 Preparation and properties of glycols

The simplest glycol is ethylene glycol (ethane-1,2-diol), a valuable industrial chemical. It is prepared by simple hydrolysis of ethylene oxide, and is used principally as an anti-freeze engine coolant and in the production of polyethylene terephthalate (Dacron).

The most general method of preparing 1,2-glycols is by the hydroxylation of ethylenic double bonds. The mechanism and stereochemistry of this reaction are discussed in Chapter 10, which should be referred to at this time. Glycols with three or more carbon atoms between terminal primary hydroxyl groups, such as butane-1,4-diol and pentane-1,5-diol, can be conveniently prepared by the lithium aluminum hydride reduction of the corresponding -dioic acids or their esters:

$$EtOOC(CH_2)_nCOOEt \xrightarrow{LiAlH_4} HOCH_2(CH_2)_nCH_2OH \qquad (1)$$

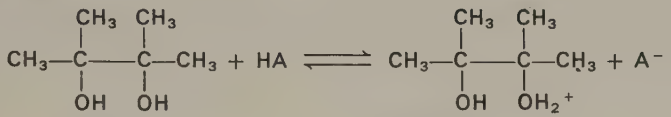
In general, methods applicable to the synthesis of alcohols can be used for the synthesis of glycols, such as reduction of diketones or hydroxyketones, or reaction of Grignard reagents with diesters or diketones.

Much of the chemistry of simple glycols containing primary or secondary alcoholic hydroxyl groups is very like that of alcohols. They can be converted by esterification into di-*O*-acyl derivatives, oxidized to the corresponding carbonyl compounds, and in many cases dehydrated to dienes. Butadiene, for example, is produced commercially by the dehydration of either butane-1,3-diol or butane-1,4-diol.

13-3 1,2-Glycols: Pinacol rearrangement

1,2-Glycols containing tertiary hydroxyl groups undergo a characteristic reaction when treated with strong acids. The reaction involves an alteration of the carbon skeleton, and is known as the *pinacol rearrangement*. An analysis of the course of this reaction with 2,3-dimethylbutane-2,3-diol (pinacol) shows the nature of the rearrangement:

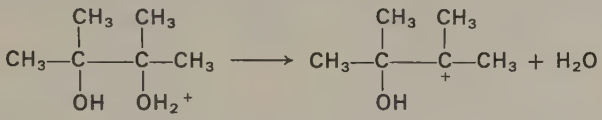
1. Protonation of the —OH group:



(2)

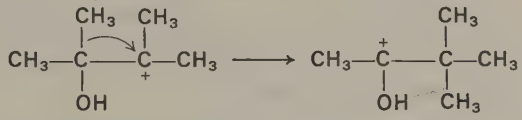
Pinacol

2. Dissociation to the carbonium ion intermediate:



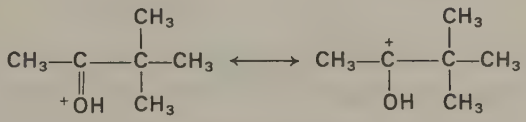
(3)

3. Formation of a more stable carbonium ion by a 1,2-shift of a methyl group:



(4)

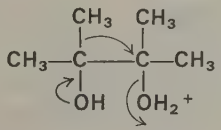
The "new" carbonium ion formed in this step is stabilized by the capacity of the oxygen atom to supply an unbonded electron pair, thus dispersing the + charge over the C—O bond:



(5)

Pinacolone (protonated)

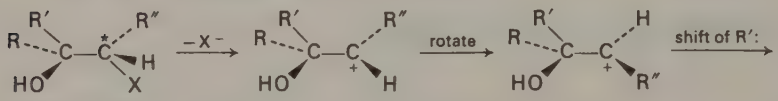
The last product is simply the protonated form of the ketone $CH_3COC(CH_3)_3$, and by proton exchange with the solvent (that is, H_2O), the product *pinacolone* is formed. Although these stages are written separately, it is probable that the loss of water from the protonated glycol and the shift of the methyl group occur as a single concerted process:



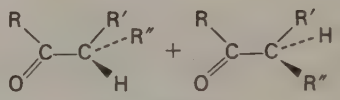
(6)

Were this not the case, the "free" carbonium ion would be able to rotate about the C—C bond so that the migrating methyl group could shift to either face of the planar (sp^2) $-\overset{+}{C}(CH_3)_2$ group. Although no evidence in support of or against this can be obtained in the case of pinacol → pinacolone itself, proof of the concerted, one-step nature of the rearrangement can be obtained if the initial glycol is asymmetric at the carbon atom at which the carbonium center is generated. Consider the following generalized case, in which the ionization of X generates the carbonium ion at the migration terminus (carbon marked * is asymmetric). Two possible courses may be envisaged:

(*a*) "Free" carbonium ion process:



Optically active



(7)

Enantiomers
(not the observed result)

(*b*) Concerted ionization-migration process:

(8)

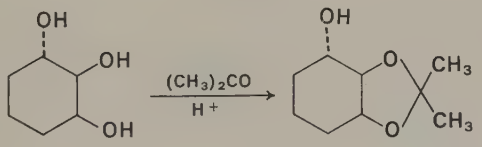
Optically active — Optically active (observed result)

Rearrangements of this kind are generally observed whenever a carbonium ion is generated adjacent to a hydroxyl-bearing carbon atom. Because there are other ways of generating carbonium ions than by the dissociation of $-\overset{|}{\underset{|}{C}}-OH_2^+$, the term "pinacol rearrangement" is used in a generic sense for a variety of related reactions.

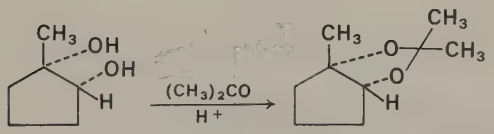
13-4 1,2-Glycols: Cyclic acetals, ketals, and related compounds

The formation of cyclic ketals and acetals by the reaction of diols with ketones and aldehydes has been described in Chapter 12. The only generally useful applications of cyclic acetal and ketal formation depend on the reactions of aldehydes and ketones with 1,2- and 1,3-glycols, for only 5- and 6-membered rings can be formed in satisfactory yields and at useful rates. Stereochemical factors are also important. The reaction between a 1,2-diol and acetone (for "protection" of the hydroxyl groups) results

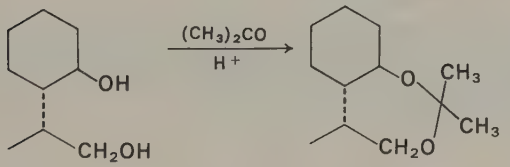
in the formation of a 5-membered cyclic ketal. If the two hydroxyl groups are those of a cyclohexanediol, ketal formation is successful if they are in a *cis*-1,2-diol configuration, usually less so (but not impossible) when they are *trans*. Moreover, the cyclic ketals formed between acetone and the hydroxyl groups on *cis*-1,2-dihydroxycyclopentane rings are quite stable and require vigorous conditions (strong aqueous acid) for hydrolysis to regenerate the diol. It should be recognized that in the latter case the *cis*-fusion of the two 5-membered rings represents a highly favored configuration. Conversely, a *trans*-1,2-cyclopentanediol does not form the acetonide, for this would lead to a highly strained *trans* ring fusion. Indeed, evidence for the *cis*- or *trans*-disposition of the hydroxyl groups in cyclic 1,2-diols can be obtained by ascertaining whether they form a cyclic ketal upon reaction with acetone. Some typical examples of cyclic ketal and acetal formation are the following:



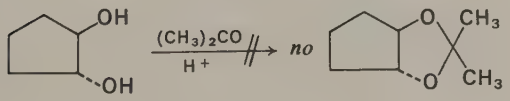
(9)



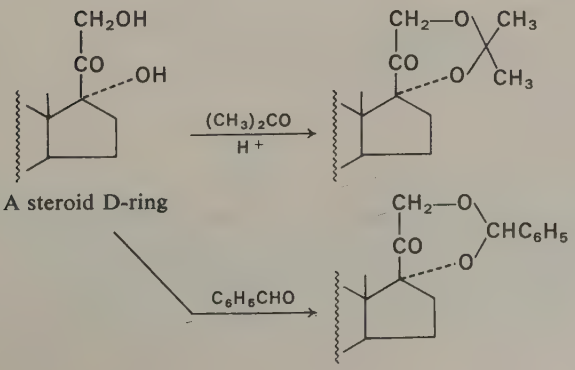
(10)



(11)

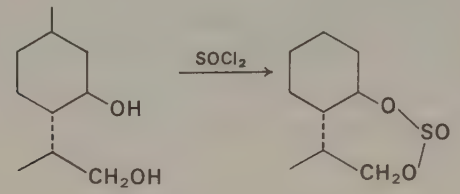


(12)

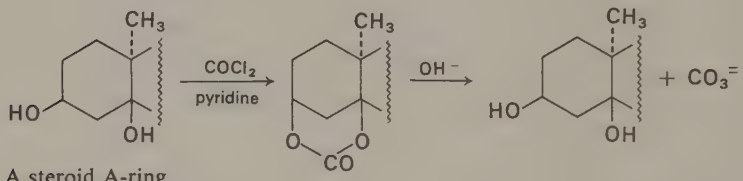


(13)

Other cyclic derivatives of 1,2-diols (or other sterically favorable diols) can be prepared; their use has certain special advantages in synthesis. Treatment of 1,3- or 1,2-diols with phosgene ($COCl_2$) or thionyl chloride ($SOCl_2$) leads to the formation of cyclic carbonates and sulfites, respectively. The formation of these cyclic esters is subject to the stereochemical factors discussed above. Cyclic carbonates are relatively more stable to acid hydrolysis than are cyclic ketals, and, being esters, are readily hydrolyzed by alkali with regeneration of the diol:



(14)

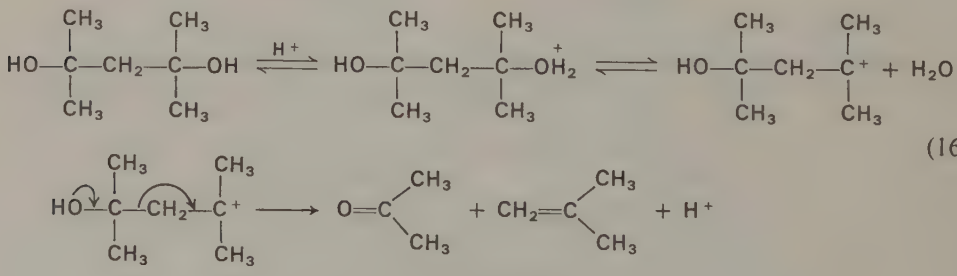


(15)

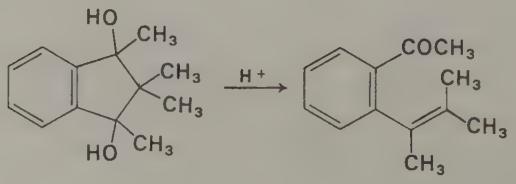
A steroid A-ring

13-5 1,3-Glycols. Acid-catalyzed cleavage

1,3-Glycols containing tertiary hydroxyl groups can cleave into two fragments when treated with strong acids. The following examples illustrate this; in the first reaction the stages of the cleavage reaction are detailed:



(16)



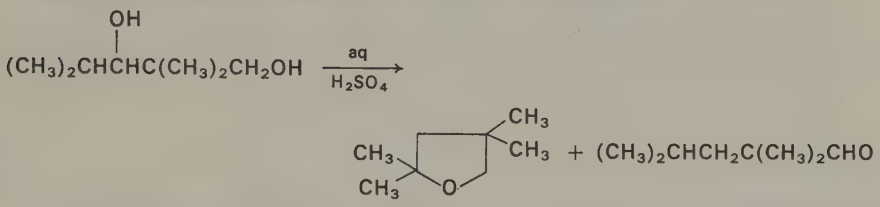
(17)

Exercise 1

Compare the pinacol rearrangement with the cleavage of a 1,3-glycol and comment upon the similarity of the two reactions.

Exercise 2

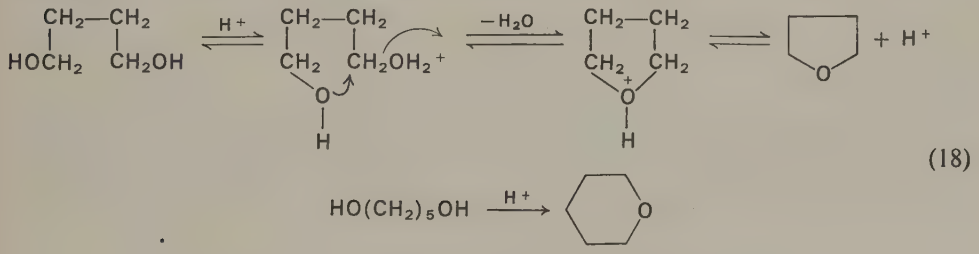
The following reaction is found in a well-known monograph:



One of the products shown is correct, the other is erroneous. Which of the products is incorrect, and what should its structure be? (NOTE: the correct and incorrect structures are isomeric.)

13-6 1,4- and 1,5-Glycols. Cyclic ether formation

1,4-Glycols are in most cases unexceptional in behavior, and react in many ways as if the alcoholic groups were quite independent. One characteristic reaction peculiar to 1,4- and 1,5-glycols is the ease with which they form cyclic ethers, by virtue of their ability to form the sterically favorable 5- and 6-membered rings. The chemistry of the ring-closure is the same as in acid-catalyzed ether formation from simple alcohols.



(18)

Exercise 3

When ethylene oxide is hydrolyzed with strong aqueous sulfuric acid, one of the products formed along with the 1,2-glycol is a six-membered cyclic di-ether, $C_4H_8O_2$. What is the structure of this ether and how is it formed?

Glycols in which the hydroxyl groups are more distant from each other than 1,5 show no unusual behavior. They act as bifunctional alcohols, in which the carbinol groups are independent.

13-7 Triols

The simplest and most important triol is glycerol, propane-1,2,3-triol. The earlier commercial source of glycerol was the manufacture of soaps by the alkaline hydrolysis of fats and oils, which are triesters of glycerol with (long chain) aliphatic ("fatty") acids. In recent years synthetic processes for the manufacture of glycerol have assumed importance; for example, the chlorination of propylene to allyl chloride, and conversion of the latter to glycerol:

$$CH_3CH{=}CH_2 \xrightarrow[500^\circ]{} ClCH_2CH{=}CH_2 \qquad (19)$$

Allyl chloride

$$ClCH_2CH{=}CH_2 \xrightarrow[NaOH]{H_2O} HOCH_2CH{=}CH_2 \xrightarrow[Cl_2]{H_2O}$$

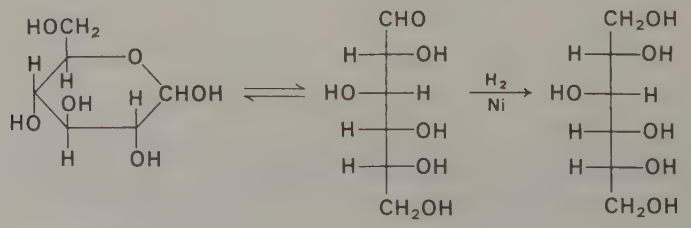
Allyl alcohol

$$HOCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2Cl \xrightarrow[NaOH]{H_2O} HOCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH \qquad (20)$$

Glycerol is used principally as a humectant (a moisture conditioner, especially in tobacco), as a softener and plasticizer of synthetic polymers, as a component of alkyd resins, and for the preparation of glyceryl trinitrate ("nitroglycerin").

13-8 Polyols

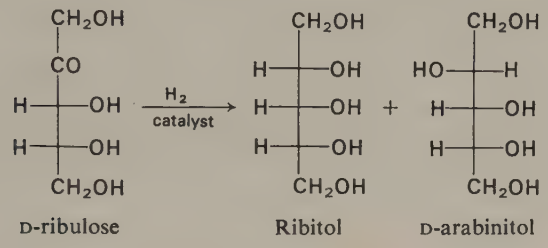
The reduction of the formyl group of aldoses or the carbonyl group of ketoses (Chapter 14) yields pentahydroxy (from pentoses) and hexahydroxy (from hexoses) compounds. D-Sorbitol is prepared by the catalytic hydrogenation of D-glucose:



(21)

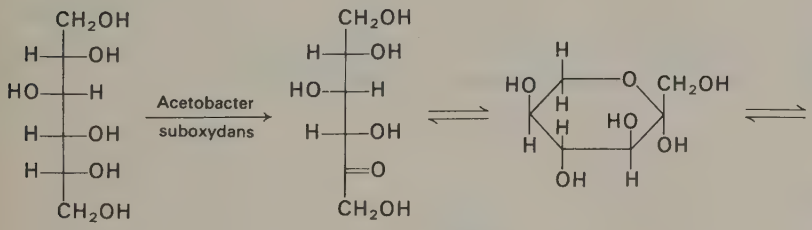
D-glucose D-sorbitol

Although the reduction of an aldose, in which the terminal —CHO grouping is reduced to —CH_2OH, does not generate a new asymmetric center, reduction of a ketose yields epimeric products (although in unequal proportions):

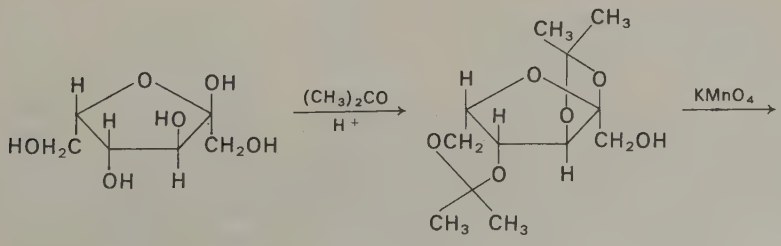


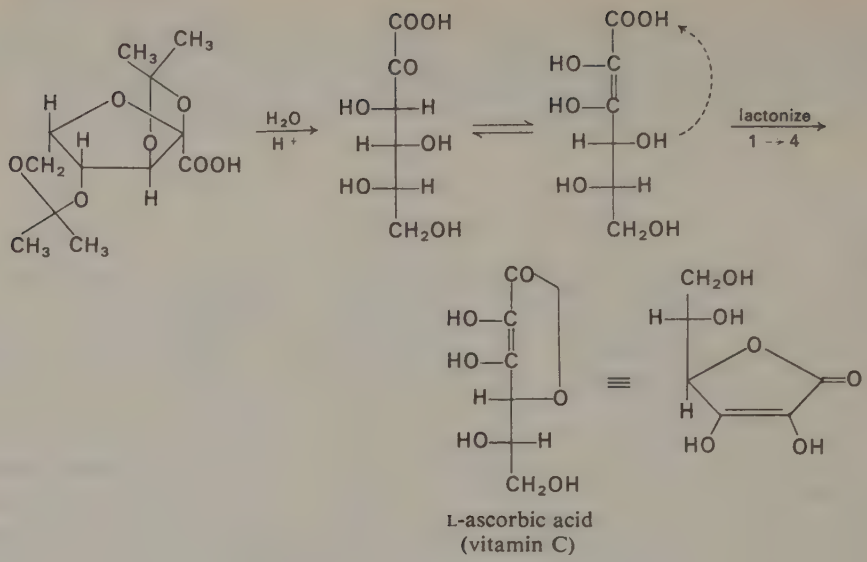
D-ribulose Ribitol D-arabinitol (22)

While the principal practical uses of polyols of this kind are as humectants (in which they are superior to glycerol), certain of them are of unique importance in special syntheses. Sorbitol is the starting material for the synthesis of the important vitamin C (L-ascorbic acid). The process starts with a biological oxidation of sorbitol, which is specifically oxidized to L-sorbose by the microorganism *Acetobacter suboxydans*. The succeeding steps in the series of transformations leading from L-sorbose to L-ascorbic acid are: (*a*) the cyclization of L-sorbose to the cyclic hemiketal, in which form it exists almost completely; and (*b*) the reaction of the four hydroxyl groups with acetone to produce two cyclic ketal groupings (acetonides). A final oxidation of the remaining (unprotected) —CH_2OH group to —COOH and hydrolysis of the ketal groupings yields the acid, which on formation of the lactone completes the synthesis of the vitamin:



Sorbitol L-sorbose



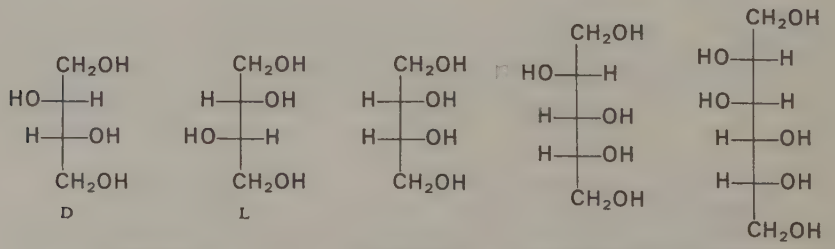


(23)

L-ascorbic acid
(vitamin C)

13-9 Natural occurrence of polyols

A large number of polyols, many of them derived from common sugars, are found in nature, usually in combined form, for example, as esters or glycosides, but in some cases as the free compounds. The simplest polyols (except for glycerol) are *threitol* and *erythritol*, of which the former can occur in enantiomeric forms. These tetritols* are found in a number of fungi (for example, *Penicillium* species). D-Arabinitol, ribitol, and five of the ten possible hexitols occur in nature as constituents of fungi, lichens, and higher plants. D-Mannitol, for example, is common, being the principal constituent of the "mannas" produced and exuded by several common trees.



D Threitols L Threitols Erythritol D-arabinitol D-mannitol

* Although the term "tetrol" would be consistent with "diol" and "triol," the 1,2,3,4-tetrahydroxy compounds are usually called *tetritols*. Similarly pentitol, hexitol, and so on. However, *systematic* names of individual tetritols may use the form "tetraol."

Exercise 4

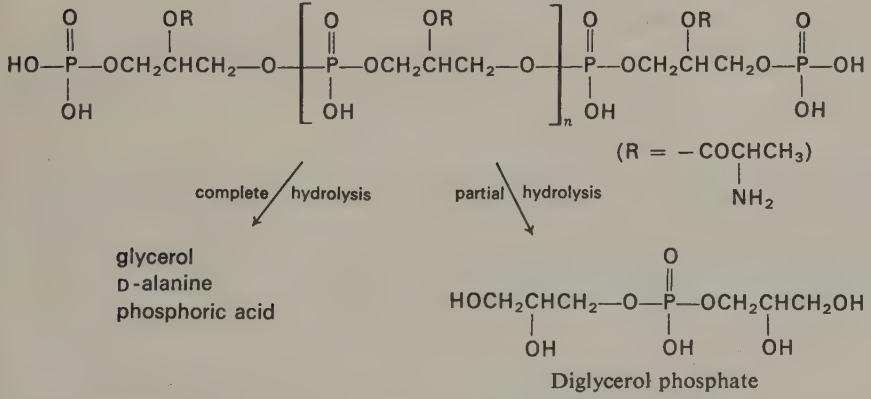
Why is the designation D or L not used in naming ribitol and erythritol?

Exercise 5

Ribitol is epimeric at one position with D-arabinitol, and is optically inactive and non-resolvable. Is this information sufficient to define its stereochemistry?

Polyols are important constituents of the cellular membranes and cell walls of many microorganisms. A class of cell-wall structural elements called *teichoic acids*, found in bacteria, consist of long chains of polyol units that have been joined by ester linkages with phosphoric acid units. The two best known of these are based upon glycerol and ribitol. The *glycerol teichoic acids* are polymers of a unit composed of glycerol, phosphoric acid, and D-alanine (α-aminopropionic acid), and can be represented by the following partial structural formula (where n is a number in the neighborhood of 20):

Glycerol teichoic acid



(24)

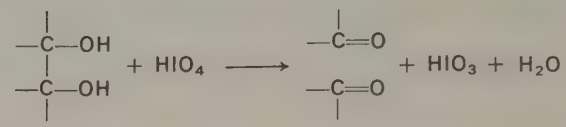
Diglycerol phosphate

Other bacterial cell-wall polysaccharides are composed of polymers based upon ribitol-1,5-diphosphate esters, but with a variety of substituents (of which one is always D-alanine) attached to the three central —CHOH— groups. It should be noted that the general structures of the teichoic acids are the same, differing in numerous details depending upon the particular microorganism in which they occur. The total structures of bacterial cell walls are, however, quite complex, and teichoic acids are not their sole constituents.

13-10 Periodic acid and lead tetraacetate oxidation of glycols and polyols

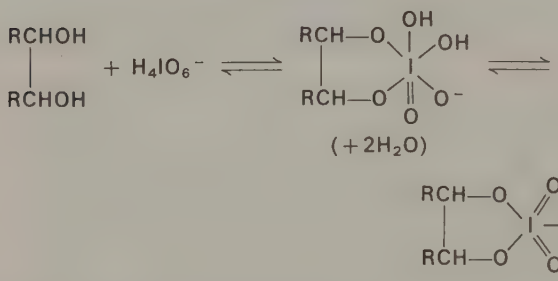
1,2-Glycols, and polyols containing adjacent hydroxyl groups, are oxidized in a specific and characteristic manner by several oxidizing agents, chief among which are periodic acid (HIO_4) and lead tetraacetate ($Pb(OCOCH_3)_4$).

The overall reaction can be represented by the simple expression



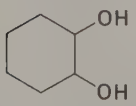
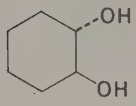
(25)

The reaction is quite general and is of wide and useful application in studies of polyhydroxy compounds, especially sugars (following chapter). Kinetic study of the reaction has led to the proposal that the reactive species is the hydrated periodate ion, $H_4IO_6^-$ ($2H_2O + HIO_4 = H_5IO_6$), and that a cyclic ester is formed as the intermediate in the reaction:



(26)

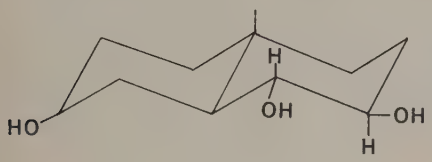
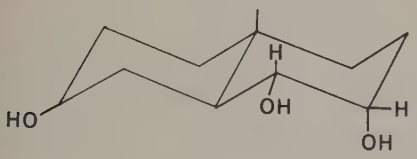
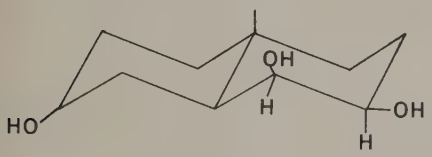
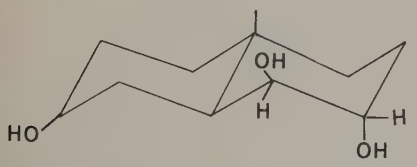
This mechanism is supported by the observations that glycols in which the hydroxyl groups are fixed in a diaxial configuration do not react with periodate, and that the rate of oxidative cleavage is greater when the hydroxyl groups are more favorably disposed for formation of the 5-membered cyclic ester ring:

	Relative rate of cleavage by H_5IO_6	*Formation of cyclic ketal with acetone*
	25	fast
	1	very slow

Cis-1,2-cyclohexanediol, which readily forms a cyclic ketal with acetone, reacts more rapidly with periodate than *trans*-1,2-cyclohexanediol, which forms a cyclic ketal with acetone very slowly.

Although the rates of periodate cleavage in steroid ring systems (Table 13-1)

Table 13-1
Relative rates of periodate cleavage of some cholestane-3,6,7-triols. Only the A and B rings are shown; the 3β-OH group is not affected

Triol		*Relative rate of cleavage*
	3β6α7β	320
	3β6α7α	84
	3β6β7β	1
	3β6β7α	0

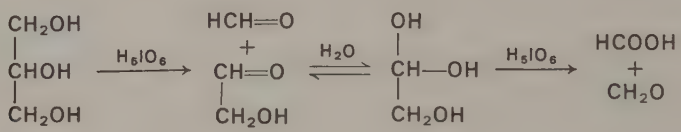
clearly do not follow the simple rule that *cis* glycols react faster than *trans* glycols, they can be reconciled with other stereochemical features of the molecules. For example, the glycols with axial hydroxyl groups (6α7α and 6β7β) are slower than the diequatorial 6,7-diol. In the steroid ring system, in which conformational mobility is constrained, the axial hydroxyl groups are hindered by neighboring groups (for example, the C-10 methyl group) or other elements of the ring system. The *trans*-diaxial (6β7α) glycol is not cleaved at all, and the 6β7β glycol is cleaved the most slowly of the other three. The axial methyl group (at C-10) would be expected to interfere with the

formation of the cyclic ester because of its proximity to the 6β hydroxyl group in the 6β7β compound, thus accounting for the slow rate of oxidative cleavage.

Periodic acid also cleaves compounds of the following types:

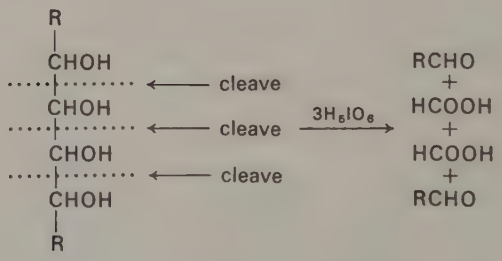
—CO—CO—	1,2-diketones
—CO—CHOH—	α-hydroxyketones and aldehydes
—CHOH—COOH	α-hydroxy acids

The consequence of this is that when three or more hydroxyl groups are present in a 1,2,3-triol, a 1,2,3,4-tetraol, and so on, *the molecule is oxidized between each pair of* OH *groupings*. This is because the first oxidation between any pair of vicinal OH groups leads to the formation of an α-hydroxyketone or aldehyde (or acid), which is then oxidized further. These subsequent steps may be represented simply as the oxidation of the hydrated form of the carbonyl group. An example is the oxidation of glycerol:



(27)

In general:

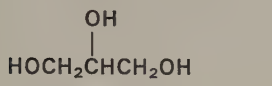
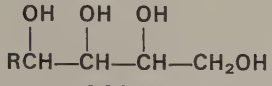
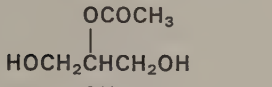
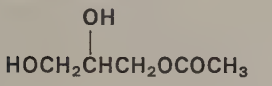


The application of periodic acid cleavage to structure analysis is of great value in organic chemistry, and most useful in the chemistry of polyols and sugars. Much information can be gained by simple and uncomplicated experimental observations, such as measurement of the number of moles of HIO_4 consumed (that is, reduced to HIO_3) in a reaction, and determination of the number of moles of *formic acid* and/or *formaldehyde* produced.

These determinations, for which experimental means are available, give the following information:

1. The number of moles of HIO_4 consumed shows the number of vicinal pairs of OH groups present in the polyol.

2. One mole of formic acid is produced for each —CHOH—CHOH—CHOH— or —CHOH—CHO grouping.
3. One mole of formaldehyde is produced for each terminal —CHOH—CH_2OH grouping.

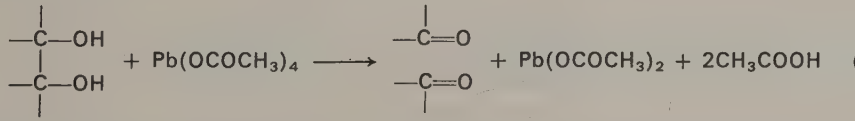
	HIO_4 *consumed*	HCOOH *formed*	HCHO *formed*
	2	1	2
	3	2	1
	0	0	0
	1	0	1

The last two examples in the above tabulation show how easily periodate can be used to differentiate between a 2-*O*-acyl and a 1-*O*-acyl ester of glycerol. The 2-acetate, in which the two hydroxyl groups are not adjacent, is unaffected. The 1-acetate contains the terminal —CHOHCH_2OH grouping; it consumes 1 mole of periodate and produces 1 mole of formaldehyde.*

Exercise 6

Find the consumption of periodate, the number of moles of formic acid formed, and the number of moles of formaldehyde formed from 1 mole of each of the following: (*a*) erythritol, (*b*) ribitol, (*c*) glycerol-1-phosphate, (*d*) cyclohexane-1,2-diol, (*e*) cyclohexane-1,2,3-triol, (*f*) cyclohexane-1,2,3,4-tetraol.

Glycols, α-hydroxyketones, and so on are oxidized by lead tetraacetate in a manner completely analogous to the periodic acid oxidation. The general expression for this reaction is



(28)

* The "consumption" of periodic acid in the above context means the conversion of HIO_4 to HIO_3 (a two-electron reduction), and can be measured by an analysis of the total oxidizing capacity of the solution before and after the reaction with the glycol.

Further discussion of this reaction, along with examples of other uses of periodic acid and lead tetraacetate, will be found in Chapter 36, in which oxidation reactions of various kinds are considered in some detail.

Further examples of the use of glycol-cleaving reagents, in particular periodic acid, will be found in the following chapter on the chemistry of sugars and sugar derivatives, where these reagents play an important role in structural studies.

Problems

1. Write the structural formulas for the following. Where appropriate, show stereochemistry by suitable projection formulas: (*a*) propane-1,2-diol, (*b*) *trans*-cyclopentane-1,3-diol, (*c*) (R)-butane-1,2-diol, (*d*) pentamethylene glycol, (*e*) tetraethylethylene glycol, (*f*) (1R:2S)-2-methylcyclohexanol.

2. Show the steps through which cyclohexanone could be converted into (*a*) *cis*-cyclohexane-1,2-diol and (*b*) *trans*-cyclohexane-1,2-diol.

3. Starting with diethyl succinate, and using any other necessary reagents, show how the following compounds could be prepared: (*a*) butane-1,4-diol, (*b*) *N*-methylpyrrolidine, (*c*) 2,2,5,5-tetramethyltetrahydrofuran.

4. If 3,4-dimethylhexane-3,4-diol were treated with aqueous H_2SO_4 under such conditions as to cause a pinacol rearrangement, what result would be expected?

5. Explain how the treatment of 3-amino-2,3-dimethyl-2-butanol with nitrous acid yields pinacolone. HINT: Treatment of a primary aliphatic amine RNH_2 with HNO_2 converts it into the unstable diazonium ion RN_2^+, which readily loses nitrogen.

6. State which of the following compounds would undergo oxidative cleavage upon treatment with periodic acid. Name the products that would be formed: (*a*) pentane-2,3,4-triol, (*b*) pentane-1,3,5-triol, (*c*) glycerol 2-acetate, (*d*) glycerol 1-acetate, (*e*) ribitol 3-acetate.

14

Carbohydrates I: Monosaccharides and derivatives

The chemistry of sugars and sugar derivatives is an ideal vehicle for the development of much of what has been discussed in foregoing chapters. Stereochemistry, which was discussed in Chapter 6, is an important part of the study of the structure of sugars and their chemical reactivity. Some of the most important sugar derivatives are the cyclic acetals known as glycosides, and the cyclic ketals formed by reaction of adjacent hydroxyl groups with a ketone (for example, acetone).

Although the amount of material in this and the following chapter is rather formidable, only the essential principles of the subject are presented and no attempt is made to provide an encyclopedic body of facts to be committed to memory. The student should concentrate upon understanding the nature of the chemical transformations described, not upon remembering a plethora of names and formulas. It will be seen that there is little in this and the next chapter that is conceptually novel, for most of the *kinds* of reactions described are applications of what has already been discussed. It is most important to perceive how a reaction first encountered as a simplified model can be applied to a more complex and realistic situation. The chemistry of sugars shows very well that the chemistry of complex organic compounds can be understood by applying the familiar principles of functional-group behavior.

14-1 What are carbohydrates?

The carbohydrates include sugars and their derivatives, both natural and synthetic; they constitute a class of compounds widespread in nature and of great biological importance. Carbohydrate chemistry, encompassing as it does a diverse range of structural types, is so complex that it is regarded by some as a specialized area of study. The nomenclature of the field is largely non-systematic, and the polyfunctional molecules that are typical of the carbohydrates often behave in ways that are different from those of their simpler monofunctional counterparts. The commonest of the sugars, glucose, is but one of sixteen stereoisomers (eight pairs of enantiomers), and although all of them show much common behavior, stereoisomerism introduces many unique aspects into their chemical properties.

The term carbohydrate originated in the observation that many compounds of the class, including those of most common occurrence—glucose, $C_6H_{12}O_6$, and sucrose, $C_{12}H_{22}O_{11}$—have the empirical composition $C_n(H_2O)_m$, and were once referred to as "hydrates of carbon." However, many natural sugars and sugar derivatives do not have compositions that correspond to those proportions, and many compounds properly called carbohydrates contain nitrogen and phosphorus. Table 14-1 lists some common and important carbohydrates, the empirical compositions of which, it can be seen, do not conform to any simple rule. The compounds in the table are typical members of this very large class of compounds.

Table 14-1
Some typical and important carbohydrates

Compound	*Empirical formula*
D-glucose	$C_6H_{12}O_6$
D-fructose	$C_6H_{12}O_6$
D-mannose	$C_6H_{12}O_6$
D-ribose	$C_5H_{10}O_5$
D-deoxyribose	$C_5H_{10}O_4$
D-gluconolactone	$C_6H_{10}O_6$
D-2-amino-2-deoxyglucose	$C_6H_{13}NO_5$
fructose	$C_6H_{12}O_6$
cellulose	$H(C_6H_{10}O_5)_nOH$
starch	$H(C_6H_{10}O_5)_mOH$
glycogen	$H(C_6H_{10}O_5)_xOH$
sucrose	$C_{12}H_{22}O_{11}$
lactose	$C_{12}H_{22}O_{11}$
L-ascorbic acid	$C_6H_8O_6$
D-sedoheptulose	$C_7H_{14}O_7$

14-2 Occurrence of carbohydrates

Carbohydrates are constituents of all living matter. Ingested as food, they provide energy and the materials of synthesis for growth and reproduction. In green plants, in which they are synthesized *de novo* by reduction of carbon dioxide, they perform these same metabolic functions and also form a part of the skeletal structure of the plants.

Carbohydrates are ultimately derived from the reduction of carbon dioxide by living plants, with the aid of the green pigment chlorophyll. The energy required for the overall process

$$xCO_2 + xH_2O + \text{energy} \longrightarrow (CH_2O)_x + xO_2 \qquad (1)$$

is the energy of sunlight, which falls both upon the land, where it is used by the forests and vegetable crops, and upon the sea, where simpler plants (the phytoplankton) in inestimably huge numbers utilize it for photosynthesis. The energy bound up in the carbohydrate molecules produced by photosynthetic organisms is available to man and other animals as the energy of food and fuels. The cycle of fixation of carbon dioxide by photosynthesis and its return to the atmosphere by various processes is shown in Figure 14-1.

The cycle of photosynthesis and oxidation (combustion of fuels, metabolism of animals and plants, decay) maintains the carbon dioxide concentration in the atmosphere at the fairly constant value of about 0.03% (300 parts per million), which corresponds to a total of about 6×10^{11} tons of carbon dioxide. In addition to this, the oceans contain an even greater amount in the form of carbonates and dissolved carbon dioxide. It has been estimated that land plants convert about 10% of the

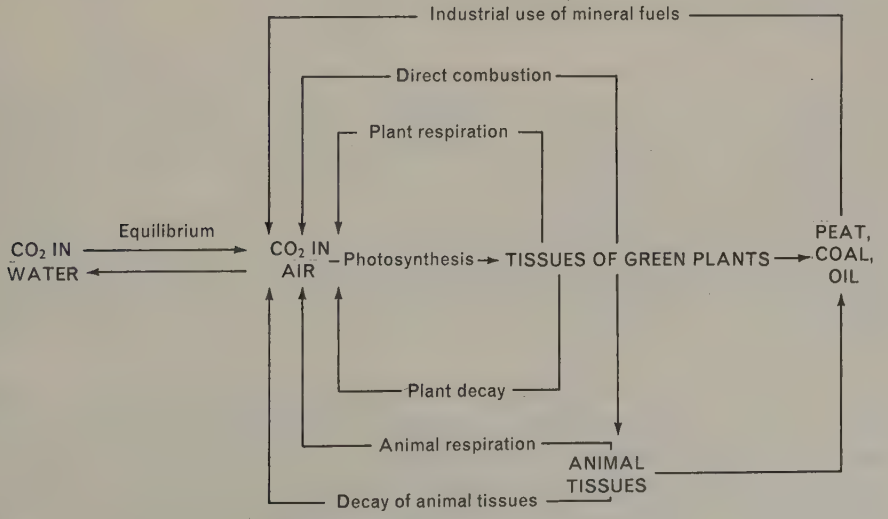


Figure 14-1
The biochemical carbon cycle.

atmospheric carbon dioxide—some 6×10^{10} tons—into carbohydrates each year. Most of this is converted into two substances, cellulose and starch, which are high-molecular-weight polymers of glucose. The formation of other sugars, among which are some of those mentioned in Table 14-1, is the result of secondary metabolic alterations by particular plant species.

Most of the natural sugars are very much alike in their main structural features. They are polyhydroxy compounds, the simpler ones being polyhydroxy aldehydes and ketones. They are usually crystalline, water-soluble substances (except for the high-molecular-weight compounds), and many are sweet to the taste.

The most familiar natural sugar is *sucrose*; more than 50 million tons per year is produced commercially from sugar beets and sugar cane. Sucrose is produced in a high degree of purity, and may be regarded as the most abundant pure organic compound. *Glucose* occurs in the free state as well as in its polymeric forms, starch, glycogen, and cellulose; it is found in many fruit juices, in body fluids, and in honey. *Fructose*, also found in body fluids and in honey, occurs as a polymer in the starch-like polyfructoside *inulin*, a reserve carbohydrate found in the roots of certain plants.

Two sugars whose importance has been emphasized by the momentous developments in biology during recent years are the five-carbon-atom compounds D-*ribose* and D-*deoxyribose*. These are found in all living organisms, combined with phosphoric acid and certain nitrogen-containing compounds in the nucleic acids RNA (ribonucleic acid) and DNA (deoxyribonucleic acid). These compounds are central to the mechanism of genetic control of the development and growth of living cells. Some aspects of their chemistry will be dealt with in Chapter 37.

14-3 Classification and terminology of sugars

The "simple" sugars, or *monosaccharides*, are polyhydroxyaldehydes (for example, glucose) or ketones (for example, fructose), referred to by the terms *aldose* and *ketose*. Six-carbon sugars are hexoses, five-carbon sugars are pentoses, and so on. Glucose is an *aldohexose*, fructose a *ketohexose*, ribose an *aldopentose*.

Oligosaccharides (Greek *oligos*, few) consist of two or more monosaccharide units joined by *glycosidic* linkages; that is, by acetal formation between the aldehyde or ketone grouping of one monosaccharide molecule and a hydroxyl group of another. When two sugars are so combined, the resulting compound is a *disaccharide*; when three, a *trisaccharide*; and so on.

Polysaccharides are high-molecular-weight carbohydrates formed by the joining of many monosaccharide units into long chains, or branching chains. Typical polysaccharides are starch, cellulose, and glycogen, all of which are polyglucoses.

Glycosides are compounds consisting of a sugar joined in acetal linkage to another molecule through the aldehyde or ketone carbonyl group of the sugar and, in

Table 14-2
The names of sugars and sugar derivatives

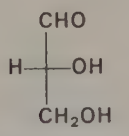
Sugar or derivative	*General name*	*Specific examples*
CHO | $(CHOH)_n$ | CH_2OH	aldose ($n = 4$, aldohexose; $n = 3$, aldopentose)	glucose $n = 4$ mannose $n = 4$ ribose $n = 3$
CH_2OH | $(CHOH)_n$ | CH_2OH	alditol	mannitol $n = 4$ arabinitol $n = 3$ erythritol $n = 2$
COOH | $(CHOH)_n$ | CH_2OH	aldonic acid	gluconic acid $n = 4$ arabonic acid $n = 3$ galactonic acid $n = 4$
CHO | $(CHOH)_n$ | COOH	alduronic acid	glucuronic acid $n = 4$ mannuronic acid $n = 4$ riburonic acid $n = 3$
COOH | $(CHOH)_n$ | COOH	aldaric acid (saccharic acid)	glucaric acid $n = 4$ galactaric acid $n = 4$ arabinaric acid $n = 3$
CH_2OH | CO | $(CHOH)_n$ | CH_2OH	ketose ($n = 3$, hexulose; $n = 2$, pentulose)	fructose (D-*arabino*hexulose) $n = 2$ ribulose $n = 2$

the commonest cases, a hydroxyl group of the other molecule, frequently an alcohol or a phenol.

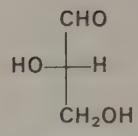
Nearly all carbohydrates are known by common names, and their derivatives by a derived terminology. Names are modified in certain standard and conventional ways for sugar derivatives. Table 14-2 summarizes the most frequently used conventions.

14-4 Stereochemistry of sugars

The simplest aldose, glyceraldehyde, exists in two enantiomeric forms; these are designated by the conventional prefixes D and L. The RS system of chiral nomenclature may be used but is not generally employed in designating the stereochemistry of sugars.



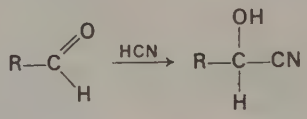
D-(+)-glyceraldehyde
R-(+)-glyceraldehyde



L-(−)-glyceraldehyde
S-(−)-glyceraldehyde

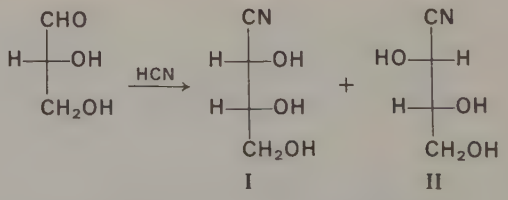
It is to be emphasized again that D and L refer to the *configurations*, and *when the formulas are written in the Fischer convention, the* D *form has the hydroxyl group on the right.** The fact that D-glyceraldehyde is dextrorotatory (+) is coincidental; many sugars of the D *series*, described below, are in fact levorotatory (−).

D-Glyceraldehyde, which has been shown by X-ray crystallographic methods to have the absolute configuration shown above, is regarded as the parent compound from which tetroses, pentoses, and so on are derived by extension of the carbon chain, starting at the —CHO group. The classical method for carrying out this chain extension is the *Kiliani-Fischer* method, which starts with the addition of HCN to the aldehyde group. This reaction, which is general for aldehydes, is shown in the following equation:



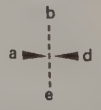
(2)

The reaction gives an enantiomeric pair of RCHOHCN; if R itself is asymmetric, the products are diastereomers. For example, the addition of HCN to D-glyceraldehyde yields two diastereomeric cyanohydrins, for while the newly generated asymmetric center can be formed in both configurations, the original asymmetric center in D-glyceraldehyde is unchanged.†



(3)

* Recall that by this convention the stereochemical arrangement



is drawn

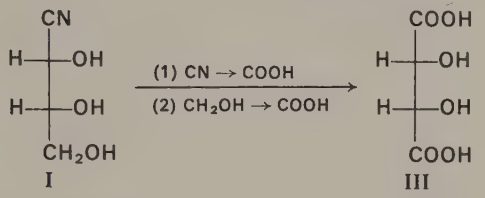
The groups on the horizontal line project *toward* the viewer.

† While the generation of a new asymmetric center in an optically active molecule usually gives rise to both configurations at the new center, they are not necessarily formed in equal proportions.

Exercise 1

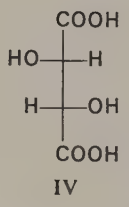
Are the cyanohydrins I and II optically inactive or optically active?

The diastereomeric cyanohydrins I and II can be hydrolyzed to the carboxylic acids; in a second operation, the —CH_2OH group can be oxidized to the —COOH group. If these operations are carried out on I, the following results are obtained:



(4)

II, by the same sequence, yields

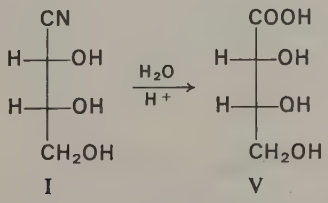


(5)

III is the optically inactive, non-resolvable, symmetrical compound *meso*-tartaric acid. IV is optically active (levorotatory) and, since it is derived from D-glyceraldehyde, is designated D-(−)-tartaric acid. These results establish the configurations of the cyanohydrins I and II.

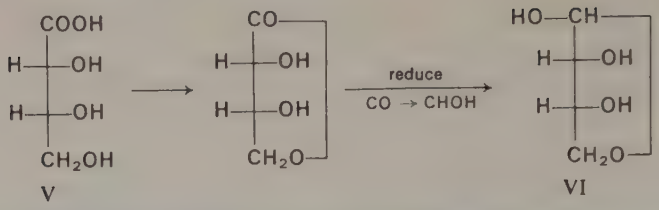
Conversion of I to the aldotetrose can be accomplished by the following series of reactions.

(*a*) Hydrolysis of —CN to —COOH:



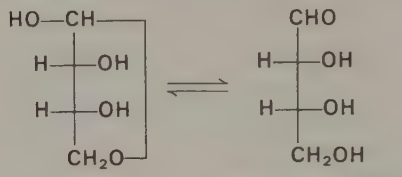
(6)

(*b*) Conversion of the carboxylic acid (V) to the lactone, and reduction of the lactone:



(7)

The reduction product VI is simply the cyclic hemiacetal of the aldotetrose, VII:

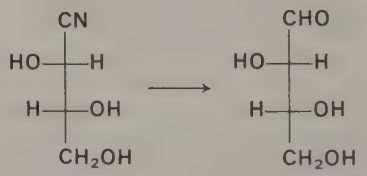


D-erythrose (VII)

(8)

Since these manipulations of the terminal groups have not involved the two —CHOH— groups, the configuration of VII must be as it is represented. This compound is called D-*erythrose*.

A similar transformation of cyanohydrin II into the aldotetrose gives D-*threose* (VIII):



D-threose (VIII)

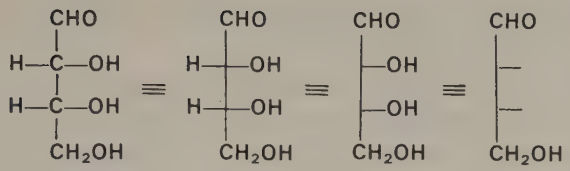
(9)

This series of reactions used in the conversion of the triose into the two tetroses can be repeated, and each tetrose converted into two pentoses, each pentose into two hexoses. Since all of the eight aldohexoses prepared in this "ascent of the series" are derived from D-glyceraldehyde without a change in configuration at the original —CHOH— group, they are all members of the D *series* of aldohexoses.

If the same complete series is derived from L-glyceraldehyde, the six-carbon sugars obtained are members of the L series; each L-aldohexose is the enantiomer of a D-aldohexose. Thus there are 16 aldohexoses: 8 of the D series, 8 of the L series. This conforms to the rule stated earlier, that with n asymmetric carbon atoms, 2^n optical isomers can exist.

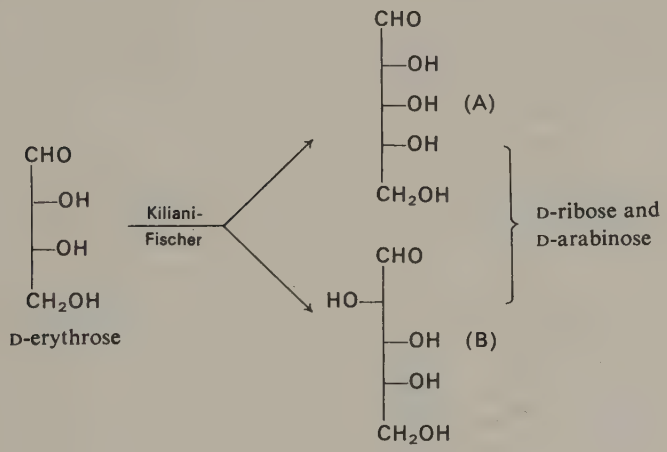
14-5 The configurations of the aldopentoses

In the following formulations, various special conventions are used: by one, only the —OH groups are shown; and by another, simple lines show the positions of the —OH groups.

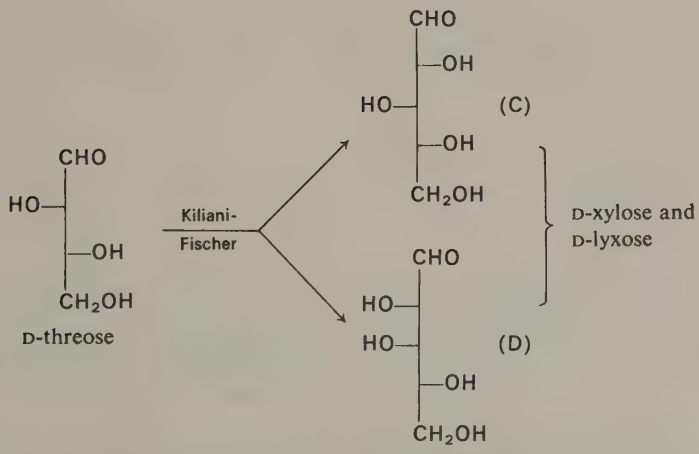


D-erythrose

If we consider only the D series (in which the lowest —CHOH— group in the Fischer convention is drawn with —OH to the right), Kiliani-Fischer chain-extension of D-threose and D-erythrose will give four D-aldopentoses:



(10)



(11)

The experimental fact is that D-erythrose, by this chain extension, gives the two sugars D-*ribose* and D-*arabinose* (which are known compounds and can be identified, for example, by melting point). This experimental result does not disclose, however,

which of the two configurations represents D-ribose; all we have learned is that D-ribose is one of the two, D-arabinose the other.

If D-ribose is reduced to the alditol (ribitol), or oxidized to the aldaric acid (ribaric acid), it is found that both of these are optically inactive and non-resolvable; they are *meso* compounds. Thus, D-ribose is A. A similar oxidation of D-arabinose to D-arabinaric acid gives an optically active product, confirming that D-arabinose is B. In the same way, it can be shown that D-*xylose* is C, and D-*lyxose* is D.

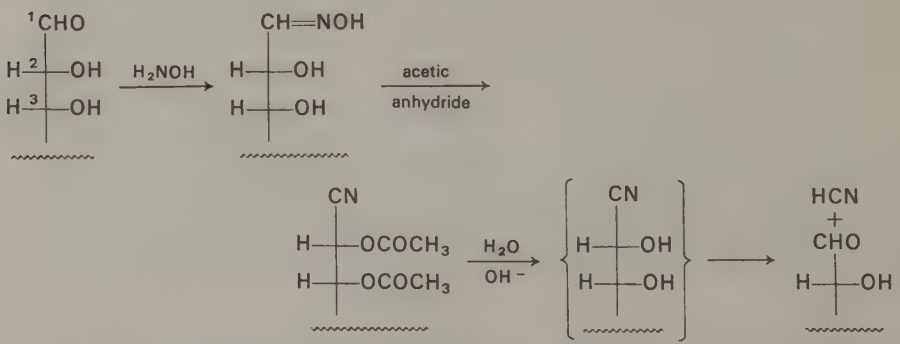
Exercise 2

Can the aldaric acid derived from D-arabinose be formed by oxidation of any other of the eight possible aldopentoses? Which one? Remember that structures drawn as Fischer projections can be turned upside-down in the plane of the page.

14-6 Degradation of the aldose chain to the next lower sugar

Several methods have been developed for converting the —$\overset{(2)}{\text{C}}$HOH—$\overset{(1)}{\text{C}}$HO grouping of an aldose to —$\overset{(2)}{\text{C}}$HO, with loss of the terminal carbon atom (and loss of chirality at C-2).

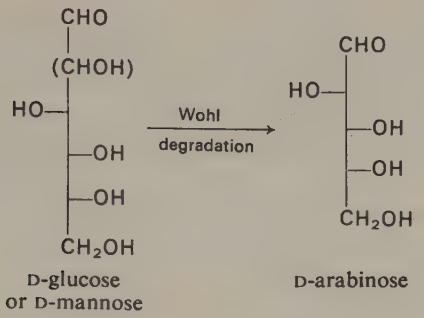
One of these methods, the *Wohl degradation*, depends upon conversion of the sugar oxime (—CH=NOH) to the nitrile (—CN), with subsequent loss of HCN. It should be noticed that the last step of this procedure is in fact the reversal of the first step of the Kiliani method of chain extension. In the following representation of the Wohl degradation, only carbon atoms 1, 2, and 3 of the aldose are shown:



(12)

If the Wohl degradation is carried out with D-glucose, the product is D-arabinose. The Wohl degradation of D-mannose also gives D-arabinose. This establishes two facts: (1) D-glucose and D-mannose differ *only* in the configuration at C-2; and (2) they both have the D-arabinose configuration at C-3, C-4, and C-5. Confirmation of this

result is found in the preparation of the osazones, discussion of which is deferred until Section 14-9.



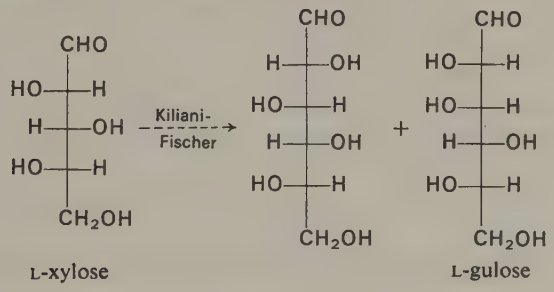
D-glucose or D-mannose — D-arabinose

(13)

14-7 Configurations of D-glucose and D-mannose

Since D-glucose and D-mannose are C-2 epimers, and the configurations at C-3, C-4, and C-5 are known, their complete stereochemistry can be established by determining the configuration of either sugar at C-2. This can be accomplished in the following way.

Two other aldohexoses, one of which is L-*gulose*, have been synthesized by chain extension of L-xylose:



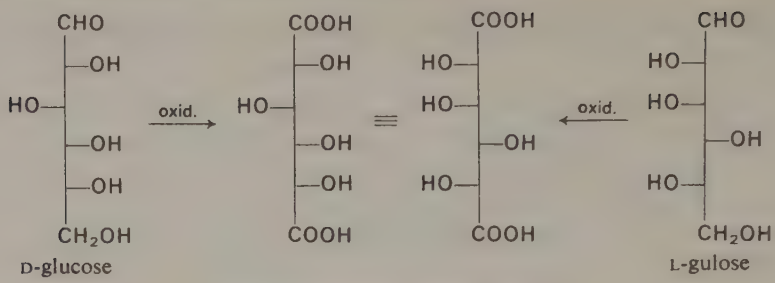
L-xylose — L-gulose

(14)

Exercise 3

Of the two aldohexoses that are formed by one-carbon chain-extension of L-xylose, one is L-gulose. What is the other? (See Section 14-10 for the structures of all of the D-aldohexoses.)

Although it is to be emphasized that the synthesis of L-gulose from L-xylose does not establish its complete configuration (it could be either of the two C-2 epimers), *it is found that* L-*gularic acid and* D-*glucaric acid are identical.* This fact establishes the configuration of D-glucose, and of L-gulose as well.



(15)

D-glucaric acid ≡ L-gularic acid
(rotate 180° in the plane of the page)

Exercise 4

Suppose D-glucose had the opposite configuration at C-2 (remembering that C-3, C-4, and C-5 are known to be as represented). Could either of the aldohexoses produced from L-xylose by chain extension give the same aldaric acid as the one from this (assumed) D-glucose?

It is significant that *there is no other aldohexose that will give the same saccharic acid as that formed from* D-*mannose*. D-Mannaric acid can be obtained *only* by oxidation of D-mannose, and from no other sugar of either the D or the L series.

Exercise 5

Inspect the structures of all of the six-carbon aldaric acids and satisfy yourself that D-mannaric acid can be obtained by end-group oxidation of no sugar except D-mannose.

14-8 Summary of the proof of the configuration of glucose

(1) The structure of D-erythrose is known because (*a*) it is derived from D-glyceraldehyde and (*b*) it can be oxidized to *meso*-tartaric acid. (2) The structure of D-arabinose is known because (*a*) it is formed, along with D-ribose, from D-erythrose and (*b*) it can be oxidized to an optically active aldaric acid. (3) The configuration of the C-2 carbon atom of D-glucose is established by its relationship to L-gulose, and the configurations at C-3, C-4, and C-5 are known because D-glucose can be degraded to D-arabinose by the loss of C-1.

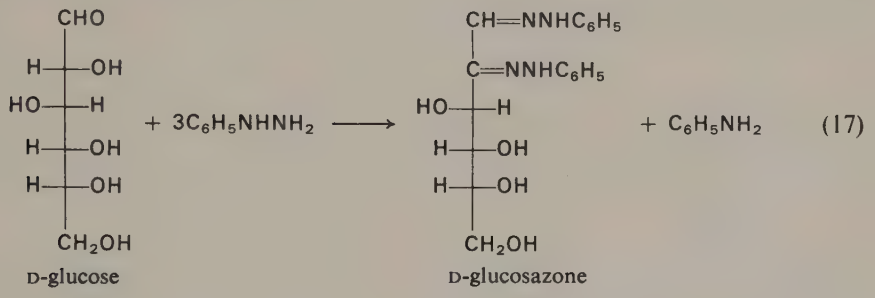
14-9 Sugar osazones

Studies of sugar chemistry were greatly aided by the discovery and application of phenylhydrazine, $C_6H_5NHNH_2$, by Emil Fischer (1884). Phenylhydrazine is a general

reagent for the preparation of derivatives of carbonyl compounds, and reacts with ordinary aldehydes and ketones according to the following equation:

$$C_6H_5NHNH_2 + R_2C{=}O \longrightarrow R_2C{=}NNHC_6H_5 + H_2O \qquad (16)$$

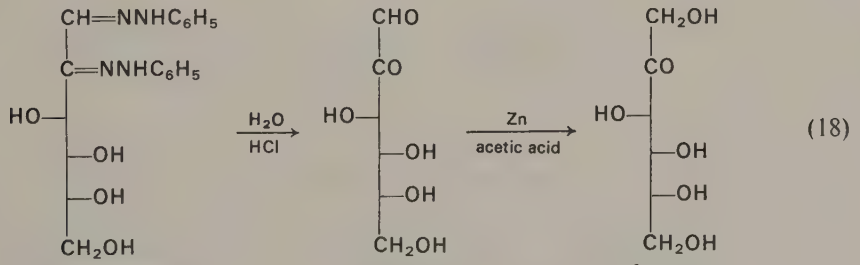
The reaction of phenylhydrazine with sugar aldehydes and ketones can proceed a step further, to give crystalline derivatives known as *osazones*. Osazones contain two phenylhydrazine residues, and are typified by *glucosazone*, formed by the reaction of phenylhydrazine with glucose:



D-glucose D-glucosazone (17)

Since the formation of glucosazone results in the destruction of asymmetry at C-2, it is apparent that D-glucose and D-mannose must yield the same osazone. Similarly, D-ribose and D-arabinose give an identical osazone, as do D-xylose and D-lyxose.

Hydrolysis of D-glucosazone converts it into *glucosone* and phenylhydrazine, and reduction of glucosone converts it into D-fructose:



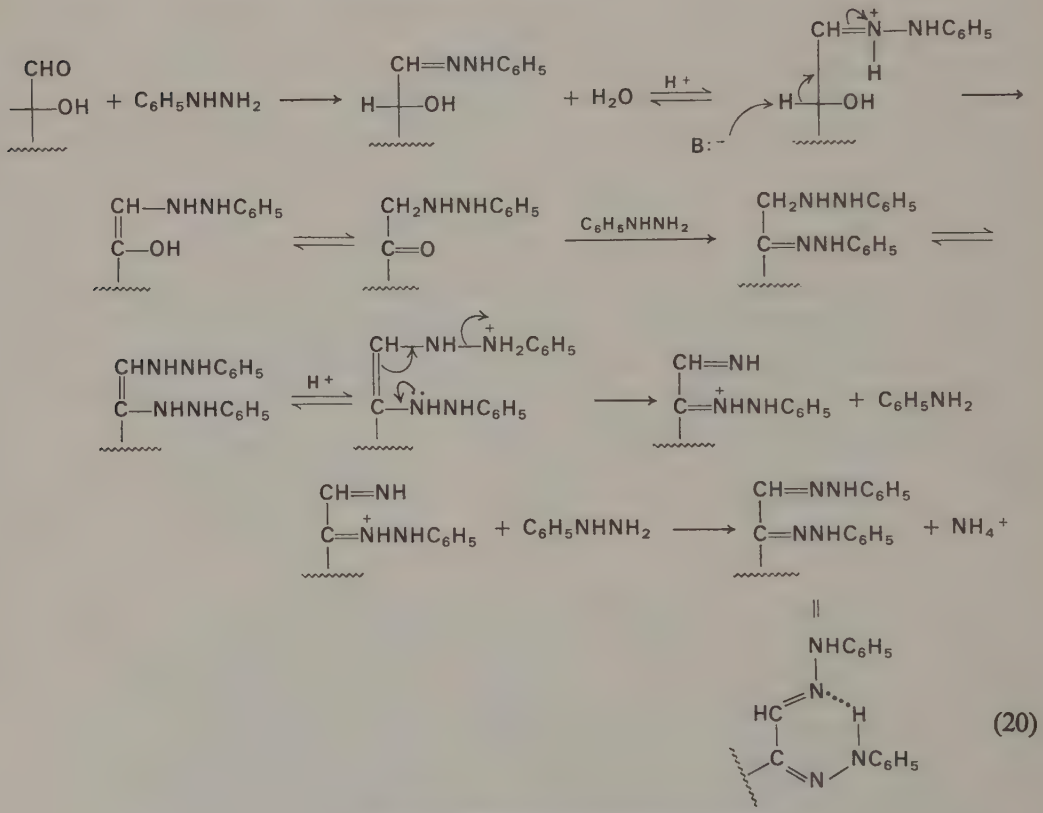
D-glucosazone D-glucosone D-fructose (a ketohexose) (18)

D-Glucose, D-mannose, and D-fructose all react with phenylhydrazine to give D-glucosazone, which is further evidence that the configurations of these three sugars are identical at C-3, C-4, and C-5.

D-glucose
D-mannose
D-fructose
} $\xrightarrow{C_6H_5NHNH_2}$ D-glucosazone (19)

It should be apparent from this that phenylhydrazine can be of great value in determining the configuration of sugars, for two aldoses that give the same osazone differ only in their configuration at C-2.

Why does not reaction with phenylhydrazine continue down the carbon chain until all of the —CHOH— groups are converted into $-\overset{|}{C}=NNHC_6H_5$ groupings? It has been suggested in answer that the osazone is stabilized by hydrogen-bond formation and the reaction does not proceed past the stages shown. The mechanism of osazone formation is shown in the following expression (where $B:^-$ is a generalized symbol for a proton acceptor, that is, a base):



(20)

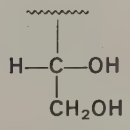
Mechanism of osazone formation

14-10 The D-series of aldohexoses

The two aldotetroses, four aldopentoses, and eight aldohexoses of the D-series are derived by successive chain extensions, starting from D-glyceraldehyde. The total development of the D-series can be represented in the following systematic way:

The aldoses of the D-series

It should be noted that the sign of optical rotation varies among the aldohexoses according to no obvious pattern. It is to be borne in mind that the series designation (D or L) represents a structural relationship, while the optical rotation is an empirical quantity that is determined by experimental measurement. When the sugars of the D-series are represented by the Fischer formulation, the last two carbon atoms are conventionally shown as



denoting their relationship to D-glyceraldehyde.

There also exists an enantiomeric series of L-aldoses, arising in the same way from L-(−)-glyceraldehyde. Of the sixteen aldohexoses, some occur in nature, while others are known only as synthetic compounds.

14-11 The cyclic structures of the sugars

The linear formulas by which the aldoses have been represented in the foregoing sections are, while not incorrect, incomplete and inadequate representations of their true structures. The typical aldohexose, for instance, exists in solution principally in the form of the *cyclic hemiacetal*. The "free aldehyde" form, while present in the hydroxyaldehyde ⇌ cyclic hemiacetal equilibrium, amounts in most cases to less than 0.1% of the compound in aqueous solution.

A number of experimental observations lead to the conclusion that, in solution, aldohexoses and ketohexoses consist of equilibrium mixtures of the free aldehyde or keto form and the cyclic hemiacetal or hemiketal form.

1. The aldoses exhibit behavior characteristic of aldehydes: they reduce Tollens' reagent (ammoniacal silver) and Fehling's solution, and are therefore called *reducing sugars*.

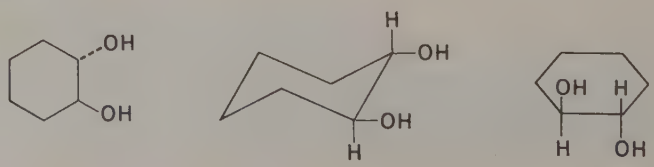
2. D-Glucose, for example, can be converted into the oxime, and, with the proper selection of experimental conditions, into the phenylhydrazone (rather than the osazone), showing that it can behave as a carbonyl compound (an aldehyde).

3. Acetylation of D-glucose gives the six-membered (pyranose) cyclic penta-acetate.

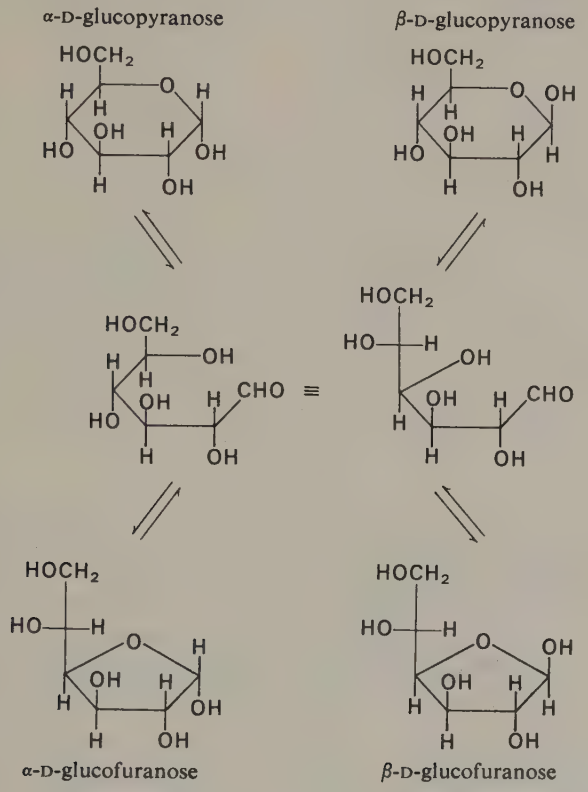
4. Treatment of D-glucose with methanol and hydrogen chloride gives not the aldehyde dimethyl acetal but two isomeric compounds, each containing but one methoxyl group.

5. Finally, the reaction of D-glucose with acetone gives a di-acetonide that is derived from the five-membered (furanose) ring form of the sugar.

These observations can be accommodated by the equilibria shown below. The five- and six-membered rings shown in these formulations are written in what are called *Haworth formulas*, which are conventional perspective representations of rings that are more accurately—but often less conveniently—drawn in conformational notation. For example, the structure of *trans*-1,2-cyclohexanediol may be represented in the following ways; the last one corresponds to the Haworth formula commonly used for sugars:

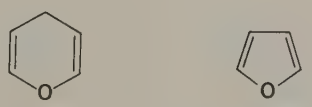


The equilibria (in solution) between the various cyclic and open-chain forms of glucose are as follows:



(21)

The terms "pyranose" and "furanose" derive from the names of the parent compounds of these ring systems:



Two distinct crystalline forms of D-glucose are known; they can be obtained by crystallizing the sugar from solutions at different temperatures. Crystallized from cold solution, glucose with a specific rotation of $+113°$ is obtained. From hot, concentrated solutions the glucose that crystallizes has a specific rotation of $+19°$. These are designated as the α and β forms, respectively.

When either of these two compounds is dissolved in water, its initial rotation is

that given above; but the optical rotations of both solutions change with time to reach the same final value, +52.5°. This phenomenon is called *mutarotation*, which denotes the *configurational change of a single chiral center in a molecule while other centers of asymmetry remain unaltered.*

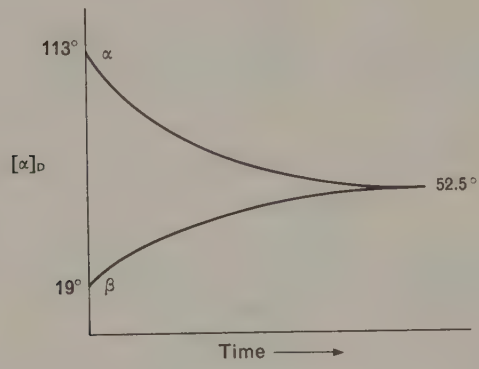
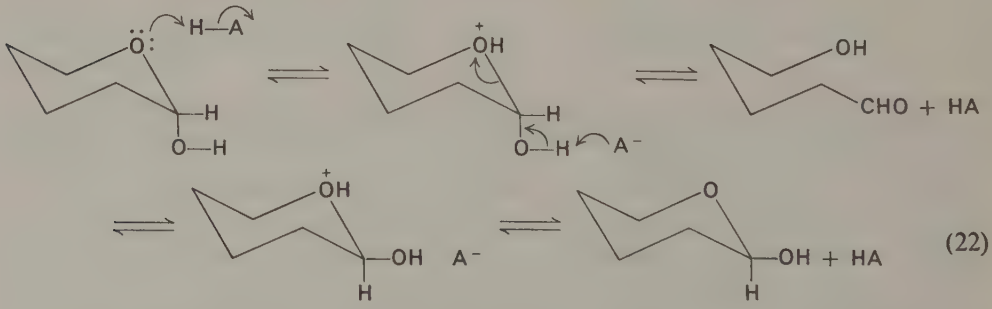


Figure 14-2
Mutarotation of glucose.

The mutarotation of glucose is not rapid in pure water or non-hydroxylic solvents, but is greatly accelerated if a trace of an acid (a proton donator) or a base (a proton acceptor) is present, and is even more rapid if both an acid and a base are present. The mechanism of the reaction that undergoes this acid-base catalysis is shown in the following scheme; it can be seen that the aldehyde form is an intermediate:

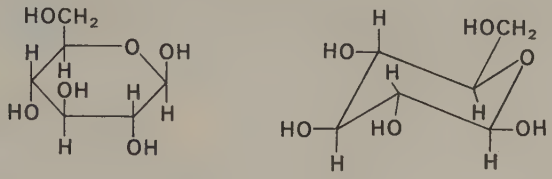


(22)

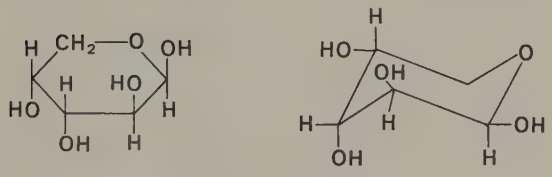
The proportion of α- and β-pyranose forms is different for each aldose. At equilibrium, the proportion of α form for D-glucose is 36%; for D-arabinose, 63%; for D-mannose, 67%; and for D-galactose, 27%. Small (and often not accurately known) amounts of the furanose and open-chain (free aldehyde) forms are also present.

Representation of the cyclic forms of sugars by conformational formulas shows more clearly the true relative dispositions of the substituents. It can be seen that in

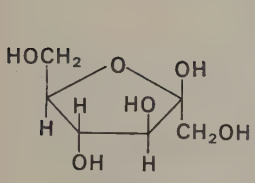
β-D-glucopyranose all of the substituents are equatorial. In the following examples the Haworth formulas are given for comparison:



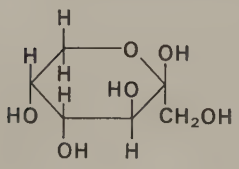
β-D-glucopyranose

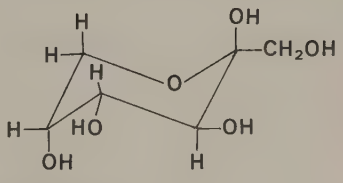


β-D-arabinopyranose



β-D-fructofuranose

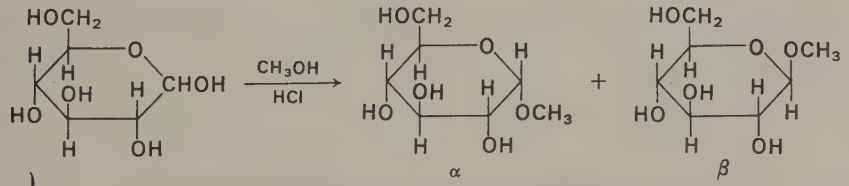




β-D-fructopyranose

14-12 Glycosides. Cyclic acetal formation

The reaction of D-glucose with methanol and a small amount of a strong acid as catalyst gives a mixture consisting principally of two isomeric compounds, each containing one methoxyl group. These compounds, called methyl α- and β-D-glucopyranoside, are the acetals formed by replacement of the hydroxyl group at the *anomeric* carbon atom (C-1) with a methoxyl group:



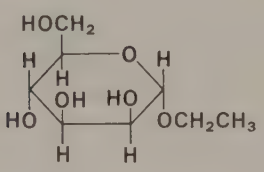
(23)

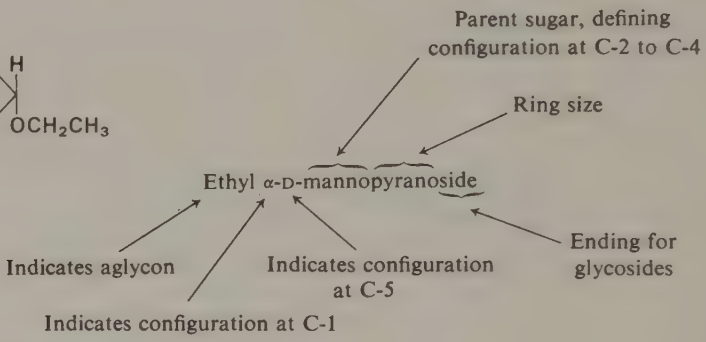
α, β -D-glucopyranose

Methyl D-glucopyranosides
(+small amounts of the methyl D-glucofuranosides)

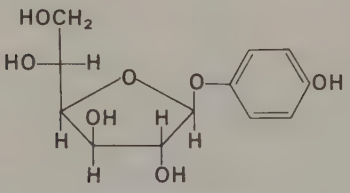
The methyl glucosides are non-reducing; they do not show mutarotation in solution; they are quite unaffected by aqueous alkali under any but extreme conditions; but, like acetals of other kinds, they are readily hydrolyzed under acid conditions to yield D-glucose and methanol.

Sugar derivatives of this class are called *glycosides*. Glycosides of specific sugars are called mannosides, ribosides, glucosides, galactosides, and so on. The hydroxyl compound released by hydrolysis of a glycoside is the *aglycon*. Thus methanol is the aglycon of methyl glucoside. The following example summarizes the nomenclature of the class:

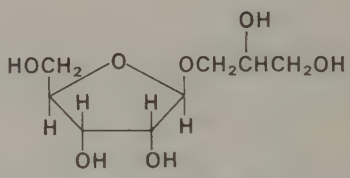




Two additional examples are



p-hydroxyphenyl β-D-glucofuranoside



1-glyceryl β-D-ribofuranoside

It should be noted that in Haworth formulas for aldoses and aldosides of the D-series the terminal —CH_2OH group lies above the plane of the ring.

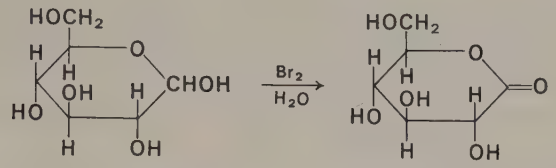
Exercise 6

Draw the Haworth formulas for (*a*) methyl α-D-arabinopyranoside, (*b*) ethyl β-D-galactopyranoside, (*c*) methyl β-D-fructofuranoside, and (*d*) 2-chloroethyl α-D-xylofuranoside.

14-13 Proof of the ring structure of sugars and glycosides

Although the aldose glycosides whose structures have been shown in the foregoing discussion have been written as 5- and 6-membered rings (that is, furanosides and pyranosides), we have not yet shown that they indeed have these structures. Moreover, no proof has been offered that α- and β-D-glucose actually exist chiefly in the pyranose forms.

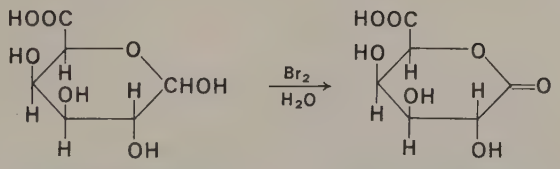
Early evidence that glucose has the pyranose structure was its ready oxidation by bromine water to give the lactone, rather than gluconic acid, as the initial product:



(24)

α or β -D-glucopyranose β-D-glucano-1 → 5-lactone

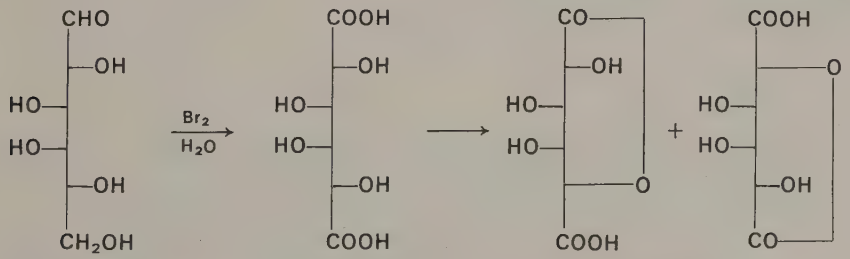
It might be argued that this reaction could be interpreted as proceeding through the open chain (acyclic) form of glucose → gluconic acid → gluconolactone, the lactonization occurring as a last step. That this view is untenable is shown by the fact that both α- and β-D-galacturonic acid are oxidized by bromine water to give the *optically active* D-galacturonic-1 → 5-lactone.*



(25)

α- or β-D-galacturonic acid (galactopyranouronic acid) D-galacturono-1 → 5-lactone (optically active)

If the aldehyde (open-chain) form of D-galacturonic acid were actually the form undergoing oxidation to the 1,6-dicarboxylic (galactaric) acid, followed by lactone formation, the resulting lactone would not be optically active, for galactaric acid is a *meso* compound, and the enantiomeric lactones would be formed with equal probability:



(26)

D-galacturonic acid (aldehyde form) A *meso* compound (non-resolvable) (Enantiomers)

* Some of the 1 → 4 lactone is also formed from the furanose sugar present in the solution, but this does not alter the conclusions.

Exercise 7

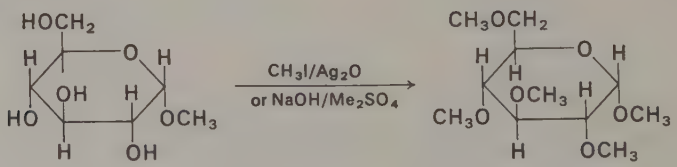
(*a*) Can an argument of this kind be used to prove that the oxidation of D-glucose to D-gluconic lactone proceeds without passing through the open-chain dicarboxylic acid? Why?

(*b*) Suggest another sugar acid of the D-series, other than D-galacturonic acid, that could be used in a similar experiment.

The ring size of glycosides was first determined by the chemical methods to be described in the following sections. The more recent use of physical data (X-ray crystallography, nuclear magnetic resonance, mass spectra, and optical rotatory dispersion) has confirmed and extended these structural conclusions, and these methods are now widely applied to the solution of structural problems in carbohydrate chemistry.

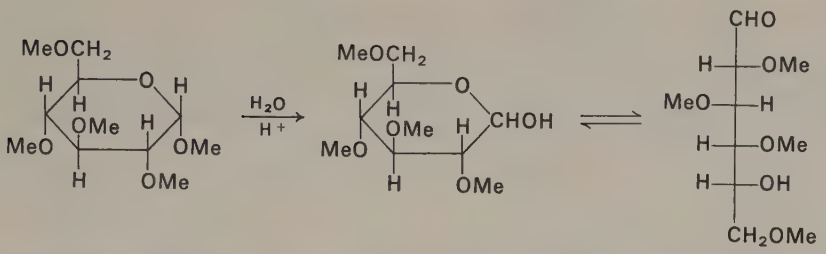
14-14 Complete methylation of glycosides

Since glycosides are stable under alkaline reaction conditions, treatment with alkali and a methylating reagent, usually methyl iodide or dimethyl sulfate, converts the free hydroxyl groups into methoxyl groups without affecting the anomeric center (C-1). The reaction is effectively a form of the Williamson ether synthesis. The reagents used may be methyl-iodide/silver-oxide (Purdie-Irvine) or dimethyl-sulfate/sodium-hydroxide (Haworth); both give the fully methylated glycoside. Experimental variants of these methods include the use of dimethyl sulfoxide as a solvent, and various other strong bases as alkali:



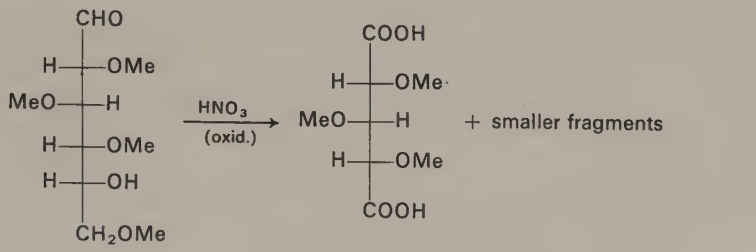
(27)

The fully methylated glycoside, which is an acetal (at C-1), is readily hydrolyzed by aqueous acid to the tetramethylated sugar, which can be represented by the aldehyde ⇌ hemiacetal forms:



(28)

Oxidation (with nitric acid) of the 2,3,4,6-tetra-*O*-methylglucose causes oxidative cleavage between C-5 and C-6* to yield *meso*-tri-*O*-methylxylaric acid (*xylo*-trimethoxyglutaric acid; compare the structure of xylose):



(29)

xylo-trimethoxyglutaric acid
(shows the presence of three adjacent —OMe groups in the original tetra-*O*-methylglucose)

This result establishes the fact that in the cyclic glucoside the ring closure was C-1/C-5, and that the glucoside has the pyranose structure.

A further application of the methylation-oxidation procedure will be described in a later section.

Exercise 8

Oxidation of 2,3,4,6-tetra-*O*-methylglucose might afford, in addition to the trimethoxyglutaric acid, some di-*O*-methyl-L-tartaric acid. Would this information be useful in the present context? Why?

14-15 Analysis of glycoside structure by periodic acid oxidation

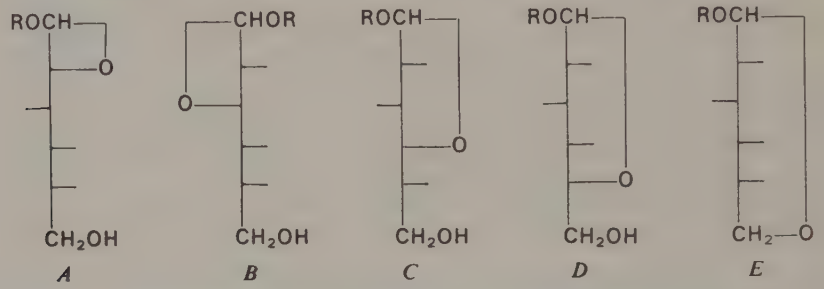
Periodic acid oxidation (Section 13-10, which should be reviewed here) provides an elegant method for the analysis of the structure of carbohydrate derivatives. Since the

---

* Oxidation could also occur between C-4 and C-5 or elsewhere, but this is irrelevant. The formation of the 2,3,4-trimethoxy compound is the significant result; smaller fragments provide no contradictory information.

reagent (sodium periodate) is used in neutral solution, the acetal grouping at C-1 is unaffected, and only *adjacent* hydroxyl groups are involved in the reaction.

Let us first of all examine what might be regarded as the possible structures for the cyclic D-glucosides. Five modes of ring closure are *a priori* possibilities:



The oxidation of these by periodate will yield the experimental results shown in the following summary:

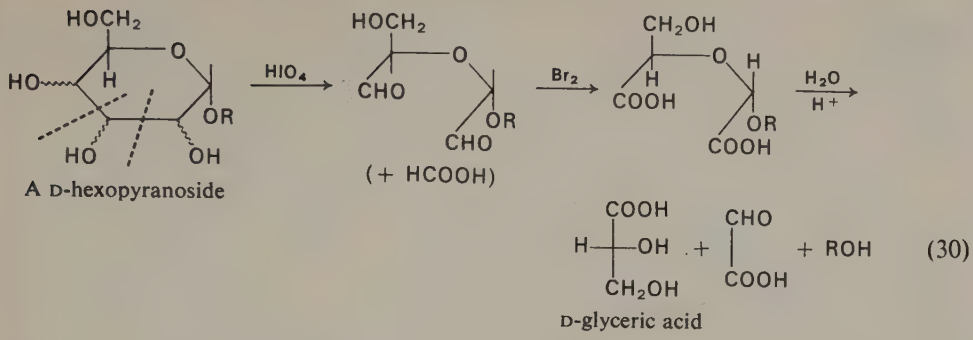
	A	*B*	*C*	*D*	*E*
moles HIO_4 consumed	3	2	2	2	3
moles HCOOH formed	2	1	0	1	2
moles CH_2O formed	1	1	1	0	0

Oxidation of methyl D-glucoside (α or β) with periodate is found experimentally to consume 2 moles of HIO_4, and to yield 1 mole of formic acid and no formaldehyde. This result is consistent only with the pyranose structure (*D*).

Exercise 9

What would be the results (HIO_4 consumed, HCOOH and HCHO formed) in the oxidation by periodic acid of (*a*) methyl D-glucofuranoside, (*b*) methyl D-ribopyranoside, (*c*) methyl D-fructopyranoside, and (*d*) methyl D-fructofuranoside?

The products formed in the oxidation of a D-aldohexopyranoside by periodic acid are shown in the following equations. Note that the configurations at C-2, C-3, and C-4 of the original glycoside need not be specified in writing this sequence of reactions:



A D-hexopyranoside

D-glyceric acid

(30)

The immediate oxidation product, besides formic acid, is a dialdehyde. In practice, a subsequent oxidation is performed to convert this dialdehyde into the dicarboxylic acid (which is easier to manipulate experimentally and to isolate, usually as a barium salt). It may be observed that four different dialdehydes (or diacids) are obtained by periodate oxidation of α-D-, α-L-, β-D-, and β-L-hexopyranosides. Hydrolysis of the diacids formed in this way from the (α or β) D-aldohexopyranosides (and from D-aldopentofuranosides) gives D-glyceric acid. Similarly the L-aldohexopyranosides and L-aldopentofuranosides, by the same degradation series, give L-glyceric acid.

Exercise 10

Show the oxidation of an L-galactopyranoside with periodic acid, including the stereochemical details of the steps leading to the final formation of L-glyceric acid.

Exercise 11

Treatment of L-arabinose with methanol-HCl gives two (α and β) methyl L-arabinosides. Total methylation of either of these with Ag_2O/MeI gives a methyl tri-*O*-methylarabinoside that upon acid hydrolysis and nitric acid oxidation gives L-*arabo*-trimethoxyglutaric acid. Write the structures of the original methyl arabinosides.

15

Carbohydrates II: Natural glycosides. Disaccharides and polysaccharides

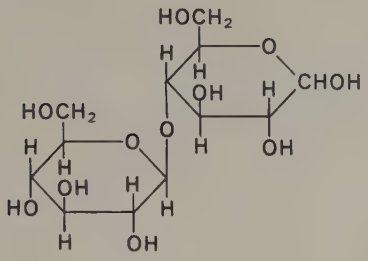
Most of the comment introducing Chapter 14 applies to this chapter as well. Much of the chemistry of sugars is that of simpler hydroxy and polyhydroxy compounds. Even the often structurally complex glycosides and polysaccharides are elaborate extensions of simpler cyclic acetals, so that much of their behavior can be understood by recognizing their kinship to simpler ethers, acetals, and polyols.

The descriptive sections on naturally occurring sugar derivatives are an introduction to a vast area of chemistry of biological importance. The glycosides and oligo- and polysaccharides, many of them of central importance in biology, are one of the largest classes of compounds found in nature.

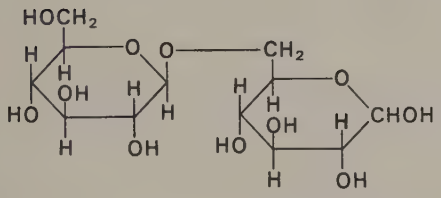
15-1 Disaccharides

Glycosides in which the aglycon is another sugar are termed *disaccharides*. Since sugars are polyhydroxy compounds, they may enter into glycosidic combination at more than one position. For example, the disaccharides *cellobiose* and *gentiobiose* are

β-D-glucopyranosides in which the 4-hydroxyl and the 6-hydroxyl group, respectively, of a second glucose molecule is attached to the glycosidic (C-1) carbon atom:



Cellobiose
4-*O*-[β-D-glucopyranosyl]-D-glucopyranose
(anomeric carbon atom may be α or β and is represented with non-committal stereochemistry)



Gentiobiose
6-*O*-[β-D-glucopyranosyl]-D-glucopyranose

Cellobiose and gentiobiose both possess the "free" (potential) aldehyde at C-1 of the aglycon sugar, and thus are *reducing* sugars. Both can be converted into the corresponding methyl glycosides (methyl cellobioside, methyl gentiobioside) by reaction with methanol-HCl.

Exercise 1

Draw the Haworth structure for methyl α-cellobioside. Is this a reducing or a nonreducing sugar?

Periodic acid oxidation of methyl cellobioside and methyl gentiobioside shows their structures:

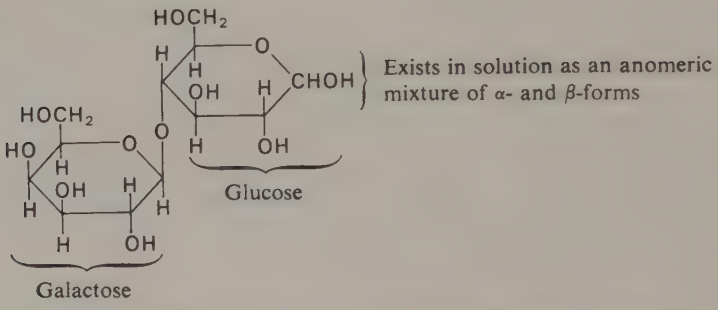
	Moles HIO_4 *consumed*	*Moles* HCOOH	*Moles* HCHO
methyl cellobioside	3	1	0
methyl gentiobioside	4	2	0

Exercise 2

Complete methylation of methyl gentiobioside by the Purdie-Irvine method, followed by acid-catalyzed hydrolysis of the product, yields two isomeric

compounds. Both are glucose tetramethyl ethers. What are their structures (use the non-cyclic aldose formulas)?

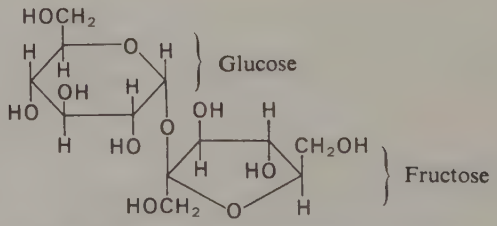
Lactose, an important disaccharide, occurs in mammalian milk, both free and as a component of larger oligosaccharide molecules. It is a reducing sugar with the following structure:



Lactose: 4-*O*-[β-D-galactopyranosyl]-(α or β)-D-glucopyranose

Non-reducing disaccharides are joined by acetal linkage between the two anomeric carbon atoms. As a consequence, they are not in equilibrium with a free aldehyde form and are not oxidized by Tollens' or Fehling's reagents.

Sucrose is β-D-fructofuranosyl-α-D-glucopyranoside. Note that the ending "-ose," found in the names of the reducing monosaccharides and disaccharides, is absent from the systematic name for sucrose. The Haworth representation of its structure is as follows:



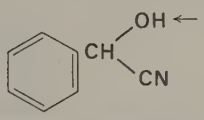
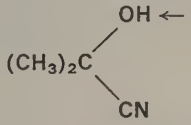
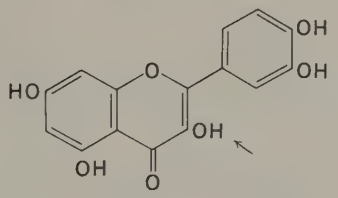
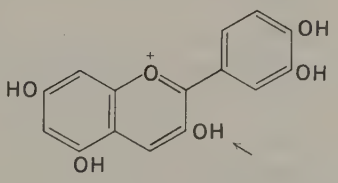
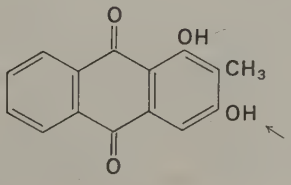
Sucrose: β-D-fructofuranosyl-α-D-glucopyranoside

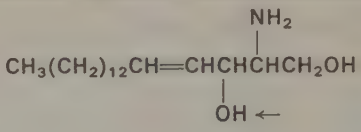
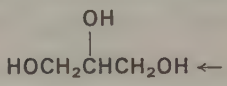
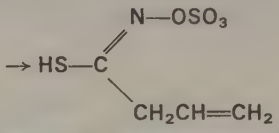
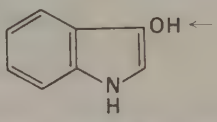
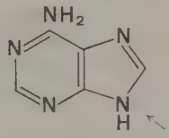
Exercise 3

What would be the result (HIO_4 consumed, HCOOH and HCHO formed) of the periodate oxidation of sucrose?

15-2 Naturally occurring glycosides

Nature abounds in glycosides of many kinds. Indeed, the vast majority of the sugars from natural sources (plants, animals, microorganisms) exist in some kind of glycosidic combination: as glycosides of some non-carbohydrate aglycon, as di- or oligosaccharides, or as polysaccharides (see Sections 15-7 ff). Many of the most important naturally occurring sugars occur as glycosides in which the attachment at C-1 is to nitrogen (Section 15-16) or sulfur (*N*-glycosides, *S*-glycosides). The aglycons of natural glycosides vary widely in structural type and include simple aliphatic alcohols, phenols, and complex hydroxyl-containing compounds. Some common and typical glycosides that occur widely in living organisms are shown in the following examples:

Sugar	*Aglycon*	*Name of glycoside and remarks*
gentiobiose (at →)		*Amygdalin*: the potentially toxic constituent of almond and peach seeds
D-glucose (at →)		*Linamarin*: one of a number of cyanide-producing glycosides of forage plants. Toxic to animals
D-glucose (at →)		*Isoquercitrin*: a widely distributed pigment (yellow) in higher plants
D-glucose (ta →)		*Chrysanthemin*: a deep red glycoside, the pigment of many red-flowered plants
D-glucose (at →)		*Rubiadin glucoside*: a pigment found in madder (*Rubia tinctorum*)

Sugar	*Aglycon*	*Name of glycoside and remarks*
D-galactose (at →)		One of a number of similarly constituted "galactolipids" found in myelin portions of nerve tissue. The —NH_2 is acylated in the native compound
D-galactose (at →)		Found in certain algae. The 2-*O*-D-galactoside is also present
D-glucose (at →)		*Sinigrin*: the "mustard-oil" precursor found in mustard seed
D-glucose (at →)		*Indican*: upon enzymatic hydrolysis, indoxyl is released and oxidizes rapidly to form the pigment *indigo*
D-ribose (β-furanose) (at →)		*Adenosine*: important in metabolism as the mono-, di-, and triphosphates AMP, ADP, and ATP

The proof of the structure of a glycoside in most cases consists in establishing the structure of the aglycon, for the sugar or sugars can be removed by hydrolysis and easily identified, usually by chromatography. The great majority of natural glucosides are β-D-glucopyranosides, although the α-glycosidic linkage is not unknown.

Two structural questions remain that are not answered by identification of the sugar(s) and the aglycon: (1) Is the glycosidic linkage α or β? (2) In a disaccharide unit, what is the position of linkage between the two sugars?

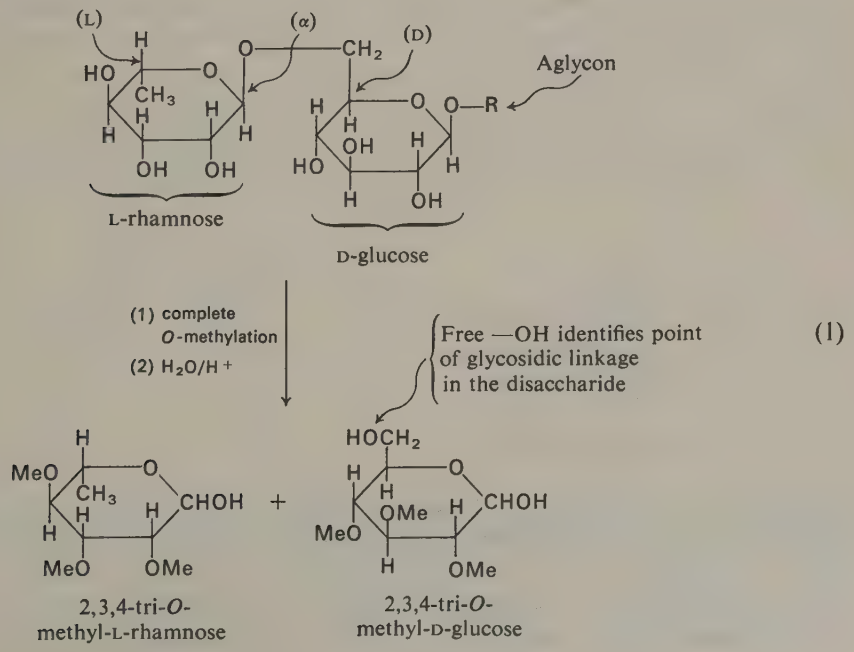
The first of these questions can often be answered by recourse to the specificity of enzymatic hydrolysis. The readily available enzyme *β-glucosidase* catalyzes the hydrolysis of β-D-glucopyranosides (for example, cellobiose, gentiobiose, methyl β-D-glucoside), but is ineffective with α-glucosides (maltose, methyl α-D-glucoside). Accordingly, the unknown glucoside can be subjected to the action of β-glucosidase and the course of the reaction followed by testing for the appearance of free glucose or of the aglycon. Other enzymes are known, some specific for β-D-glucuronisides, some for α-D-glucopyranosides, some for α-L-arabinofuranosides, and so on. Many such enzymes are derived from unique natural sources and are not usually readily available, so this method is of limited application.

With the development of sophisticated instruments, physical methods of analysis

have assumed importance in recent years. In particular, nuclear magnetic resonance (Chapter 26) provides clear and unambiguous answers to many questions of structure. Useful as these techniques are, specific examples of their use would require detailed analysis beyond the scope of our discussion.

Chemical methods of analyzing glycoside structure include those that have been described in the discussion of the disaccharides: (1) oxidation by periodic acid; and (2) complete methylation followed by hydrolysis, and identification of the partially methylated sugar or sugars.

The second procedure, for example, can be used to determine the structure of the disaccharide *rutinose*, which is the sugar component of a number of naturally occurring glycosides. Complete hydrolysis of a rutinoside yields the aglycon (which is not pertinent here) and a mixture of L-rhamnose and D-glucose. Carefully regulated hydrolysis of the original glycoside yields L-rhamnose and a glucoside. This indicates that the rutinoside is constructed in the order L-rhamnose-D-glucose-aglycon. It remains to determine (*a*) whether the glycosidic rhamnose-glucose and glucose-aglycon links are α or β and (*b*) which hydroxyl group of the glucose residue is attached to C-1 of rhamnose. The first of these questions can be answered by enzymatic hydrolysis and by optical rotation data. The second question is answered by complete methylation of the original rutinoside, followed by acidic hydrolysis. The results obtained by these methods show that the original glycoside is a 6-*O*-[α-L-rhamnopyranosyl]-β-D-glucoside:

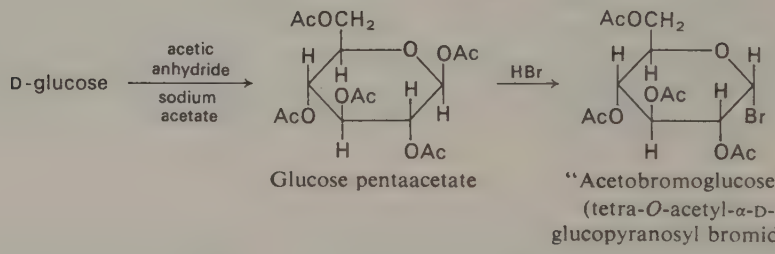


(1)

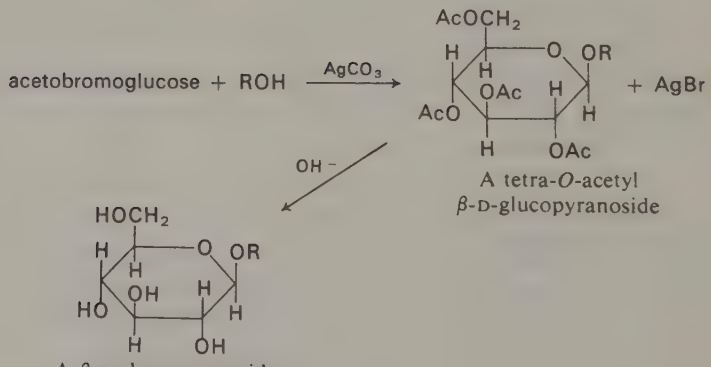
15-3 Functional derivatives of glucose: *O*-acylation

The *O*-methylation of sugars has been described in foregoing sections. Other *O*-substituted derivatives include the *O*-acyl derivatives, such as glucose pentaacetate. The reaction of ordinary glucose (that is, the α/β mixture) with acetic anhydride at elevated temperatures (for example, 100°C) yields β-D-glucopyranose penta-*O*-acetate, probably because the reaction of acetic anhydride with the equatorial β-hydroxyl group at C-1 is rapid, and mutarotation maintains the presence of the β-anomer. If pure α- and β-D-glucopyranose are separately acetylated in pyridine solution at low temperature (0°), acetylation proceeds faster than mutarotation, so that α- and β-anomeric pentaacetates are formed.

Sugar acetates are of special value in the synthesis of glycosides and other sugar derivatives. One of the most useful procedures involves (1) conversion of glucose pentaacetate into the tetra-*O*-acetylglucopyranosyl bromide by reaction with HBr in acetic acid, and (2) replacement of the bromine by reaction (nucleophilic displacement) with a hydroxyl-containing compound (the aglycon of the resulting glycoside):



(2)



(3)

The general synthetic sequence shown in these equations has been applied to the synthesis of countless glycosides* of all kinds; the nucleophilic agents may be alcoholic

* Similar 1-α-bromo sugar acetates can be prepared by the reaction of HBr with acetylated mono- and disaccharides of many kinds.

and phenolic compounds, other sugars (leading to oligosaccharides), or purines and pyrimidines (yielding nucleosides).

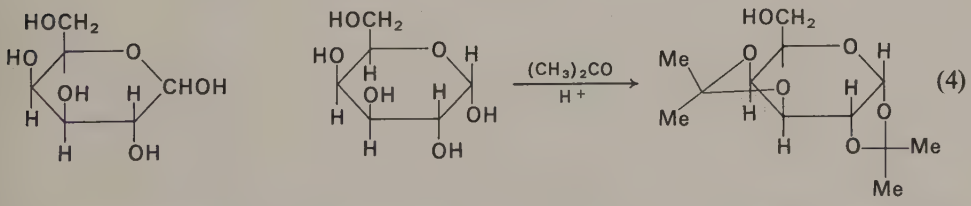
Exercise 4

Devise a synthesis of gentiobiose with glucose and methyl β-D-2,3,4-tri-*O*-acetyl-glucopyranoside as starting materials.

15-4 Functional derivatives of glucose: Cyclic ketals (acetone derivatives)

The reaction of acetone with 1,2-diols to form cyclic ketals (discussed in Chapter 13) is a reaction with wide application to carbohydrate chemistry. Its use in the synthesis of ascorbic acid has been described in Section 13-8. The advantage of these cyclic ketals (often called by the simple term "acetonides," or more systematically "isopropylidene sugars") is that the ketal grouping survives most experimental conditions at neutral or alkaline pH, but can readily be removed by hydrolysis under acidic conditions to regenerate the hydroxyl groups.

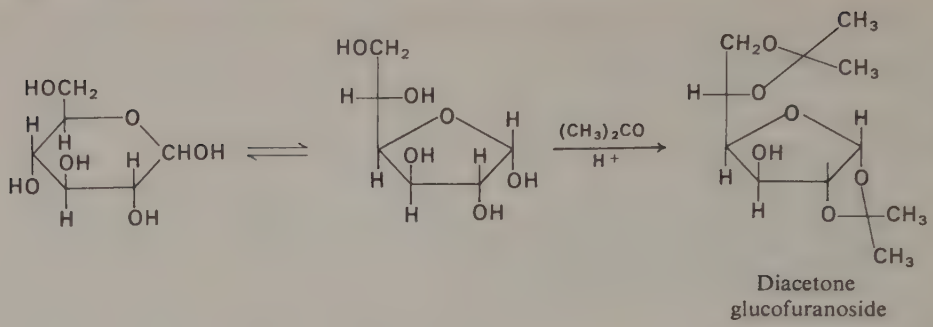
The preferential formation of acetonides from *cis*-1,2-diols and the very slow rate of reaction of acetone with *trans*-1,2-diols are clearly demonstrated by the reactions of D-mannose, D-galactose, and D-glucose with acetone. In D-galactose, as can be seen in the Haworth formula, the 1-α- and 2-hydroxyl groups and the 3- and 4-hydroxyl groups constitute two pairs of *cis*-1,2-diols. Thus, D-galactose in the pyranose form readily forms a di-acetonide in which the $—CH_2OH$ group remains free:



(4)

D-galactopyranose α anomer 1,2:3,4-diacetone D-galactose

D-Glucose could react in the α-pyranose form to give only the 1,2-acetonide; but when it rearranges (in the usual equilibrium) to the furanose, then the 1,2:5,6-di-acetonide can form, and is the product that is actually formed. In this case, the 3-hydroxyl group remains free:

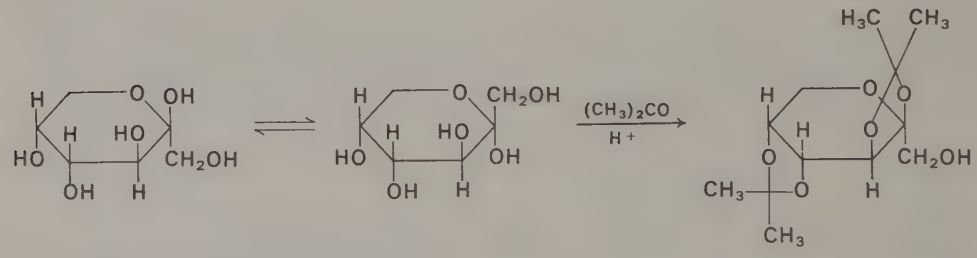


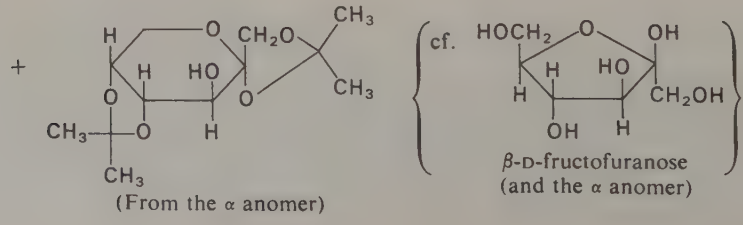
(5)

Exercise 5

D-Mannose reacts with acetone to give a diacetone derivative that is still a reducing sugar. (NOTE: The diacetone derivatives of glucose and galactose are non-reducing.) What is its structure?

D-Fructose forms two acetonides, one derived from the α-pyranose form, the other from the β-pyranose form. Only in β-fructopyranose are the hydroxyl groups at C-3 and at the anomeric (C-2) carbon atom in a *cis* relationship; therefore, in α-fructopyranose, acetonide formation takes place between the two hydroxyl groups (1 and 2) at which no stereochemical restrictions exist, and between the *cis* 4- and 5-hydroxyl groups:



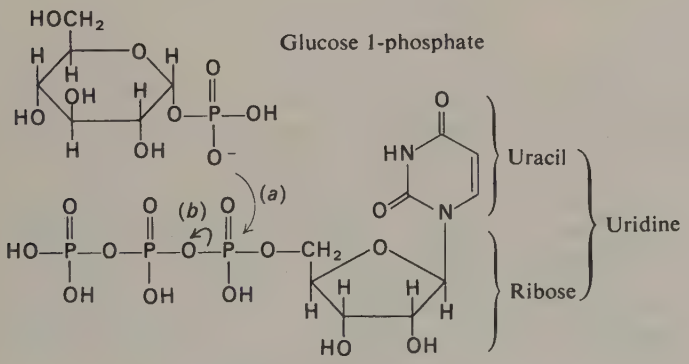


(6)

15-5 The biosynthesis of glycosides and disaccharides

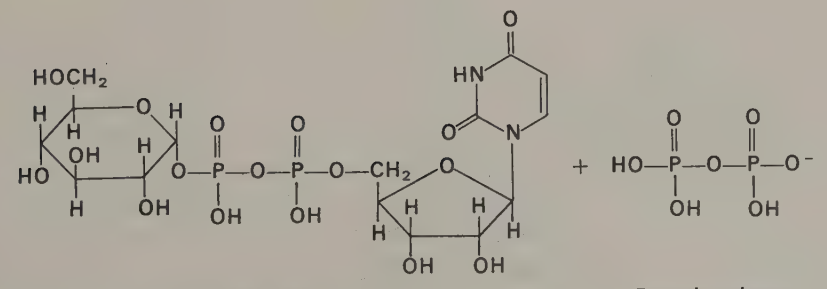
The synthesis of glycosides (in which class disaccharides and polysaccharides may be included) takes place in living organisms by a reaction course that bears a striking resemblance to the synthetic methods in which acetobromoglucose takes part (Section 15-3). The "reagent" in a natural synthesis (when glucose is the sugar involved) is a complex compound whose structure may be expressed briefly as purine-ribose-phosphate-phosphate-glucose. Several such compounds are known as specific glycosylating agents, one of them being uridine-diphospho-glucose, commonly referred to as UDP-glucose.

UDP-glucose is formed by the reaction of α-D-glucopyranose 1-phosphate with uridine triphosphate. The reaction is essentially a nucleophilic displacement on phosphorus, in which the displaced ("leaving") group is the anion of the strong acid pyrophosphoric acid:



Uridine triphosphate (UTP)

(7)

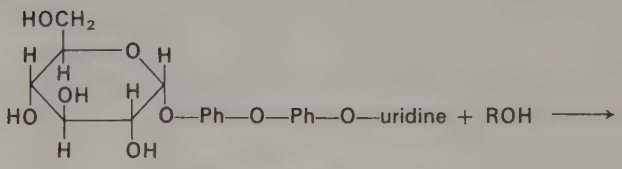


UDP-glucose

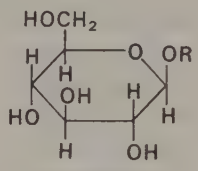
Pyrophosphate

(*a*) Nucleophilic attack
(*b*) Displacement of pyrophosphate

UDP-glucose can now act as a *glucosylating agent*, for the UDP anion is displaceable by nucleophilic attack at C-1 of the sugar (just as Br^- is displaced when acetobromoglucose acts as a glucosylating agent):



UDP-glucose

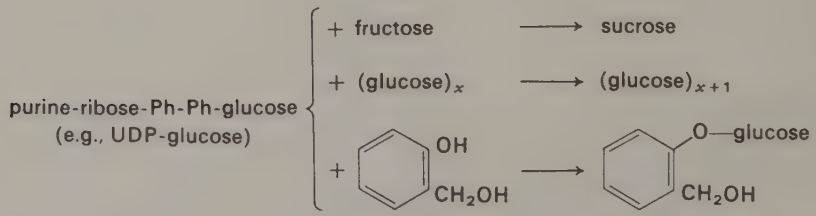


+ uridine—O—Ph—O—PhO^- (8)

A glucoside

The last expression is somewhat oversimplified, but only in mechanistic detail. The reaction of acetobromoglucose with nucleophiles is a unimolecular (S_N1) reaction in which the loss of Br^- precedes attack of the nucleophile. Although the detailed kinetics of the enzyme-catalyzed reaction of the UDP-glucose with a nucleophile are not as clearly definable, because the cellular reactions occur in an enzymatic milieu, it is possible that the same route is followed.

UDP-sugars (and other purine-ribose-phosphate-phosphate-sugars) are responsible for the formation of glycosides, oligosaccharides, and polysaccharides in reactions such as the following:



(9)

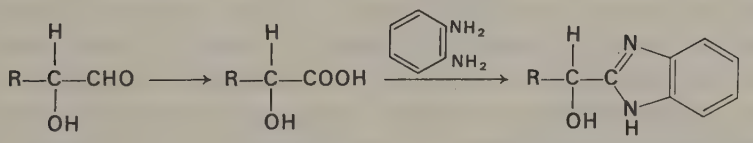
Salicin

These reactions are mediated by specific protein molecules that characterize the total enzyme system that is involved, and that are in many cases specific for the particular purine-sugar prosthetic group and for the substrate being glycosylated.

15-6 Identification of sugars

Identifying a sugar is often an important part of determining the structure of a naturally occurring glycoside. When the glycoside is hydrolyzed, usually by dilute aqueous acid, the sugar is liberated and can be isolated from the hydrolysis mixture. There are a number of ways of establishing its identity. It is not always necessary to isolate the sugar as a pure crystalline compound, but when this is done it can be identified by its physical properties (melting point, optical rotation, spectral data) and by direct comparison with an authentic specimen of known identity.

Sugars that are obtained only in dilute solution can be identified either by direct comparison with known sugars on paper chromatograms or by the preparation of crystalline derivatives. The osazones, prepared with the use of phenylhydrazine, can be used in the latter method. Another class of sugar derivatives that are valuable in identification are the *benzimidazoles*; these are formed upon reaction of *o*-phenylenediamine with aldonic acids, which are formed by mild oxidation of aldoses:



(10)

Aldose Aldonic acid Benzimidazole derivative

The benzimidazoles are valuable derivatives. One reason is that the —CHOH— group at C-2 is still present, so the total asymmetry of the sugar molecule is preserved. This is in contrast to the osazones: mannose and glucose give the same osazone, but they provide different benzimidazoles.

Many color tests have been devised to distinguish between different classes of sugars (aldopentoses from aldohexoses, ketones from aldoses, and so forth), but few of these can be used to identify individual sugars.

Recent developments in instrumental methods have provided additional analytical devices that can be used to separate and identify the constituents of mixtures of sugars in very small samples. Vapor-phase chromatography cannot often be applied to sugars themselves, for, like most polyhydroxy compounds, they usually have high melting points are are quite involatile. However, conversion of the sugars into acetates or trimethylsilyl derivatives (—OH → —$OSi(CH_3)_3$) renders them sufficiently volatile to be separated on vapor-phase chromatographic columns and identified. In some cases the poly-*O*-methylated sugars produced in the course of structure proof by complete methylation (Section 14-14) can be separated by vapor-phase chromatography. Paper, column, and thin-layer chromatography also have numerous applications to the analysis and identification of sugars and sugar derivatives.

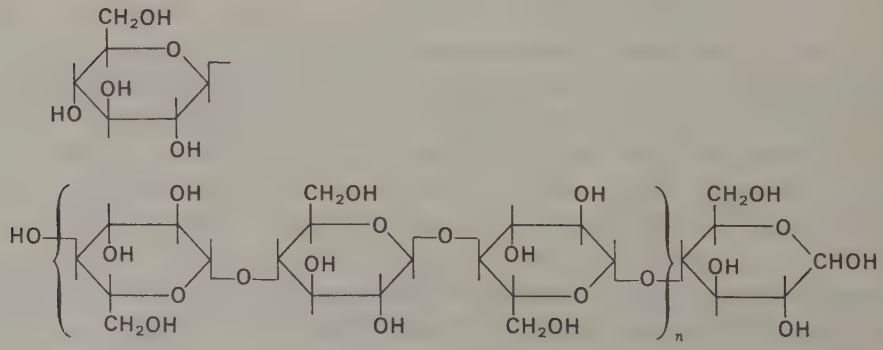
15-7 Polysaccharides

The vegetation of the earth contains enormous amounts of chemically combined carbon, mostly in the form of two polyglucoses, starch and cellulose. These polysaccharides are exceedingly complex, and consist of from hundreds to thousands of glucose units linked together in long chains. An exact structure cannot be written for any of the polysaccharides, but many years of investigation of these substances has brought our knowledge of them to the point at which we can describe the structures of many of them with a reasonable degree of completeness.

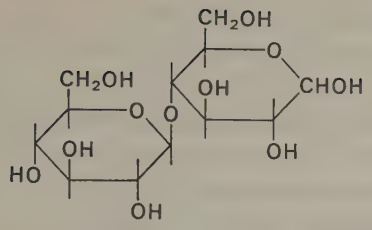
15-8 Cellulose

Cellulose is the most widely distributed plant polysaccharide. It is the main constituent of the cell walls of plants and, in association with another (non-carbohydrate) polymer, lignin, is the structural material of woody plants. Cellulose occurs in almost pure form as cotton and certain other plant fibers (flax, ramie fiber). Wood cellulose (wood pulp) is prepared by treating wood to remove lignin and hemicelluloses (lower-molecular-weight cellulose-like polysaccharides), leaving the cellulose as a pure, or nearly pure, white residue. The economic importance of cellulose can be readily appreciated when it is realized how widely paper products and cotton textiles are used.

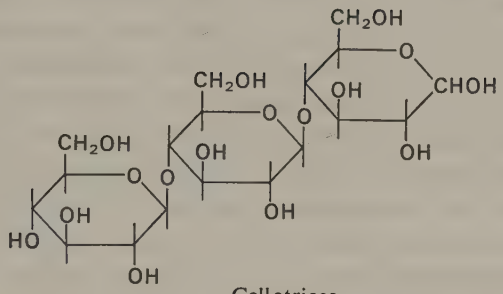
The composition of cellulose corresponds to $(C_6H_{10}O_5)_x$, where x is a very large number. The substance is a condensation polymer of glucose—complete hydrolysis gives a nearly quantitative yield of this sugar. Under milder conditions of hydrolysis the oligosaccharides cellobiose, cellotriose, and cellotetrose have been isolated. When to these observations are added the results of methylation studies, which have shown that 2,3,6-trimethyl-D-glucose is almost the only product, the structure of cellulose can be described: it is a long chain of 1,4-linked β-D-glucopyranose units:



Cellulose



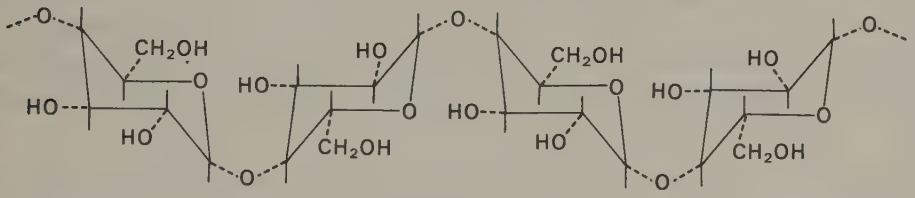
Cellobiose



Cellotriose

Attempts to measure the molecular size of cellulose have met with many difficulties. Physical measurements of viscosity, osmotic pressure, and ultracentrifugal sedimentation indicate that untreated native cellulose has a molecular weight of around 600,000, and thus consists of a chain of about 3000–4000 glucose units. The strength of cellulose fibers is due both to the covalent bonds in these long chains and to the hydrogen bonding between the hydroxyl groups in adjacent chains.

The cellulose chain is better represented so as to show the conformations in the chair form:



Cellulose

15-9 Enzymatic degradation of cellulose

Cellulose is not digested by man, but certain animals (ruminants) are able to utilize it as food because they maintain in their alimentary tracts colonies of microorganisms that produce enzymes known as "cellulases." The cellulolytic bacteria thus provide simultaneously for their own needs and those of the host animal by converting cellulose into metabolically useful glucose.

Cellulases are widely distributed in nature, being found in the digestive juices of the snail *Helix pomatia*, in many bacteria and fungi, in the seedlings of some plants, and in some nematodes. The function of cellulases in bacteria and fungi is to provide

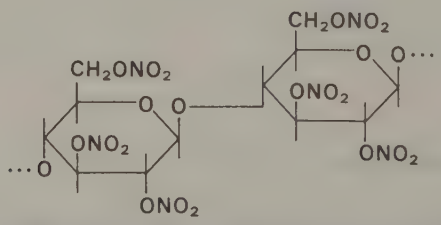
glucose as an energy source; on the other hand, plant pathogens may use cellulases as an aid in penetrating the cellulosic membranes of plant cells to gain entry into their hosts.

The economic importance of the cellulases is very great indeed. The deterioration of cellulosic textiles by bacterial and fungal attack is a serious and costly problem, particularly in tropical regions. Much study has been devoted to methods of reducing the attack of microorganisms upon textiles and paper products. Some of the measures that have been used are impregnation of textiles with fungicides and bactericides, coating with substances (for example, paraffin and plastics) impervious to fungal and bacterial attack, and dyeing with mineral dyes (containing heavy metals). Some attempts have been made to alter the chemical structure of cellulose itself by introducing substituents into the molecule (at the hydroxyl groups). The problem is still one of major importance, and it received particular attention during the last war, when the deterioration of stores and equipment in humid tropical regions represented a grave logistic problem.

15-10 Practical uses of cellulose

Cellulose in the form of cotton, wood pulp, linen, and ramie is used directly in textile and paper products; chemically altered cellulose has also provided many interesting and useful materials.

Nitration of cellulose is the conversion of cellulose into a polynitrate ester by treatment with nitric and sulfuric acids. The product, known as *guncotton*, is a useful explosive. *Nitrocellulose*, as the material is also called, is a cellulose nitrate, and though the extent to which the hydroxyl groups are esterified varies with the conditions of the process used, fully nitrated cellulose would have the following (partial) structure:



Guncotton approaches this degree of conversion. Less completely nitrated cellulose is known as *pyroxylin*, a mixture of which with camphor (which reduces the brittleness of the pyroxylin) is the common moldable plastic known commercially as Celluloid.

The most widely used ester of cellulose is the acetate. *Cellulose acetate* is produced in very large amounts for use as a fiber (rayon) and as a molding plastic. The incorporation of other acyl residues produces mixed acetate-propionate, acetate-butyrate,

and other esters, materials with a wide range of physical properties and industrial applications. Cellulose *ethers*, in which the —OH groups of cellulose have been converted into $—OCH_3$ or $—OC_2H_5$ groups, are made by treating cellulose with alkali and the appropriate alkyl chloride. The use of chloroacetic acid gives carboxymethyl cellulose (CMC), a widely used industrial material, in which $—OCH_2COOH$ groups have replaced some of the —OH groups.

The use of cellulose itself in artificial fibers and films is accomplished by precipitating cellulose from solution in the form of threads or sheets. Cellulose is not soluble in any solvent, but may be brought into solution by chemical means. The cuprammonium process utilizes an ammoniacal solution of copper hydroxide (Schweitzer's reagent). Cellulose dissolves in this reagent by forming a complex with copper ion. The solution is forced through a tiny orifice into a solution of sulfuric acid, where the copper-ammonia-cellulose complex is decomposed and the cellulose is precipitated as a thread or filament.

In the "viscose" process, the cellulose is converted into a sulfur-containing ester called a xanthate.* The process may be illustrated in simplified form by the equation

$$(C_6H_{10}O_5)_x \xrightarrow[CS_2]{NaOH} \left\{C_6H_9O_4—O—C(=S)S^-Na^+\right\}_x \qquad (11)$$

Cellulose xanthate

The solution of cellulose xanthate can be extruded as a filament (to produce threads and yarns of "viscose rayon") or a sheet (to produce Cellophane). The viscose solution is extruded into dilute sulfuric acid, which decomposes the xanthate, liberating cellulose:

$$\left(C_6H_9O_4—OC(=S)—SNa\right)_x \xrightarrow{H_2SO_4} (C_6H_{10}O_5)_x + CS_2 + Na_2SO_4 \qquad (12)$$

(Numerous technical details are omitted from these brief descriptions, which mention only the main features of the processes.)

15-11 Starch

Starch, like cellulose, is a polyglucoside; but starch, unlike cellulose, is composed of glucose residues linked by α-glucosidic unions. Starch is a reserve plant polysaccharide: it is the form in which glucose is stored in plants, chiefly in roots and tubers (for

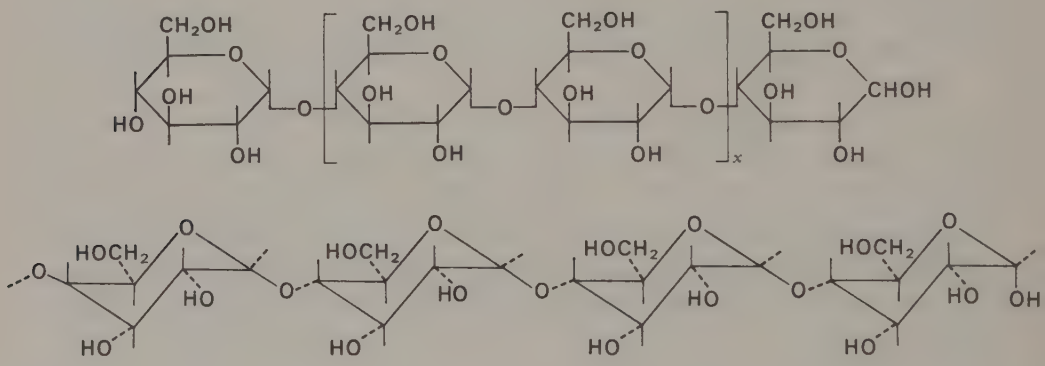
* The formation of xanthates is a general reaction of alcohols:

$$ROH + CS_2 \xrightarrow{NaOH} R—O—C(=S)SNa$$

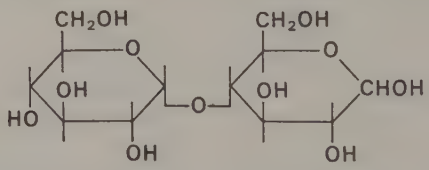
example, potatoes), and from which the glucose may be mobilized for metabolic uses by enzymatic hydrolytic or phosphorolytic breakdown. In animals, the reserve polysaccharide is a starch-like substance called glycogen.

Starch is not a single substance. Starches from different sources differ somewhat in their makeup, although there is an essential similarity between them. Starches consist of two polysaccharides, called *amylose* and *amylopectin*. Most starches consist of about 20% of amylose and the remainder amylopectin. These two substances may be separated by swelling the starch granules in warm water; the amylose diffuses out into solution, leaving the amylopectin as an insoluble residue. Both amylose and amylopectin give only D-glucose upon complete hydrolysis, and hence differ only in the manner in which the individual glucose units are combined in the polymers.

Amylose is essentially a linear polyglucoside in which 1,4-linked glucose units are joined by α-glucosidic bonds:



Partial hydrolysis of starch yields maltose:

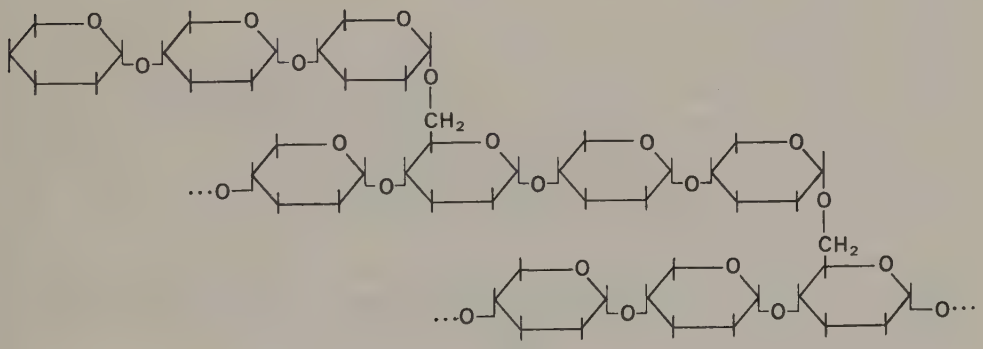


Maltotriose and maltotetrose, the corresponding tri- and tetrasaccharides (compare with cellotriose), are also obtained by partial hydrolysis under suitable conditions.

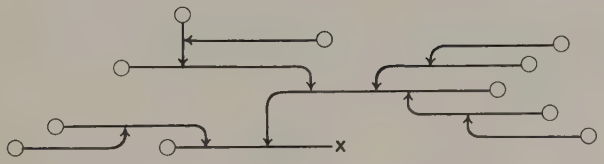
Amylose gives a blue color with iodine, whereas amylopectin gives a red to violet color. It has been suggested that the amylose chain is coiled into a helical configuration and that the iodine molecules are able to fit inside this coil in a linear chain of iodine atoms separated by a single iodine-iodine distance.

15-12 Amylopectin

Amylopectin differs from amylose in that it contains 1,6 linkages in addition to 1,4 linkages. When the Purdie-Irvine methylation procedure (Section 14-14) is applied to amylopectin there results in addition to 2,3,6-tri-*O*-methyl glucose (the product characteristic of 1,4-linked amylose and cellulose) some 2,3-di-*O*-methyl glucose and a remarkably high proportion of 2,3,4,6-tetra-*O*-methyl glucose. The tetramethyl glucose is derived from a terminal unit. The conclusion has been reached that amylopectin consists of *branched chains*, each branch consisting of 20 to 25 glucose units bound by 1,6 linkages to a "backbone" of α-1,4-linked units:



or in schematic form:



Probable structure of amylopectin

x = reducing end group
→ = α-1,6-linkages, origin of 2,3-di-*O*-methyl glucose
○ = end group giving 2,3,4,6-tetra-*O*-methyl glucose
— = chains of α-1,4-linked glucopyranose units

Exercise 6

Show how 2,3,4,6-tetra-*O*-methylglucose is derived from fully methylated amylopectin.

15-13 Glycogen

Glycogen is an animal reserve polyglucose similar in constitution to the amylopectin component of vegetable starches. It is found mostly in the liver and in muscle tissue.

Glycogen can be returned to the pathways of carbohydrate metabolism by hydrolytic or phosphorolytic breakdown into glucose or glucose-1-phosphate. The latter is the more important route. Since glycogen, like amylopectin, consists of chains of 1,4-linked glucose molecules to which branching chains are attached by 1,6 linkages, the enzymatic breakdown requires a number of distinct *phosphorylases*, each with the ability to cleave the polymer at a different glycosidic linkage.

15-14 Enzymatic hydrolysis of starch

Enzymes capable of hydrolyzing starches abound in nature. The mobilization of starch (and glycogen) requires its eventual conversion into glucose. The important enzymes for accomplishing this in humans are the salivary amylases and the amylases of the digestive tract (principally from the pancreas). These enzymes convert starches into maltose and the polysaccharide fragments that remain after the side chains of amylopectin have been degraded down to the 1,6 branches. Enzymes are known that can degrade amylose chains by removing one terminal nonreducing residue at a time; others act only on the α-1,6 linkages of the amylopectin molecule.

Dextrins are the polysaccharide fragments that result from the enzymatic hydrolysis (by amylases) of the side chains of starch. The term "dextrin" is also applied to the substances that are formed by heating (200–250°C) dry starch or by the partial hydrolysis of starch with dilute acids. The material so formed is soluble in water, yielding a solution known as mucilage, which is used as an adhesive for paper and as a sizing material for textiles.

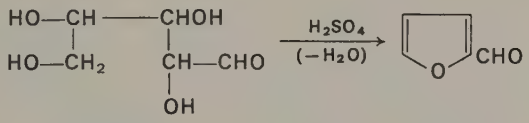
15-15 Other polysaccharides

Although starch and cellulose are the most ubiquitous of the plant polysaccharides, many others are known.

The *polyuronides* are polysaccharides that yield *uronic acids* on hydrolysis. The most important of these are the *pectins*. Pectins are found in most plants, especially in fruits, and are extracted in commercial quantities, chiefly from apples and citrus fruits, for use in making jellies and in altering the consistencies of foodstuffs by virtue of the power of pectins to form gels. Citrus pectin is chiefly a partially methylated (on —COOH) polygalacturonic acid, in which α-1,4-linked galacturonic acid units are present. Pectins are commonly found associated with other polysaccharides, notably *arabans* (polyarabinose) and *galactans* (polygalactose).

Alginic acid is a pectin-like polysaccharide (poly-β-D-mannuronic acid) found in seaweed.

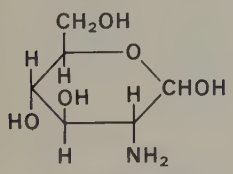
Polymeric pentoses, known as *pentosans*, abound in nature. These may be composed of essentially one sugar, as is xylan, a 1,4-linked polyxylose; or they may consist of two or more monosaccharides in polyglycosidic union. Many plant gums (such as the resinous exudates found on the bark of nonconiferous trees) and mucilages (the viscous juices of certain fleshy leaved plants) are polysaccharides of this kind. Pentosans occur widely in plants, very commonly in straws and seed hulls of plants of the grass family (oats, wheat, barley, and others). Oat hulls, straw, and corn cobs are abundant commercial sources of pentosans and are the raw materials for producing the important industrial chemical furfural. Furfural is formed by treating pentoses (and pentosans, which yield pentoses by hydrolysis) with hot, dilute sulfuric acid:



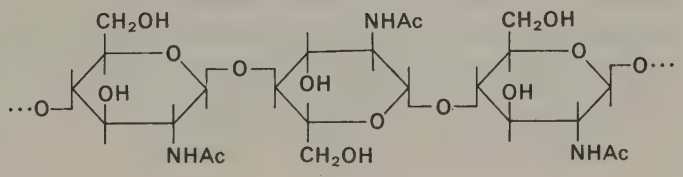
A pentose Furfural (13)

15-16 Polysaccharides containing nitrogen and sulfur

Polysaccharides that contain nitrogen and sulfur play very important roles in the physiology of animals. Chitin, the structural material of insect and crustacean shells, is a 1,4-linked polysaccharide composed of *N*-acetyl glucosamine units:



D-glucosamine



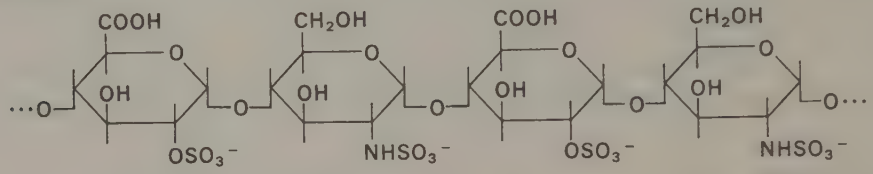
Chitin

Hydrolysis of chitin by *chitinase*, an enzyme found in the intestinal tract of the snail, gives *N*-acetyl-D-glucosamine in high yields, and degradation of chitin by sulfuric acid and acetic anhydride (acetolysis) gives chitobiose hexaacetate, analogous to the cellobiose octaacetate similarly derived from cellulose.

Exercise 7

Write the structure of chitobiose hexaacetate.

Heparin is a complex nitrogen- and sulfur-containing polysaccharide that plays a vital role in the regulation of the clotting of blood. It is prepared commercially largely from animal lung tissue, and is widely used clinically as an *anticoagulant*, especially in the treatment of thromboses and cardiac circulatory disease. The structure of heparin is not known with certainty in all details, but the following structure has been proposed:



It is probable that an additional one or two of the remaining four hydroxyl groups shown in this tetrasaccharide unit is also present in sulfated form (as $—OSO_3^-$ instead of —OH), and that native heparin has five or six sulfate residues per tetrasaccharide unit. This point is still uncertain, however, and remains to be established by further studies. The molecular size of heparin is not known; it has been estimated that its molecular weight is about 20,000, but this figure is far from certain.

Seaweed (algal) polysaccharides often contain sulfur in the form of sulfate groupings, like those in heparin, and occur in the plants as salts of magnesium, calcium, sodium, and potassium.

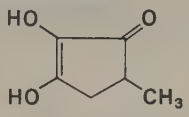
Attempts have been made to introduce sulfuric ester groupings into polysaccharides such as starch and dextrins, xylans, and so forth, with the aim of producing synthetic heparin-like substances. Many such esters have been prepared and do indeed have anticoagulant properties, and some have been tested in clinical practice, but none has yet been found equal or superior to natural heparin. Certain of them produce toxic side-reactions when administered to humans.

Problems

1. Write the structures of the two D-aldotetroses, D-threose, and D-erythrose. Write equations showing their (*a*) reaction with phenylhydrazine; (*b*) conversion, through the Kiliani reaction, into the D-aldopentoses; (*c*) reduction to butanetetrols; (*d*) oxidation to the *-onic* acids; (*e*) degradation, through the Wohl reaction, to glyceraldehyde. Show the stereochemistry involved.
2. Show how D-ribose is converted, by way of the cyanohydrin (Kiliani) reaction, into a pair of aldohexoses. Write the configurational formulas for these two aldohexoses and answer the following questions about them. (*a*) Would they give the same or different osazones? (*b*) Would the C_6-dicarboxylic acids derived from them by oxidation be optically active? (*c*) Would they reduce

Fehling's solution? (*d*) What would be the product or products if they were degraded by the Wohl degradation to aldopentoses?

3. D-Erythrose, an aldotetrose, can be oxidized to *meso*-tartaric acid, and by the Kiliani synthesis it gives D-ribose and D-arabinose. By the Wohl degradation both D-altrose and D-allose give D-ribose. D-Altrose and D-talose give the same hexitol (hexahydroxyhexane) when reduced. D-Talose and D-galactose (an aldose) give the same osazone. Using this information write the linear projection formulas for D-talose, D-allose, D-altrose, and D-galactose, and show the transformations that have been described.

4. Methylreductinic acid has the structure  Write the structure of the monoanion that would be formed by ionization of the *more acidic* of the two hydroxyl groups. Explain why the OH group you chose is the more acidic of the two.

5. L-Rhamnose ($C_6H_{12}O_5$) is a naturally occurring methyl aldopentose, also called L-mannomethylose. It forms an osazone, a tetraacetate, and upon vigorous oxidation yields 1 mole of acetic acid. Among the products of a milder oxidation is L-trihydroxyglutaric acid (optically active). Methyl rhamnopyranoside (α or β) reacts with 2 moles of HIO_4 to yield 1 mole of formic acid, no formaldehyde, and a dialdehyde $C_6H_{10}O_4$, which can be oxidized to a dicarboxylic acid, $C_6H_{10}O_6$, with bromine water. When this diacid is hydrolyzed with dilute HCl there is formed methanol, glyoxylic acid (HOOC·CHO), and L-(+)-lactic acid. Using the above information write the structure of L-rhamnose (use the linear projection formula), and formulate the reactions described.

6. A glucoside (A), $C_7H_{14}O_6$, yielded methanol and D-glucose when hydrolyzed with acid. It reacted with periodic acid, consuming 2 moles of the reagent and yielding 1 mole of formaldehyde and no formic acid. Complete methylation of the glucoside (A) yielded a tetra-*O*-methyl glucose (C). Oxidation of C gave L-1,2-dimethoxysuccinic acid, some methoxyacetic acid, but no glutaric acid derivatives. Write the Haworth projection formula for A and show the reactions described.

7. Draw the Haworth and the conformational formulas for (*a*) β-D-glucopyranose, (*b*) β-D-ribopyranose, (*c*) lactose, (*d*) salicin, (*e*) cellotriose.

8. Ascorbic acid is readily oxidized to dehydroascorbic acid, $C_6H_6O_6$; and dehydroascorbic acid is readily reduced to ascorbic acid. At what structural site does this facile, reversible oxidation occur? HINT: Dehydroascorbic acid does not have the acidic character of ascorbic acid.

9. Why does D-glucose react with (excess) acetone to give the diacetone derivative of D-glucofuranose, rather than the 1,2-acetonide of D-glucopyranose?

10. Examine the structure of heparin, and suggest how one might prepare, starting with an available polysaccharide such as cellulose or starch, a partially synthetic compound that could be expected to show heparin-like physiological activity.

16

Organic nitrogen compounds. Amines and ammonium compounds

The properties and chemical behavior of amines described in this chapter will reflect two topics discussed in previous chapters. These are (1) the basic character of amines and (2) their nucleophilic properties; both of them depend upon the presence, on the nitrogen atom, of an unshared (non-bonding) electron pair.

Alkylation of amines, a typical nucleophilic displacement reaction, leads finally to quaternary ammonium compounds, in which four groups are bonded to nitrogen. The stereochemistry of these compounds has been alluded to in Chapter 6. Quaternary ammonium compounds are of great importance in biological systems and some of them play a central role in cellular metabolism and nerve activity. Their formation by biological alkylation reactions has been discussed in Chapter 8.

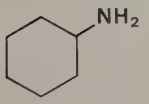
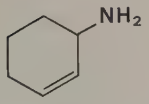
A biologically significant feature of the metabolism of amines is their dealkylation by an oxidation reaction. Probable mechanisms for this reaction are proposed and compared with oxidative dealkylation under non-biological conditions. The student will notice that these reactions are initiated by attack of the oxidant upon the non-bonding electron pair of nitrogen. We shall stress the view that most of the reactions of amines depend upon their essentially nucleophilic properties.

16-1 Amines. Classes and nomenclature

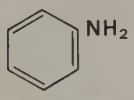
Amines are the common organic bases. They are organic derivatives of ammonia in which one or more of the hydrogens are replaced by alkyl or aryl groups:

NH_3	RNH_2	R_2NH	R_3N
	Primary amines	Secondary amines	Tertiary amines

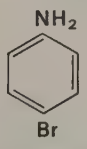
In the following examples, it will be noted that naming may be systematic or trivial, and that the $—NH_2$ group may be called *amino* when used in a substitution name:

CH_3NH_2	Methylamine
$(CH_3CH_2)_2NH$	Diethylamine
$(CH_3)_2CHNHCH_3$	Methylisopropylamine
$(CH_3)_3CNH_2$	*t*-butylamine*
$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HNH_2$	*sec*-butylamine
$H_2NCH_2CH_2NH_2$	Ethylenediamine (1,2-diaminoethane)
$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HN(CH_3)_2$	2-dimethylamino-4-methylpentane
	Cyclohexylamine
	3-aminocyclohexene

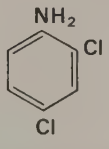
Aromatic amines are usually named as derivatives of the parent compound, aniline:



Aniline



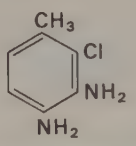
p-bromoaniline



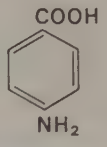
2,4-dichloroaniline

* Notice that *tertiary*-butylamine is a primary amine and so is *sec*-butylamine.

but the amino group may be named as a substituent:

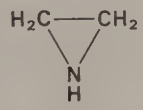


2-chloro-3,4-diaminotoluene

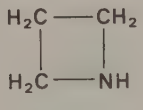


p-aminobenzoic acid

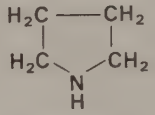
Heterocyclic amines, in which one or more nitrogen atoms are included in a ring, embrace a wide variety of compounds, some of which will be described separately in Chapter 35. The simplest of these are the 3- to 6-membered heterocyclics:



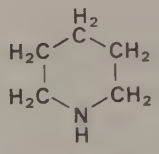
Aziridine
(ethyleneimine)



Azetidine



Pyrrolidine



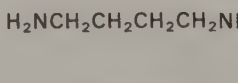
Piperidine

Pyrrolidine and piperidine are stable secondary amines, somewhat stronger bases than dialkylamines, but otherwise similar in chemical behavior. The corresponding tertiary amines (the *N*-methylated compounds) are named *N*-methylaziridine, *N*-methylpiperidine, and so on.

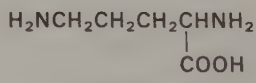
16-2 Naturally occurring amines and their synthetic structural analogues

Nature, notably in the plant world, provides an enormous number of basic compounds. A great many of these are primary, secondary, and tertiary amines in which the amino group is a component of a molecule that is in most cases of complex structure. Although the chemistry of alkaloids and other naturally occurring amines is far too extensive a subject to be dealt with here in detail, some examples may be given.

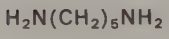
The simple diamines putrescine and cadaverine occur (as their names suggest) in decomposing animal matter. They are derived by decarboxylation of the widely distributed amino acids ornithine and lysine:



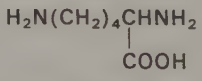
Putrescine



Ornithine

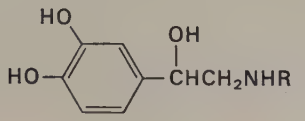


Cadaverine

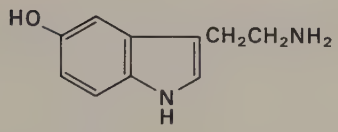


Lysine

(−)-*Epinephrine* and the corresponding primary amine, (−)-*norepinephrine*, are substances important in the activity of the sympathetic nervous system. Along with *serotonin*, they also participate in the activity of the central nervous system:

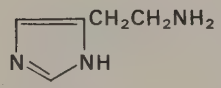


R = H: norepinephrine
R = CH_3: epinephrine

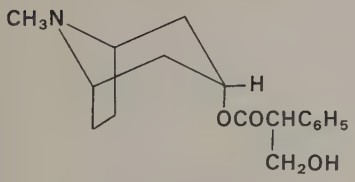


Serotonin

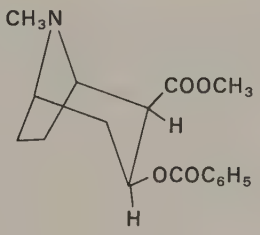
Histamine, a potent physiologically active substance, is released from body tissues in allergic reactions:



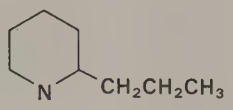
Among the *alkaloids* (the term is usually applied only to compounds occurring in plants) are such familiar—and often medicinally important—compounds as *atropine*, *cocaine*, *morphine*, *nicotine*, *coniine*, *tryptamine*, *ephedrine*, and *quinine*. It will be seen that, apart from the complexity of the total structures of these compounds, they are primary, secondary, or tertiary amines, and are similar in that respect to the simpler amines described earlier:



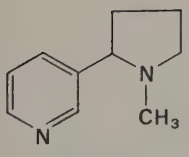
Atropine



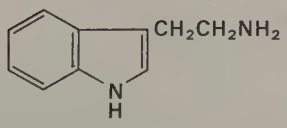
Cocaine



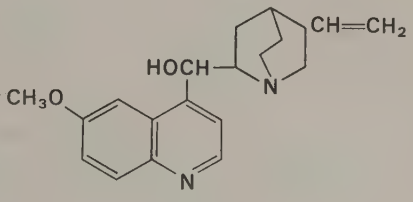
Coniine



Nicotine

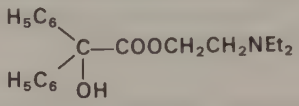
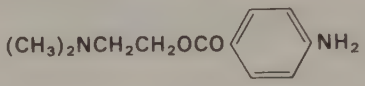
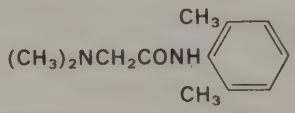
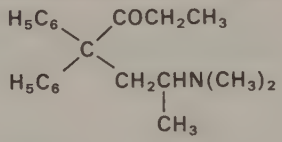
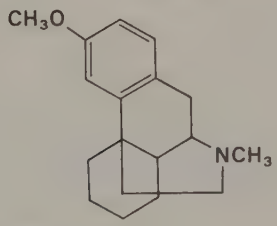
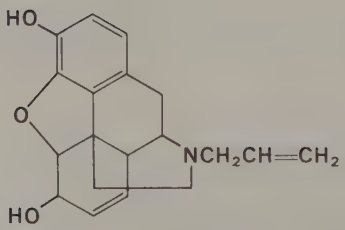
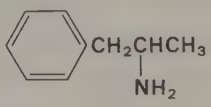
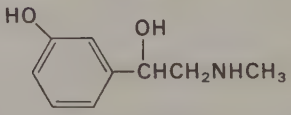


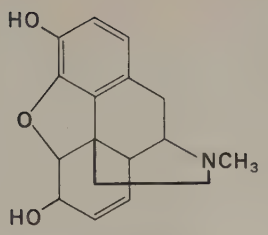
Tryptamine



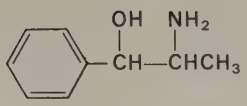
Quinine

Table 16-1
Physiologically active natural amines and their synthetic analogues

Natural Amine	*Synthetic Analogue*	
atropine		
cocaine		procaine
		lidocaine
morphine		methadone
		dextromethorphan
		nalorphine
ephedrine		amphetamine (benzedrine)
		neosynephrine



Morphine



Ephedrine

Most of the naturally occurring amines have profound physiological effects upon the animal organism, varying over the complete range from the extremely toxic (for example, nicotine and coniine) to the therapeutically beneficial (for example, cocaine, quinine, and morphine). In their search for new and effective drugs, chemists have synthesized thousands of organic compounds containing an amino group (acyclic or cyclic) as one structural element. Many of these compounds are modeled upon the structure of a natural alkaloid, and for each clinically useful alkaloid there have been prepared many synthetic structural analogs with related or similar physiological activity or with antagonistic effects. Some of these have taken their place in practical therapy along with the natural compound, but few of them have entirely displaced the natural drug. It will suffice here to give a few examples (Table 16-1) that contain the amino grouping.

16-3 Basicity of amines. Ammonium salts

Amines are the common organic bases; the pH of aqueous solutions of aliphatic amines is in the alkaline range, and with a suitable indicator many of them can be titrated with strong acids to sharp endpoints. Alkylamines compare in base strength with ammonia; arylamines are considerably weaker. Some representative values are given in Table 16-2.*

Exercise 1

How can you account for the fact that pyrrolidine and piperidine are stronger bases than dimethylamine?

---

* The strength of an amine as a base is usually given as the pK_a of its conjugate acid, the protonated amine. The stronger the amine, the weaker the conjugate acid; thus, *the stronger the amine the higher the* pK_a *value.*

Table 16-2
pK_a values for some representative amines

Amine	pK_a
ammonia	9.3
methylamine	10.6
dimethylamine	10.7
trimethylamine	9.8
ethylamine	10.7
pyrrolidine	11.3
piperidine	11.2
aniline	4.6
diphenylamine	0.9

It should be noted that alkylamines are bases about 1.4 pK units stronger than ammonia, and that aniline is a very much weaker base than these. Diphenylamine is a very weak base and is protonated to an appreciable degree only in strongly acidic media. Triphenylamine (not in the table) is not at all basic by ordinary criteria; it would be called a neutral compound. It should also be apparent that the protonated form of an amine with a pK_a of the order of 1 (that is, whose protonated form is a strong acid) will largely dissociate (hydrolyze) in aqueous solution to form the free amine. Thus diphenylamine is not soluble in dilute (say 0.1 N) aqueous HCl, and if water is added to its hydrochloric acid salt the free amine will precipitate.

Salts of amines may be named simply as substituted ammonium salts, but some trivial variants of this nomenclature are also used:

$CH_3NH_3^+Br^-$ Methylammonium bromide (methylamine hydrobromide)

This formula is sometimes written $CH_3NH_2 \cdot HBr$.

Protonated amines with complex structures, such as atropine and morphine, cannot conveniently be named as ammonium salts, and it is customary to designate their salts by such names as atropine sulfate, codeine phosphate, and benzedrine sulfate. This usage is of course quite arbitrary, for the endings "sulfate," "phosphate," and so on are used in other contexts to designate esters of these acids.

16-4 Quaternary ammonium compounds

Most amines of moderate basicity, such as the tertiary alkylamines, are sufficiently nucleophilic to react with alkyl halides to form *quaternary ammonium* salts:

$$R_3N: + R'X \longrightarrow (R_3\overset{+}{N}R')X^- \qquad (1)$$

This will be recognized as an example of the nucleophilic displacement reaction, and will therefore be affected by the structural factors that determine the rate and course of such reactions. For most practical purposes S_N2-reactive halides or sulfonic acid esters, such as methyl iodide, benzyl bromide, allyl bromide, dimethyl sulfate, and methyl methanesulfonate, are found to be of greatest preparative value. Cyclization by intramolecular alkylation can also occur.

Quaternary ammonium salts are named as substituted ammonium compounds:

$(CH_3)_4\overset{+}{N}I^-$	Tetramethylammonium iodide
$C_6H_5\overset{+}{N}(CH_3)_3ClO_4^-$	Trimethylanilinium perchlorate
$C_6H_5CH_2\overset{+}{N}(C_2H_5)_3Br^-$	Benzyltriethylammonium bromide

More complex quaternary ammonium compounds are usually named by using the suffixes "methiodide," "methosulfate," and so on, as in "atropine methiodide." Many of the common and important compounds of this class also bear non-systematic (trivial) names:

$(CH_3)_3\overset{+}{N}CH_2CH_2OHCl^-$	Choline chloride
$(CH_3)_3\overset{+}{N}CH_2CH_2OCOCH_3$	Acetylcholine*
$(CH_3)_3\overset{+}{N}CH_2COO^-$	Betaine

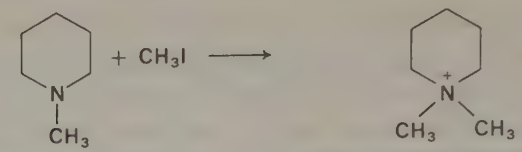
Quaternary ammonium compounds are sometimes erroneously called strong bases. It is true that the compound $R_4\overset{+}{N}OH^-$ is dissociated in solution and is a strong base, but the base is the hydroxide ion. It is therefore recommended that the strong bases be explicitly called quaternary ammonium hydroxides.

Quaternary ammonium salts are in most cases crystalline compounds, often with sharp and reproducible melting points. They are valuable as *derivatives* for the *characterization and identification* of tertiary amines. The quaternizing reagent most commonly used for this purpose is methyl iodide. The salts are usually insoluble in aprotic organic solvents (for example, benzene and ether), soluble in water and alcohol:

$$(CH_3)_3N + CH_3I \longrightarrow (CH_3)_4\overset{+}{N}I^- \qquad (2)$$

---

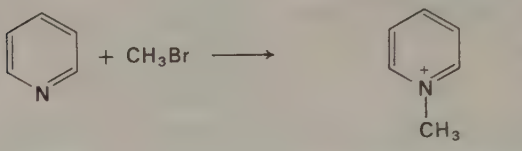
* The name of the anion is not always specified in a name, especially for physiologically important compounds in which the active entity is the organic cation, because in solution there is often no necessary relationship between the cation and any specific anion. In this loose but common usage, the name applied to the quaternary ammonium compound often refers only to the cationic species. Thus, one may speak of "tetraethylammonium" as a substance.



(3)

N-methylpiperidine

N,*N*-dimethylpiperidinium iodide
(or *N*-methylpiperidine methiodide)



(4)

Pyridine

N-methylpyridinium bromide

The use of quaternary ammonium compounds in synthesis (for example, of olefins) and structure proof (for example, the Hofmann degradation) is described elsewhere (for example, Chapter 10).

16-5 Physiologically important quaternary ammonium compounds

One of the simplest quaternary ammonium compounds is tetraethylammonium, Et_4N^+, usually employed as the crystalline chloride. It is a potent agent for blocking nerve impulses at autonomic ganglia, and is used for this purpose in pharmacological studies. Among the responses to this ganglionic blockade is the lowering of blood pressure, but tetraethylammonium has been supplanted for this clinical purpose by more effective agents of other kinds.

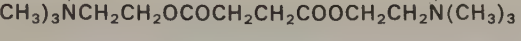
The structurally quite simple quaternary ammonium compound decamethylene-bis(trimethylammonium bromide), usually referred to by the common name *decamethonium*, is a potent agent for blocking the transmission of nervous impulses at the neuromuscular junction. The effect of this is to produce flaccidity of the muscle, and a paralysis similar in kind (but not in detailed mechanism of action) to that caused by the paralyzant drug "curare," or (+)-tubocurarine.

$$(CH_3)_3\overset{+}{N}(CH_2)_{10}\overset{+}{N}(CH_3)_3 \cdot 2Br^-$$

Decamethonium

Decamethonium, which is prepared by the reaction of 1,10-dibromodecane with trimethylamine, contains a long chain of saturated carbon atoms, and is therefore very resistant to chemical attack and, consequently, to metabolic degradation. For this reason its blockade of nerve-muscle transmission is long-acting and its clinical use (muscular relaxation during surgery) is sharply restricted. A structurally related compound, *succinylcholine*, produces a similar blockade of the neuromuscular junction

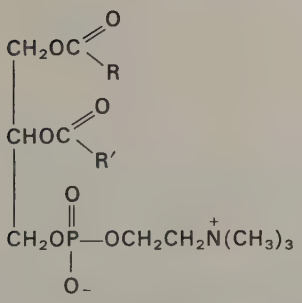
but, since it is an ester, is readily hydrolyzed by tissue esterases to form succinic acid and choline, neither of which evokes a paralyzant response. Hence, succinylcholine produces a muscular relaxation similar to that produced by decamethonium, but of short duration. It will be noted that in decamethonium and succinylcholine the two ammonium "heads" are about the same distance apart:



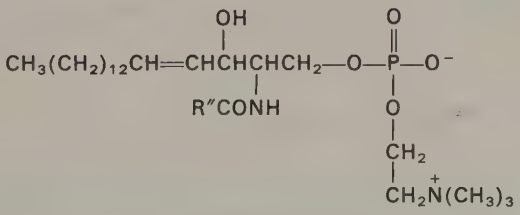
Succinylcholine

Many compounds bearing quaternary ammonium groups separated by distances comparable to those between the nitrogen atoms in decamethonium and succinylcholine are also "curare-like" in their action, and a number of them have found clinical use.

Many quaternary ammonium salts are extremely important in the chemistry of living organisms. The rather simply constituted compound *choline*, $HOCH_2CH_2\overset{+}{N}(CH_3)_3$, is a structural component of many cellular constituents. Its acetate, the ester *acetylcholine*, $CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3$, is one of the essential mediators of nerve activity. Choline is also found in cellular membranes and nerve tissue in combination with glycerol, fatty acids, and phosphoric acid, or in complex phosphoric acid esters of other kinds. Two classes of such compounds are the *lecithins* and the *sphingomyelins*, constituents of fatty and nerve tissues. In the structures shown here, RCO—, R′CO—, and R″CO— represent the acyl groups of long-chain fatty acids. Since R, R′, and R″ can be from any of several structurally similar fatty acids, it is possible for a number of lecithins to exist whose chemical and physical properties are nearly the same. In these, choline is combined as a phosphate ester:



A lecithin



A sphingomyelin

It will be noted that these compounds possess a special kind of structural makeup:

they consist of a large "fatty" portion, which is lipid-soluble (*lipophilic*), and an ionic portion, which is lipid-insoluble (*lipophobic*) and *hydrophilic*.*

$$\underbrace{CH_3(CH_2)_n\cdots\cdots}_{\text{Lipophilic}}\underbrace{OP\bar{O}_2OCH_2CH_2\overset{+}{N}(CH_3)_3}_{\text{Hydrophilic}}$$

Many clinically important drugs are tertiary amines, usually administered orally as the water-soluble salts (for example, as hydrochlorides). The salts are, of course, in equilibrium with the free base at physiological pH values, so that, depending upon the pK_a of the amine, a certain proportion of the free amine exists in solution:

$$R\overset{+}{N}HMe_2 + H_2O \rightleftharpoons RNMe_2 + H_3O^+ \qquad (5)$$

Exercise 2

Derive a general expression for the proportion of free amine in the $R\overset{+}{N}HR_2 \rightleftharpoons RNR_2$ equilibrium as a function of the pH of the (aqueous) solvent medium (assumed constant) and the pK_a of the amine.

The neutral, often lipophilic amine is absorbed in the gastrointestinal tract and enters the bloodstream, in which it is transported to the sites of its action. Cations, however, are poorly absorbed, and many drugs containing quaternary ammonium groupings are relatively much less physiologically active upon oral administration or topical application, even though the tertiary amine and its methiodide may be pharmacologically comparable in their effects when tested upon isolated tissues.

16-6 Preparation of amines

The preparation of primary amines by the *N*-alkylation of ammonia suffers from the limitation that it is difficult to avoid the formation of di- and tri-alkylation products.

---

* Numerous other compounds with these essential characteristics are known to contain, instead of choline residues, other hydrophilic residues. Among these are compounds with the end groupings $-OPO_2OCH_2CH_2\overset{+}{N}H_3$, $-OPO_2OCH_2\underset{\displaystyle NH_3^+}{\underset{|}{C}}HCOO^-$, and $-OPO_2O$-sugar. In the last one, the hydrophilic "end" is a non-ionic grouping rich in water-solubilizing —OH groups.

Proton exchange at the intermediate stages, with successive alkylation, proceeds to give mixtures as shown in the following equations:

$$NH_3 + RX \rightleftharpoons RNH_3^+ + X^- \quad (6)$$

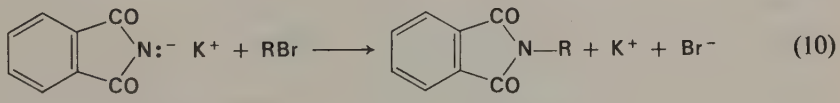
$$RNH_3^+ + NH_3 \rightleftharpoons NH_4^+ + RNH_2 \quad (7)$$

$$RNH_2 + RX \rightleftharpoons R_2NH_2^+ + X^- \quad (8)$$

$$R_2NH_2^+ + NH_3 \rightleftharpoons R_2NH + NH_4^+ \quad (9)$$

A large excess of ammonia favors the production of the primary amine. The formation of tertiary amines can often be accomplished successfully by the reaction of secondary amines with alkyl halides.

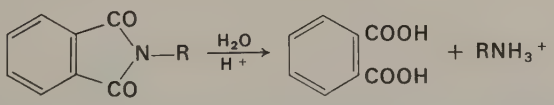
In the *Gabriel synthesis* of amines the nucleophile is the anion derived from phthalimide by converting it into the potassium salt. Alkylation of this with an alkyl halide yields an *N*-alkylphthalimide. This is a diacylamine and is not nucleophilic, so further alkylation does not occur:



(10)

Potassium phthalimide An *N*-alkylphthalimide

Hydrolysis of the *N*-alkylphthalimide with aqueous acid yields the protonated amine and phthalic acid:



(11)

Reduction of nitrogen-containing compounds of other kinds provides numerous methods for the synthesis of amines:

1. $R—NO_2 \longrightarrow RNH_2$
2. $RCONH_2\ (—NR_2) \longrightarrow RCH_2NH_2\ (—NR_2)$
3. $RC{\equiv}N \longrightarrow RCH_2NH_2$
4. $R_2C{=}NOH \longrightarrow R_2CHNH_2$

Procedure 1 is commonly used to prepare aniline and other aminobenzene derivatives. The reducing agent is often a metal-acid combination (for example, Sn/HCl).

Reactions 2 and 3 are best carried out with $LiAlH_4$ or B_2H_6 as the reducing agent. Nitriles can also be reduced catalytically.

Reduction 4 can be performed with hydrogen and a platinum catalyst, or with sodium/alcohol.

Amines can be prepared from carboxylic acid derivatives by means of the Hofmann or the Curtius degradation. These reactions involve molecular rearrangements, the mechanisms of which are described in Section 34-8.

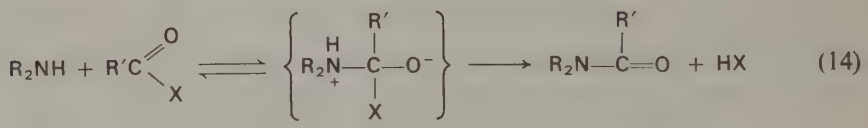
$$RCONH_2 \xrightarrow[\text{(Hofmann)}]{Br_2/NaOH} RNH_2 + CO_2 \qquad (12)$$

$$RCOCl \xrightarrow[\text{(Curtius)}]{NaN_3} RNH_2 + N_2 \qquad (13)$$

16-7 Reactions of amines: *N*-Acylation

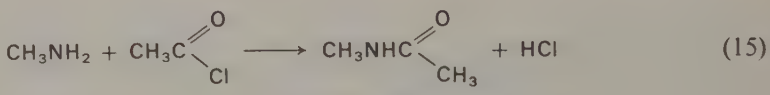
The chemical reactivity of amines is due to their basic and nucleophilic character, for which the unshared electron pair or nitrogen is responsible. Protonation and alkylation of amines have been discussed in foregoing sections.

Acylation of primary and secondary amines is a reaction in which amines, acting as nucleophilic reagents, attack the carbonyl group of carboxylic acid derivatives:



(14)

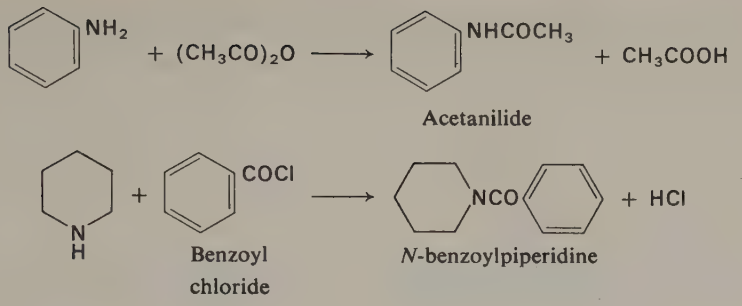
In this general equation, X is most often halogen or an acyloxy group, the *acylating agents* thus being acyl halides or acid anhydrides. These reactions are rapid and can in most cases be completed in a short time at ordinary temperatures:*



(15)

N-methylacetamide

* The HCl produced in this reaction protonates the starting amine, thus rendering it nonnucleophilic. Consequently, one half of the amine would not be acylated if equimolal quantities of reactants were used. The use of an excess of the amine or the addition of another base permits complete utilization of the acyl halide.



(16)

(17)

Esters may also act as acylating agents in a process that can be termed amide-ester interchange; but since esters are much less reactive toward nucleophilic agents than are acyl halides and acid anhydrides, the reaction is very slow and ordinarily requires heating or extended reaction periods. Ammonia reacts in the same way to give unsubstituted amides:

$$CH_3NH_2 + CH_3COOEt \rightleftharpoons CH_3CONHCH_3 + EtOH \qquad (18)$$

$$NH_3 + CH_3COOEt \rightleftharpoons CH_3CONH_2 + EtOH \qquad (19)$$

The initial phase of the reactions of amines with acid derivatives is qualitatively the same in all cases: an attack of the nucleophilic amine upon the electrophilic carbonyl group. Further discussion of this and related reactions will be found in Chapter 23.

Amides (*N*-acyl amines) are no longer basic compounds. They are neutral, and insoluble in dilute aqueous acids.

Exercise 3

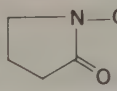
Account for the fact that acetamide, CH_3CONH_2, is a much weaker base than methylamine.

Tertiary amines do not yield *N*-acyl derivatives with acyl halides or anhydrides, for there is no hydrogen atom on nitrogen to combine with the departing $:X^-$ (in the general equation (14) above). Although the equilibrium

$$R_3N + CH_3COCl \rightleftharpoons R_3\overset{+}{N}-\underset{Cl}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-O^- \rightleftharpoons R_3\overset{+}{N}-\overset{CH_3}{\overset{|}{C}}=O + Cl^- \qquad (20)$$

is real, in most cases it does not lead to a stable, isolable product. Addition of water to the reaction mixture results in hydrolysis of the acid derivative and recovery of the amine.

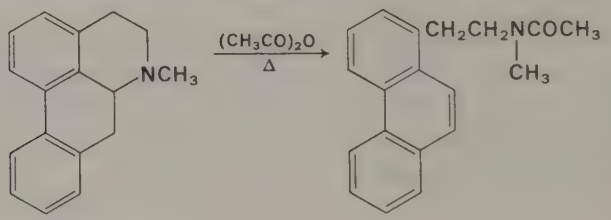
Exercise 4

Under certain conditions, *N*-acylation of a tertiary amine can occur as an intermediate step in a reaction. For instance, $(CH_3)_2NCH_2CH_2CH_2COCl$ is converted by heating into the cyclic amide 

. What is the fate of the methyl group that is lost, and what is the complete reaction sequence? (HINT: Assume as the first step attack of the amino nitrogen upon the carbonyl carbon atom.)

Exercise 5

A reaction related to the one in the preceding exercise is the following:



Suggest an explanation for this result.

Acyl derivatives of amines are valuable in a number of ways. Since the *N*-acetyl and *N*-benzoyl derivatives of primary and secondary amines are usually crystalline solids they are useful as *derivatives for identification of amines*. Primary amides (*N*-acyl derivatives of ammonia), $RCONH_2$, can be reduced with lithium aluminum hydride to primary amines, and can also be used as starting materials for the preparation of primary amines by the Hofmann degradation (Chapter 34).

Secondary ($RCONHR'$) and tertiary ($RCONR'_2$) amides show no exceptional behavior aside from reduction (to RCH_2NHR' and $RCH_2NR'_2$). *N*-Formyl amines (amides of formic acid, RCH_2NHCHO) can be reduced with lithium aluminum hydride to the *N*-methylamines

$$RCH_2NHCHO \xrightarrow{LiAlH_4} RCH_2NHCH_3 \qquad (21)$$

This is often a useful method for *monomethylation* of an amine, for in preparing *N*-methylated amines by alkylation with, for example, methyl iodide, it is difficult to avoid di- and tri-methylation (see Section 16-6).

16-8 Reactions of amines: Nitrous acid*

Tertiary aliphatic amines do not react with nitrous acid except to undergo simple protonation. On the other hand, secondary amines undergo *N*-nitrosation to form *N*-nitroso compounds:

$$R_2NH + HONO \longrightarrow R_2N{-}N{=}O + H_2O \qquad (22)$$

N-Nitrosoamines (commonly called nitrosamines) are amides of nitrous acid and, like other *N*-acyl amines, are neutral compounds. It can thus be seen that reaction with nitrous acid provides a means of separating a mixture of a secondary and a tertiary amine:

$$\begin{aligned} R_2NH &\xrightarrow[HCl]{NaNO_2} R_2N{-}NO && \text{A neutral compound, insoluble in aqueous acid; extractable with organic solvent} \\ R_3N &\xrightarrow[HCl]{NaNO_2} R_3\overset{+}{N}Cl^- && \text{Soluble in water or aqueous acid; not extractable with organic solvent; } R_3N \text{ recoverable unchanged} \end{aligned} \qquad (23)$$

The *N*-nitrosoamine, an amide, can be isolated and hydrolyzed with acid, to regenerate the amine.

Primary aliphatic amines react with nitrous acid to yield unstable intermediate *diazonium salts*; these decompose spontaneously with evolution of nitrogen and the formation of products that can in most cases be accounted for by supposing that the loss of N_2 from RN_2^+ occurs first, followed by the reaction of the resulting carbonium ion in the usual ways. The probable course of the amine/nitrous-acid reaction, termed *diazotization*, is as follows, using a primary amine as an example:

$$\begin{aligned} &RCH_2NH_2 + HONO \rightleftharpoons RCH_2\overset{H}{\underset{H}{\overset{|}{\underset{|}{N^+}}}}{-}\overset{OH}{\overset{|}{N}}{-}O^- \rightleftharpoons RCH_2NH{-}\overset{OH}{\overset{|}{N}}{-}OH \xrightleftharpoons{H^+} \\ &RCH_2NH{-}\overset{OH}{\overset{|}{N}}{-}OH_2^+ \rightleftharpoons RCH_2\overset{H}{\overset{|}{N}}{=}N{-}OH \rightleftharpoons \\ &RCH_2N{=}N{-}OH_2^+ \rightleftharpoons H_2O + RCH_2N{=}N^+ \longleftrightarrow RCH_2\overset{+}{N}{\equiv}N \end{aligned} \qquad (24)$$

* Nitrous acid, a very unstable compound, is generated in the presence of the amine by the use of aqueous sodium nitrite and a strong acid (for example, HCl).

It may be noted that the loss of N_2 from $RCH_2N_2^+$ is an energetically favored reaction, for the stable nitrogen molecule constitutes an excellent leaving group.

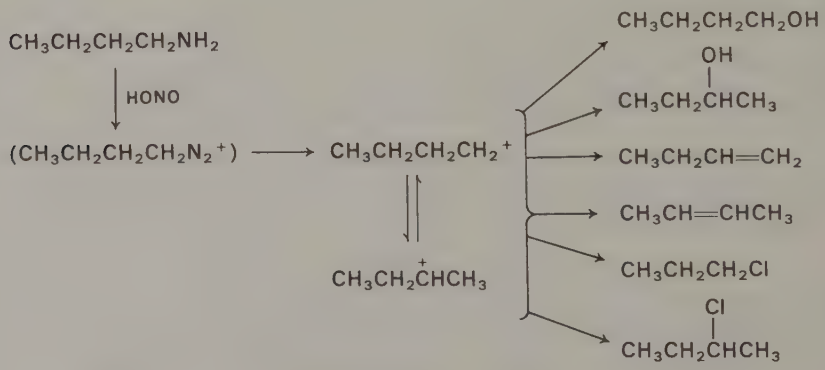
The formation of nitrogen in the reaction of primary amines with nitrous acid is essentially quantitative, and has been used in analytical procedures. The Van Slyke gasometric method for determining amino nitrogen depends upon the reaction of amino acids with nitrous acid and measurement of the nitrogen liberated:

$$\begin{array}{l} \mathrm{NH_2} \\ | \\ \mathrm{RCHCOOH} \end{array} + \mathrm{HONO} \longrightarrow \begin{array}{l} \mathrm{OH} \\ | \\ \mathrm{RCHCOOH} \end{array} + N_2 + H_2O \qquad (25)$$

Whether primary alkyldiazonium salts react strictly by the S_N1 route or by attack of the solvent upon the diazonium ion by an S_N2 mechanism is not always certain; it is not likely, for instance, that $CH_3N_2^+$ will form CH_3^+ ions. Although methanol and ethanol are formed in fair yields in the reaction of methylamine and ethylamine with nitrous acid, these reactions could be regarded as proceeding by nucleophilic displacement by attack of water on the diazonium ion:

$$CH_3NH_2 + HONO \longrightarrow (CH_3N_2^+) \xrightarrow{H_2O} CH_3OH + N_2 \qquad (26)$$

However, higher primary alkylamines give complex mixtures of products, all of which can be accounted for by postulating the intermediate formation of a carbonium ion. For example, *n*-butylamine reacts as follows in the presence of sodium nitrite in aqueous hydrochloric acid:



(27)

The complexity of the products of reactions of this kind diminishes their value as preparative methods.

16-9 Reactions of amines: *N*-Oxides

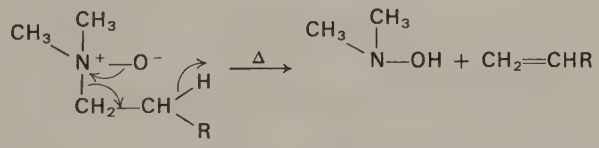
Tertiary amines can be oxidized by hydrogen peroxide or peroxycarboxylic acids to give *N*-oxides:

$$R_3N + H_2O_2 \text{ (or } R'CO_3H) \longrightarrow R_3\overset{+}{N}\!-\!\overset{-}{O} + H_2O \text{ (or } R'COOH) \qquad (28)$$

N-Oxides are common in nature; along with the corresponding tertiary amines, they are often found in plants, where they are the products of enzymatically catalyzed oxidation by molecular oxygen. They are much weaker bases than the tertiary amines (pK_a of $(CH_3)_3\overset{+}{N}\!-\!\overset{-}{O}$ is 4.7), but sufficiently nucleophilic to react with alkylating agents to give *N*-alkoxytrialkylammonium salts:

$$(CH_3)_3\overset{+}{N}\!-\!\overset{-}{O} + CH_3I \longrightarrow \{(CH_3)_3\overset{+}{N}\!-\!OCH_3\}\,I^- \qquad (29)$$

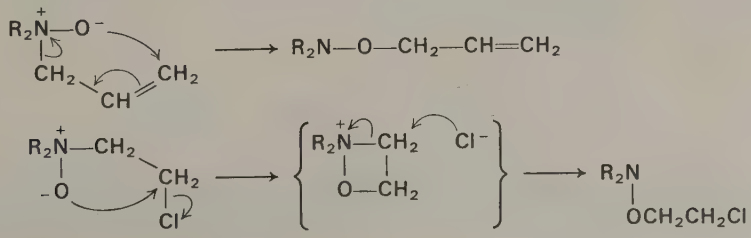
Amine oxides are highly polar compounds by virtue of the semipolar $\overset{+}{N}\!-\!\overset{-}{O}$ bond. Trimethylamine oxide has a dipole moment of 5.0 D. They are very hygroscopic and tend to form stable hydrates, for example, $(CH_3)_3NO\cdot 2H_2O$. They are unstable to heating; when one of the attached groups can be eliminated as an olefin, the following reaction occurs:



(30)

This elimination proceeds in a *cis* manner as an intramolecular process.

The nucleophilic character of the oxygen atom and the tendency for the positively charged N atom to acquire the electron pair of the N—O bond lead to reactions that are related to this elimination reaction:



Amine oxides can be reduced by metal-acid combinations (for example, zinc/sulfuric-acid) to regenerate the tertiary amine.

Amine oxides can serve as a means of dealkylating tertiary amines. Treatment of an amine oxide $R_2\overset{+}{N}(CH_3)—\bar{O}$ with hot acetic anhydride results in demethylation according to the following equation:

$$R_2\overset{+}{N}(CH_3)—O^- + (CH_3CO)_2O \longrightarrow R_2NCOCH_3 + HCHO + CH_3COOH \qquad (33)$$

The amide formed can be hydrolyzed to yield the secondary amine R_2NH.

Exercise 6

Formulate a reasonable course for this demethylation reaction.

Amine oxides of heterocyclic nitrogen compounds (for example, pyridine) are discussed in Chapter 35.

16-10 Reactions of amines: Dealkylation

The removal of one of the alkyl groups from a tertiary amine is not often possible, but it can be accomplished under some circumstances. The $—\overset{+}{N}R_3$ group is displaceable by nucleophilic attack; for instance:

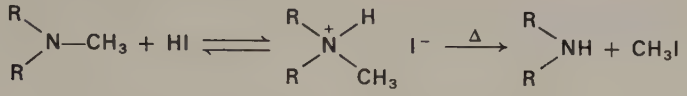
$$Cl^- + CH_3—\overset{+}{N}R_3 \longrightarrow CH_3Cl + NR_3 \qquad (34)$$

The reaction shown here can indeed be accomplished, but requires rather severe conditions. In a comparable reaction, when trimethylamine hydrochloride is heated methyl chloride is evolved:

$$(CH_3)_3\overset{+}{N}H + Cl^- \xrightarrow{\Delta} CH_3Cl + (CH_3)_2NH \qquad (35)$$

A variant of this reaction is used for the quantitative determination of $\diagdown\!\!\diagup N—CH_3$ groups by the *Herzig-Meyer method.* The *N*-methylamine is heated with hydriodic

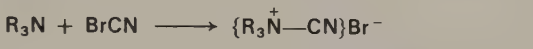
acid, and methyl iodide formed in the reaction volatilizes from the reaction mixtures to be collected and determined separately.*



(36)

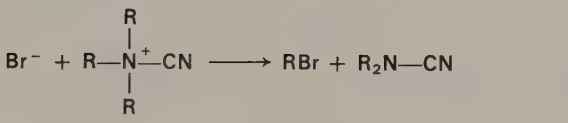
In general, dealkylations carried out in this way are of limited preparative value since, under the vigorous conditions required, side reactions of other kinds may occur.

The *von Braun reaction* involves the use of cyanogen bromide. This reagent brings about dealkylation according to the equation



(37)

followed by

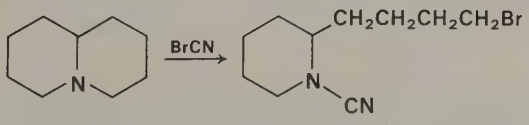


(38)

Hydrolysis of the *N*-cyanoamine yields a carbamic acid derivative, which readily loses CO_2 to form the secondary amine:

(39)

The alkyl group that is removed from R_3N in the cyanogen bromide reaction is the one most susceptible to nucleophilic attack by the bromide ion. Thus, methyl, allylic, and primary alkyl groups are most readily removed. The reaction has been extensively employed in studies of naturally occurring alkaloids, most of which are tertiary amines, as a step in their degradation to simpler compounds. Ring opening can occur:

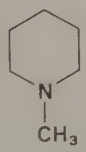
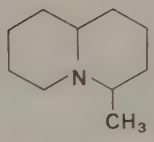


(40)

* The reaction of the recovered methyl iodide with excess alcoholic silver nitrate yields silver iodide, which can be determined gravimetrically.

Exercise 7

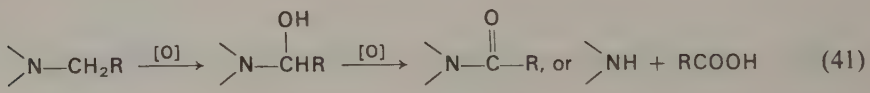
What would be the products formed in the von Braun cyanogen bromide reaction with each of the following tertiary amines:

(*a*) $(CH_3)_2NCH_2CH{=}CH_2$ (*b*)  (*c*) 

HINT: The attack of bromide ion upon $R_3\overset{+}{N}CN$ would occur at the position most susceptible to nucleophilic displacement.

16-11 Reactions of amines: Oxidative dealkylation

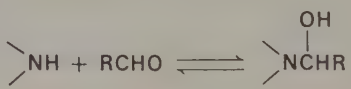
The oxidation process



$$\text{>N—CH}_2\text{R} \xrightarrow{[O]} \text{>N—CHR(OH)} \xrightarrow{[O]} \text{>N—C(=O)—R, or >NH + RCOOH} \qquad (41)$$

while rather limited in its generality, has occasionally been used advantageously in the laboratory; but its greatest importance lies in the widespread occurrence of the first step in biological dealkylation reactions.

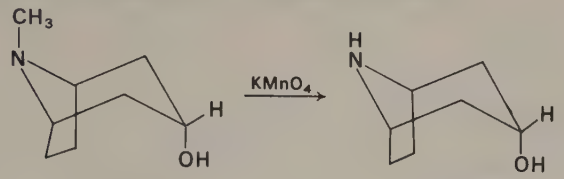
Two aspects of this reaction should first be considered. The intermediate α-hydroxyamine, >NCHOHR, may be regarded as the product of addition of the aldehyde RCHO to a secondary amine:



$$\text{>NH + RCHO} \rightleftharpoons \text{>NCHR(OH)} \qquad (42)$$

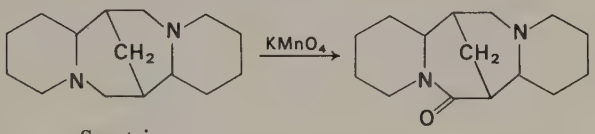
Consequently, dissociation and further oxidation of the aldehyde to the corresponding carboxylic acid can be expected, with the overall result that the secondary amine is the final product. However, when the α-hydroxyamine is in a cyclic structure, dissociation is less likely to occur and oxidation to the amide is the final result:

Oxidative demethylation to a secondary amine*



Tropine Nortropine (43)

Oxidation of a tertiary amine to an amide



Sparteine (44)

The oxidizing agents used in reactions of this kind [$KMnO_4$, $K_3(Fe(CN)_6)$] are capable of attacking other centers in many molecules and thus the use of this reaction is limited to those compounds without functional groups readily susceptible to oxidative attack by the oxidant used.

Biological oxidative dealkylation (usually demethylation) is an important process in the metabolism of mammals. Occurring chiefly in the liver, in the presence of molecular oxygen and under the catalytic influence of enzymes present in mitochondria and microsomes, the process serves two purposes: (1) demethylation of normal metabolic materials, for example,

$$\underset{\text{}}{(CH_3)_2NCH_2COOH} \longrightarrow \underset{\text{Sarcosine}}{CH_3NHCH_2COOH} + HCHO \qquad (45)$$

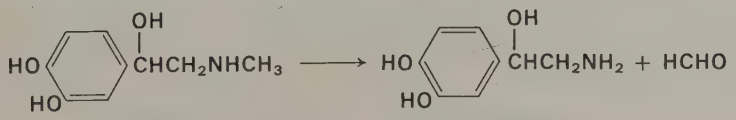
N,N-dimethylglycine

$$\underset{\text{Sarcosine}}{CH_3NHCH_2COOH} \longrightarrow H_2NCH_2COOH + HCHO$$

Glycine

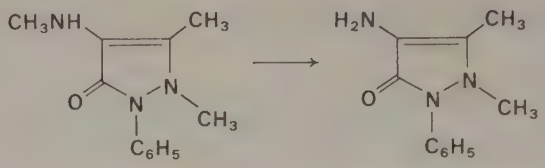
and (2) the metabolic degradation of foreign materials, such as drugs. Although drug metabolism takes many forms, the *oxidative demethylation* of compounds containing *N*-methyl groups is one of the well-known processes. Removal of one or more *N*-methyl groups from morphine, cocaine, *N*-methyl barbiturates, chlorpromazine, imipramine, nicotine, butynamine, and numerous other compounds has been observed both *in vivo* and in isolated liver-tissue preparations (slices, homogenates).

Some biological dealkylations of this kind are illustrated by the following examples; these occur *in vivo*, principally in the liver:



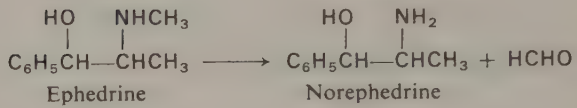
Epinephrine Norepinephrine (46)

* Further oxidation of the formaldehyde, eventually to CO_2, will ordinarily occur.



(47)

4-aminoantipyrene



(48)

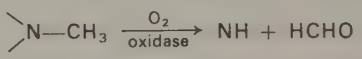
Ephedrine Norephedrine

N-methylaniline ⟶ aniline + HCHO (49)

N-ethylaniline ⟶ aniline + CH_3CHO (50)

The biological significance of metabolic degradations of these and other kinds cannot be expressed in categorical terms. In some cases, the altered (for example, demethylated) drug is physiologically inert, and so demethylation is a *detoxification* process. In others, the metabolite may be more active than the parent compound, or may be responsible for some of the undesirable clinical side effects of the drug.

The detailed nature of the oxidative reactions involved in the overall change



(51)

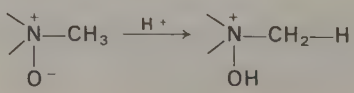
is not known with certainty, but may be interpreted as involving (*a*) the formation of an *N*-oxide, (*b*) rearrangement of the *N*-oxide to the methylolamine, and (*c*) dissociation into the amine and formaldehyde:

(52)

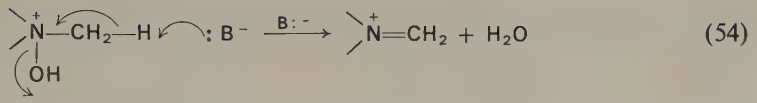
However, the possibility cannot be entirely excluded that the conversion of $—CH_3$ into $—CH_2OH$ is a direct insertion of oxygen into a C—H bond and does not require intermediate *N*-oxide formation.

N-Oxides are well-known natural compounds. Numerous alkaloids co-occur in nature as the tertiary amines and the corresponding *N*-oxides. Many drugs that are tertiary amines are converted into *N*-oxides *in vivo*, and excreted as such. Thus, *N*-oxidation may be accepted as a common biological process and it is an acceptable hypothetical first step in the *N*-demethylation reaction.

The process by which the *N*-oxide is converted into the methylolamine can be represented briefly as follows:

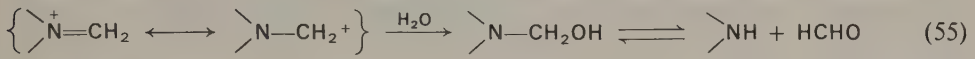


(53)



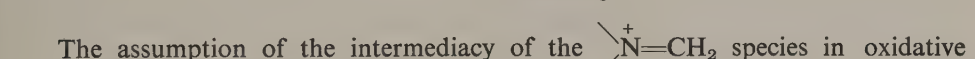
(54)

The structure $\overset{+}{\text{N}}{=}\text{CH}_2$ is electrophilic and can accept a molecule of water to produce the methylolamine, which can then dissociate into the secondary amine and formaldehyde:



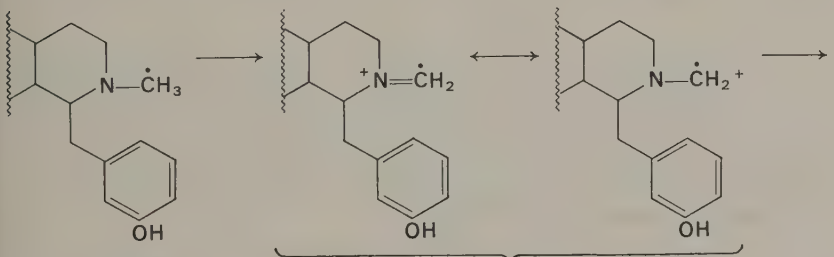
(55)

Although the elimination of OH^- in equation (54) is not a highly favored process, biologically acceptable alternatives can easily be suggested. It would be mechanistically acceptable for the nucleophilic oxygen atom of the *N*-oxide to undergo acetylation (with acetyl coenzyme A) or phosphorylation, yielding an intermediate in which the displaceable acetate or phosphate anion would fit the requirements of the process:



(56)

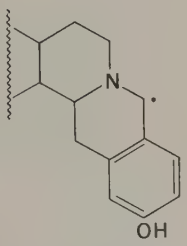
The assumption of the intermediacy of the $\overset{+}{\text{N}}{=}\text{CH}_2$ species in oxidative dealkylation is supported by certain natural processes in which the electrophilic character of this grouping can account for the observed reactions. An example is the ring-forming process formulated below. Isotopic labeling experiments have shown that the carbon atom of the $\text{N}{-}\dot{\text{C}}\text{H}_3$ group is incorporated into the ring ($\dot{\text{C}} = {}^{14}\text{C}$):*



(57)

(fed to the plant)

Probable intermediate, not isolated



* This process occurs in the biosynthesis of certain alkaloids. Only that part of the alkaloid that participates in this reaction is shown here.

The final product is isolated from the plant, and the location of $\dot{C}$ established by suitable degradation procedures.

16-12 Aromatic amines

Aniline and its derivatives show many reactions similar to those of aliphatic amines. *N*-Alkylation, *N*-acylation, protonation, and quaternary salt formation proceed in the same manner, but because of the much lower basicity of aromatic amines there are quantitative differences (rate, equilibrium) between the reactions of the two classes of amines.

There is, however, a sharp distinction between the characters of the diazonium salts formed by diazotization of aliphatic and aromatic primary amines. Those formed from the latter are sufficiently stable to be preserved in solution and used as reagents for a variety of synthetic purposes. They are described in Chapter 32.

Much of the chemistry of aromatic amines concerns the effect of amino groups upon the aromatic ring, and the effect of substituents on the ring upon the properties of the amino group. These will be the subject of a later chapter.

Problems

1. Write the structural formulas of the following compounds. Where relevant, show stereochemistry by suitable projection formulas: (*a*) *N*,*N*′-dimethylethylenediamine, (*b*) (S)-2-diethylamino-1-propanol, (*c*) *trans*-1,2-diaminocyclohexane, (*d*) 2,3-dibromoaniline, (*e*) *N*-ethylpyrrolidine, (*f*) *N*,*N*-dimethylpiperidinium bromide, (*g*) *N*-methylatropinium chloride, (*h*) spermine, (*i*) sphingosine, (*j*) *N*-methylamphetamine.

2. What is the pH of a 0.1 *N* solution of dimethylamine hydrochloride?

3. Show how the following amines can be synthesized, using any reasonably available starting materials: (*a*) *n*-butylamine, (*b*) ethylenediamine, (*c*) methylethylamine (from *N*-methylacetamide), (*d*) isopropylamine, (*e*) triethylamine oxide, (*f*) *N*-ethylacetamide.

4. *N*-methylacetamide can be prepared by heating ethyl acetate with an excess of methylamine. Write the equations showing the course of the transformation.

5. Explain why the initial step $\rangle N—CH_3 \rightarrow \rangle N—CH_2OH$ provides an acceptable description of the course of oxidative *N*-demethylation.

6. Treatment of *N*-methylpiperidine oxide with methyl iodide yields a salt,

$(C_7H_{16}NO)^+I^-$. What is its structure and what is the mechanism of the reaction? (HINT: See Section 16-9.)

7. What products would result from the following reactions?
   (*a*) triethylallylammonium bromide + NaOEt →
   (*b*) ethylamine + methyl formate →
   (*c*) trimethylamine + cyanogen bromide →
   (*d*) dimethyl sulfate + pyridine →
   (*e*) acetylcholine + aqueous NaOH →

17

Spectroscopic properties. Ultraviolet and infrared spectra

The last several decades have seen the development by physical and analytical chemists and the adoption by organic chemists of a number of instrumental methods for measuring the physical properties of organic compounds. The most generally used of these are

Ultraviolet (UV) and visible absorption spectra
Infrared (IR) absorption spectra
Nuclear magnetic resonance (NMR) spectra
Mass spectra (MS)

These have proved to be of incalculable value in the study of the structures of organic compounds and are now used in all chemical laboratories. No account of organic chemistry would be complete without a discussion of how these technics are applied and the data interpreted.

The descriptions of these physical methods in this and the following chapter are necessarily brief; each of the four technics listed above is the subject of an extensive literature and, in most modern chemistry curricula, of special courses of study. It is, however, important that the student gain an early acquaintance with them.

Measurement of the physical characteristics of organic compounds has two essentially distinct uses. One of these is simply analytical: spectral data may be used to

identify organic compounds, by a procedure comparable to matching the fingerprints of a suspect with those on file.

The other use of such data is in defining the functional groups and the structural characteristics of a compound, thus making it possible to propose a structure for a new compound or to select the most probable structure from among several "candidate" structures.

It should be pointed out that the use of physical measurements cannot always lead infallibly to the correct structure. Chemical evidence is usually needed to complete the total structure proof. But the arduous and time-consuming chemical manipulations used by chemists before the advent of modern physical measurements are now seldom necessary, and the rapid and confident assignment of total structures to new and often complex organic compounds is commonplace.

17-1 Absorption spectrometry. Energy transitions

Molecules can exist at a number of possible energy levels, into which they can be placed by absorption and emission of radiant energy. At ordinary temperatures and in the absence of external sources of excitation, molecules occupy the lowest energy levels and are in their *ground state.* In this condition the electrons in the bonding orbitals and non-bonding orbitals (unshared electrons) are in their most stable disposition about the atomic nuclei. The electrons are in ground-state orbitals. Absorption of energy provided by appropriate radiation can cause the electrons to reside in available orbitals (unoccupied in the ground state) at higher energy levels. A molecule in this unstable condition, as a result of the absorption of energy, is in an *excited state.*

The electronic transitions of greatest importance in organic chemistry involve the absorption of energy in the range of about 2 to 150 kcal/mole. These energies, usually

Table 17-1
Energy values associated with radiation of various wavelengths

Wavelength	*Description*	ΔE *(kcal/mole)*
2000 Å	ultraviolet	143
4000 Å	ultraviolet, visible	72
8000 Å	visible	36
5 microns	infrared*	6
15 microns	infrared*	2

* Absorption of light in the infrared region is not accompanied by transitions in electronic energy levels. It leads to changes in the vibrational energies of molecules. These will be dealt with further on.

provided by irradiation with monochromatic light, can be expressed in terms of the wavelength of the light absorbed (as shown in Table 17-1) according to the relationship

$$\Delta E = h\nu = \frac{hc}{\lambda}$$

ΔE = energy transition on light absorption
h = Planck's constant
ν = frequency (Hz, cycles/second)
c = velocity of light = 3×10^{10} cm/sec
λ = wavelength (cm)

17-2 Spectrophotometric measurements

It is fortunate for practical reasons that the energies required for electronic transitions in the most useful region of the spectrum are provided by light of wavelengths that are experimentally easily accessible. Ultraviolet light (about 1800–4000 Å) is provided by a hydrogen-discharge lamp, and visible light (about 4000–8000 Å) by an ordinary tungsten-filament lamp. These are contained in an instrument such as the one represented in Figure 17-1.

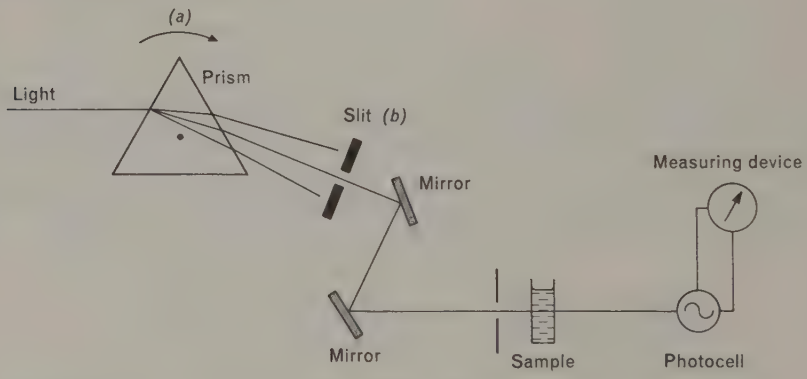


Figure 17-1
A schematic diagram of the essential elements of a spectrophotometer for the measurement of absorption spectra.

When the measurement of light intensity is made with a photocell, the instrument is called a *spectrophotometer*. Rotation of the prism (*a*) (Fig. 17-1), which is coupled with a calibrated wavelength dial, causes a continuous change in the frequency of the light that passes through the slit (*b*) and from there through the sample. When the wavelength of light selected is such that its energy corresponds to a transition of the molecule from the ground state to a higher energy level, light is absorbed by the compound and the photocell reading falls. Let us suppose that the compound used absorbs

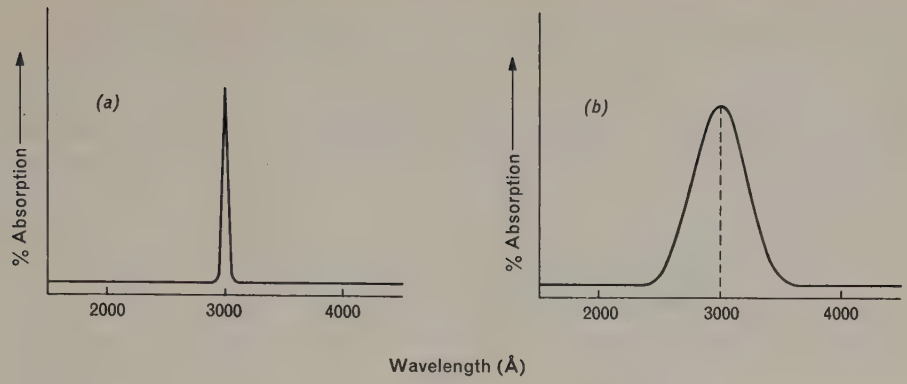


Figure 17-2
Absorption spectrum of a compound with an absorption maximum at 3000 Å. (*a*) Idealized spectrum; (*b*) what an actual spectrum would be like.

light of wavelength 3000 Å. The plot of the proportion of light absorbed vs. the wavelength of light incident upon the sample will be like that shown in Figure 17-2. This graph is an *absorption spectrum.* Figure 17-2(*a*) is highly idealized, for ordinary molecules are complex in structure and exist in various vibrational and configurational states, and thus undergo electronic transitions over a small *range* of frequency. Absorption spectra do not, therefore, show simple sharp absorption peaks; rather, an actual absorption spectrum of a molecule with an *absorption maximum* (λ_{max}) at 3000 Å would ordinarily look more like the one shown in Figure 17-2(*b*).

17-3 Units in general use

The commonly used units for expressing the wavelengths of ultraviolet and visible light are *nanometers* (nm, 10^{-9} meter) and *millimicrons* (mμ); the former term is becoming the more frequently used. Thus 2000 Å = 200 mμ = 200 nm.

For the infrared region, the scale may be expressed in wavelength (microns, μ) or *wave number.* The latter is generally preferred. The wave number is the reciprocal of the wavelength in cm. Thus, for wavelength (λ) = 5 μ = 5 × 10^{-4} cm, the wave number = $\frac{1}{5} \times 10^{-4} = 2000\ \text{cm}^{-1}$.

Exercise 1

Express the following wavelengths as wave numbers: (*a*) 5.78 μ, (*b*) 6.66 μ, (*c*) 3.33 μ, (*d*) 11.0 μ, (*e*) 9.52 μ.

17-4 Color and absorption spectra

Organic compounds range from colorless to yellow, orange, red, blue, and green. The color of a compound is often a valuable clue to its structure, and useful conclusions can often be drawn simply from visual examination of a compound. Table 17-2 shows

Table 17-2
The relationship between the wavelength of light (λ_{max}) absorbed by a compound and the visible color of the compound

λ_{max}(*nm*)	*Light absorbed*	*Visible color*
below 350	ultraviolet region	colorless
400	violet	yellow
450	blue	orange
500	blue-green	red
530	yellow-green	violet
550	yellow	blue
600	orange-red	green-blue
700	red	green

the relationship between the visible color of a compound and the region of its principal absorption maximum.

In common parlance, color "deepens" in going from yellow to blue. In this sense, a bathochromic* shift in the wavelength of absorption is a shift toward the red end of the spectrum with a "deepening" of the visible color.

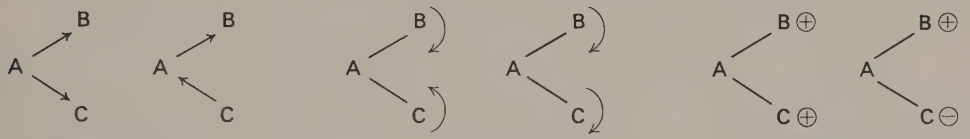
17-5 Vibrational energy levels. Infrared (IR) absorption spectra

The constituent atoms of organic molecules are not rigidly fixed, but occupy average positions with respect to one another. They do undergo small motions in which their relative positions change. These motions have their origins in the repulsive and attractive forces between atomic nuclei and the electrons involved in the bonds between the atoms. The molecule can be likened to an assemblage of balls of various masses joined by springs of various degrees of elasticity. The relative positions of the atoms can alter by the *stretching* or *bending* of the interatomic bonds. These stretching and bending vibrations have definite quantized frequencies that are characteristic of the atoms and the nature of the bonds (single, double, and so on) between them.

* From Greek *bathos* (depth) and *chroma* (color).

When light incident upon the molecule is of the same frequency as that of the stretching or bending vibration, light (energy) is absorbed, the amplitude of the vibration increases, and the molecule is in an excited state. The absorption of light is recognized by a diminution of the light transmitted through the sample being observed, with a change in the photocell reading and the recording of an *absorption peak*. As in the case of UV–visible absorption, infrared absorption occurs over a small range of frequency and the recorded spectrum contains an array of peaks of various degrees of sharpness, properly referred to as *absorption bands*.

The vibrational modes that we shall be most concerned with are (*a*) the stretching of bonds and (*b*) the bending of bonds, with a consequent wagging of the atoms with respect to each other. These can be simply expressed as follows:



Vibrational transitions require much less energy than electronic transitions, and are caused by light of lower energy (longer wavelength; see Table 17-1 and footnote).

Infrared spectra of organic molecules are usually quite complex. Since in a polyatomic molecule there are numerous kinds of vibrational modes, an infrared spectrum ordinarily contains a great many separate absorption peaks. For example, in the spectrum of the relatively simple compound *n*-butyl vinyl ether, $CH_3CH_2CH_2$-$CH_2OCH{=}CH_2$, measured with a commercial IR spectrophotometer, there can be discerned more than 25 separate absorption peaks in the range 700–3500 cm^{-1} (3–15 μ).

An IR spectrum is unique to a given compound. For this reason one of the important uses of IR spectrometry is the identification of organic compounds by matching the spectrum of the compound under study with that of a known compound. If the compounds are the same—and equally pure—the spectra will of course be identical in every detail. If the compounds are not the same (even if they are closely similar in structure) the difference in at least some details of the spectra will reveal their non-identity.

17-6 Characteristic regions of the IR spectrum

The most useful application of IR spectroscopy is to the recognition of functional groupings and specific bond types in organic molecules. The C-H bonds in sp^3-, sp^2-, and *sp*-hybridized carbon atoms have quite different and highly characteristic stretching and bending frequencies; and such prominent functional groupings as C≡C,

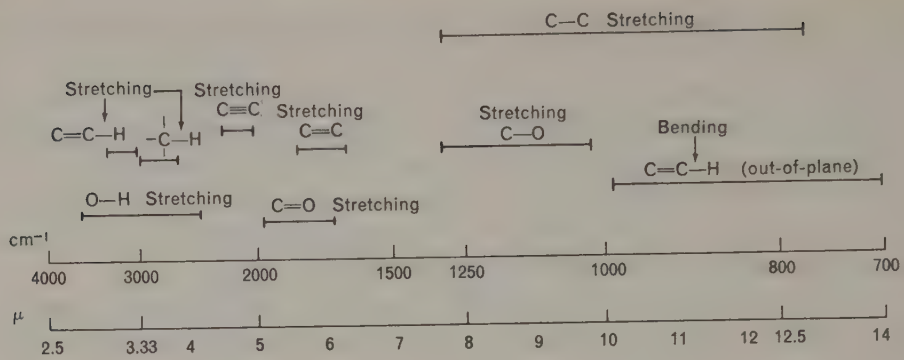


Figure 17-3
Spectral regions characteristic of various stretching and bending vibrational modes of some common structural units.

C=C, C=O, C=S, C=O, and so on show absorption peaks in well-defined regions of the IR spectrum.

In Figure 17-3 is shown the IR spectral range, with some of the regions in which characteristic absorption peaks are found.

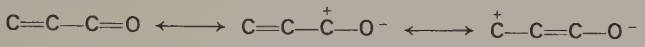
Several points are to be noted in this chart. The stretching frequency of C≡C is higher than that of C=C; that of C=O is higher than C—O. The shorter, stronger bonds require higher energy for vibrational (stretching) transitions. This is also illustrated by the C=O stretching frequency of saturated and unsaturated (conjugated) aldehydes (Table 17-3). The effects of conjugation upon the C=O stretching frequency can be described in terms of the resonance concept. In all of the carbonyl groups in the aldehydes in Table 17-3 the contribution

Table 17-3
The infrared C=O stretching frequency* of some aldehydes

Compound	C=O *stretching frequency* (cm^{-1})
acetaldehyde	1733 (in CCl_4)
acrolein	1704 (in CCl_4)
2,4-hexadienal	1677 (in $CHCl_3$)
2,4,6-octatrienal	1664 (in $CHCl_3$)

* Higher frequencies correspond to higher wave numbers.

describes the charge delocalization in the double bond. When carbon-carbon double bonds are conjugated with C=O, the contribution of additional forms

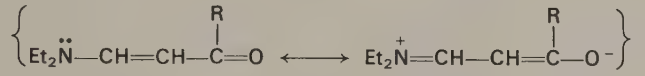


allows further lengthening of the C=O bond by augmenting the relative contribution of C—O forms to the hybrid. Thus the C=O bond in the conjugated aldehydes has more *single-bond character* than in acetaldehyde, and the single-bond character is enhanced with increasing conjugation. The result is that the stretching frequency decreases as conjugation increases; the wavelength of absorption increases.

Another illustration of the effect of resonance-caused bond-lengthening on the infrared absorption frequency is found in the pair of compounds

$CH_2{=}CH{-}COCH_3$	C=O stretching 1689 cm^{-1} (in CCl_4)
$Et_2N{-}CH{=}CH{-}COCH_2CH_3$	C=O stretching 1664 cm^{-1} (in CCl_4)

In the diethylamino compound, the ability of the R_2N— grouping, with its unshared electrons on nitrogen, to contribute in the following way



causes an appreciable increase of the C=O bond length and a marked decrease in the carbon-oxygen stretching frequency.

17-7 Interpretation of IR spectra

In Figures 17-4 to 17-8 are shown the IR spectra of a number of organic compounds. The compounds selected are rather complex, but this selection has been made quite deliberately, for it is important to recognize that *characteristic molecular groupings* can be recognized in complex spectra, even though a great many of the absorption peaks cannot be usefully or confidently interpreted. The multiplicity of separate peaks in the region between about 1500 and 750 cm^{-1} (7 to 13 μ) can be regarded as a pattern that is unique for each compound, as a fingerprint is unique for each person. In fact, this region is often called the "fingerprint" region, and its greatest value is for establishing identity by direct matching of spectra, without further detailed interpretation. The following description of the significant features of these spectra will show how IR spectral data can be used to interpret structure.

The spectra in Figure 17-4 are those of the compounds whose structures are shown on the figure. Compound 4*a* contains a hydroxyl group (O—H stretching at

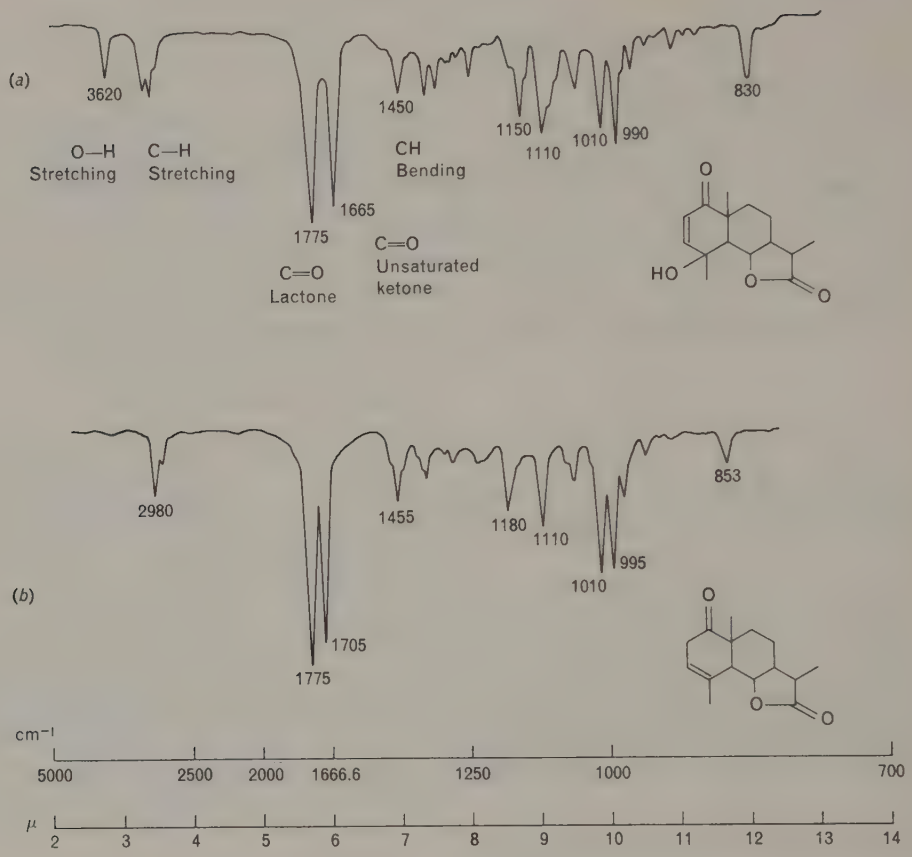


Figure 17-4
IR absorption spectra of two similar compounds.

3620 cm^{-1}), a conjugated ketone carbonyl group (C=O stretching at 1665 cm^{-1}) and a five-membered ring containing a carbonyl group in an ester grouping (a cyclic ester of this kind is called a *lactone*) (C=O stretching at 1775 cm^{-1}). The group of peaks near 1400 cm^{-1} (7 μ) represent C—H bending in the various $—CH_3$ and $—CH_2—$ groups of the molecule. The fingerprint region contains peaks for various other vibrational transitions that will not be discussed in detail.

Compound 4*b* can be seen to possess many of the same structural features as 4*a*, but the carbonyl group and carbon-carbon double bond *are not conjugated*, and the ketone C=O stretching frequency is 1705 cm^{-1}. The lactone C=O is seen at the same

position as in 4*a*; clearly the alteration in the structure of the left-hand ring has no appreciable effect upon the rest of the molecule. The C—H bending peaks are again seen near 7 μ, and the fingerprint region shows some differences from that of 4*a*. The small peak at about 850 cm^{-1} in 4*b* is due to out-of-plane bending of the =C—H hydrogen atom.

Figure 17-5 shows the spectra of two modifications of the structures of Figure 17-4. Compound 5*a*, it can be seen, resembles 4*b* very closely in the positions of the

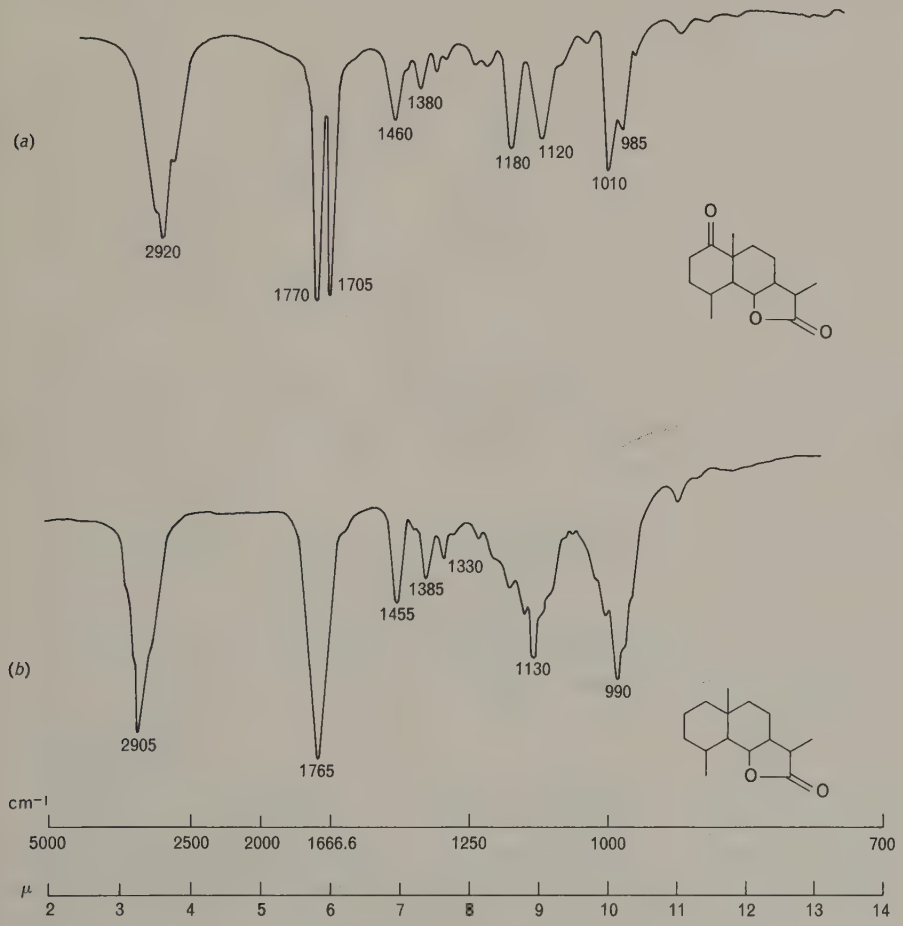


Figure 17-5
IR absorption spectra of two compounds similar to those in Figure 17-4.

C=O stretching absorptions. This shows that the nonconjugated double bond in 4*b* has no appreciable effect upon the absorption frequency of the C=O group, for this is 1705 cm^{-1} in both 4*b* and 5*a*. The C—H bending vibration at 853 cm^{-1} in 4*b* is missing in 5*a*, which contains no carbon-carbon double bond.

Compound 5*b* lacks the ketone carbonyl group, but the lactone carbonyl group is seen in the peak at 1765 cm^{-1}. This frequency is somewhat lower than might be expected (it is at 1770 to 1775 cm^{-1} in 4*a*, 4*b*, and 5*a*), but such small differences are sometimes observed. The remainder of the spectrum of 5*b* contains no other noteworthy features.

The three spectra shown in Figure 17-6 are those of the sterol cholesterol and two

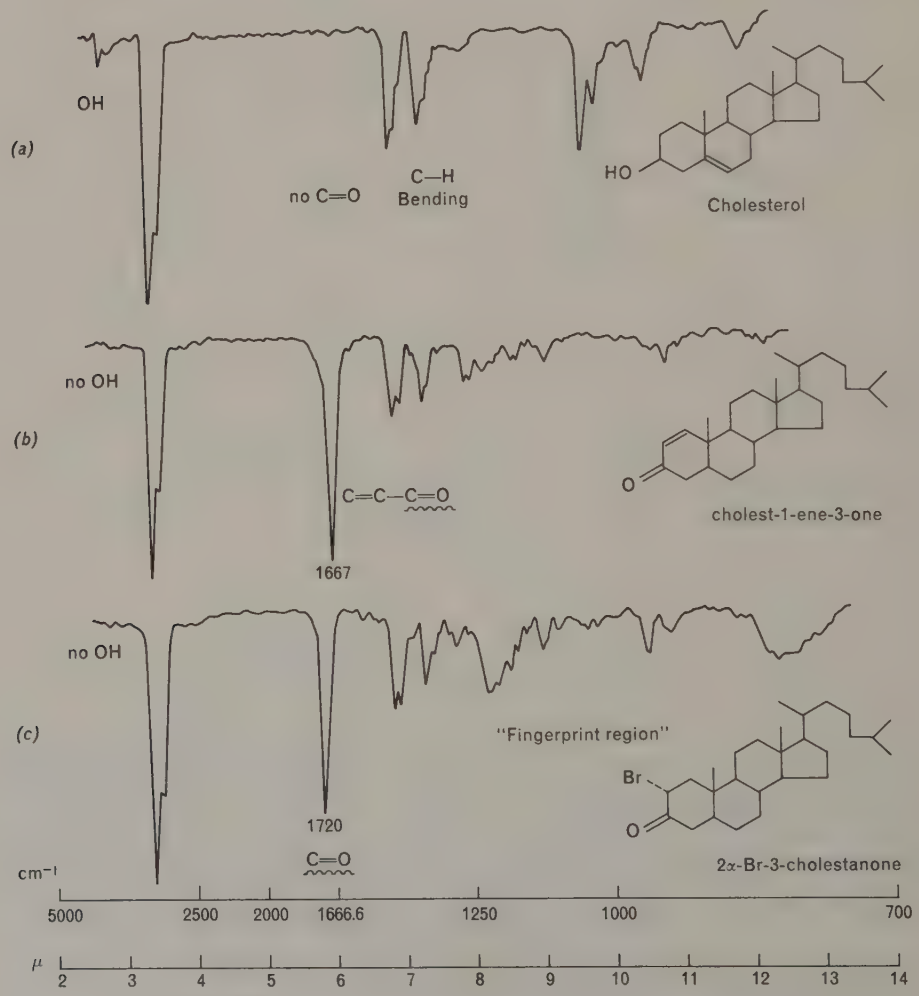


Figure 17-6
IR absorption spectra of cholesterol and two of its derivatives.

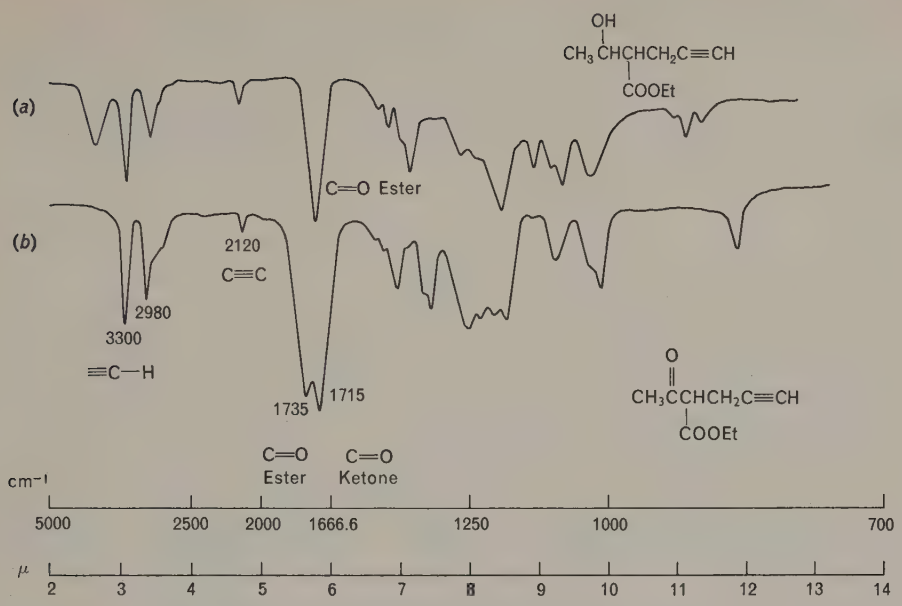


Figure 17-7
IR absorption spectra of two similar acetylenic compounds.

of its derivatives. The spectrum of 6*a*, cholesterol itself, shows the hydroxyl group absorption at about 3500 cm^{-1}, and a peak near 840 cm^{-1} due to the out-of-plane bending vibration of the hydrogen attached to the C=C grouping. The characteristic C—H bending frequencies near 7 μ are again seen (compare Figures 17-4 and 17-5).

Compound 6*b* contains the system C=C—C=O, and shows the C=O stretching at 1667 cm^{-1} (compare 4*a*). The OH peak is absent, and other features of the spectrum resemble (but are not identical with) those of 6*a*.

Compound 6*c* shows the ketone carbonyl peak at 1720 cm^{-1}, an indication that is not in the system C=C—C=O.* The fact that this frequency is higher than that of the ketone carbonyl group in 5*a* (1705 cm^{-1}) is due to the effect of the bromine atom in the adjacent (α) position. Again, spectra of 6*b* and 6*c* are similar (but not identical) in the fingerprint region.

The spectrum of Figure 17-7(*b*) shows two carbonyl stretching frequencies: that at 1715 cm^{-1} is due to the carbonyl group in CH_3CO; that at 1735 cm^{-1} is due to the carbonyl group of the ester grouping. Compound 7*a* is obtained by reducing the C=O group of 7*b* to CHOH. Only the ester group is now seen in the 1700 cm^{-1} region, and an OH peak at about 3600 cm^{-1} is now present.

---

* Since carbonyl groups in five-membered rings (cyclopentanones) show their stretching frequency at about 1745 cm^{-1}, the introduction of a conjugated double bond lowers this to the region of 1710 to 1720 cm^{-1}. Thus, a peak at 1720 cm^{-1} is not unequivocally diagnostic of the system of compound 6*c*; it could represent an α,β-unsaturated five-membered-ring ketone.

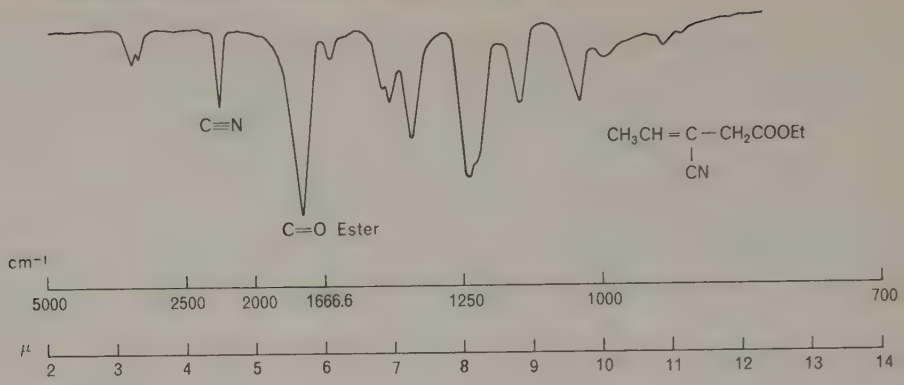


Figure 17-8
IR absorption spectrum of ethyl 3-cyano-3-pentenoate, showing some resemblance to those in Figure 17-7.

Two features of the spectra of both 7*a* and 7*b* are the sharp peak at 3300 cm^{-1} and the weak absorption at 2120 cm^{-1}. These are important diagnostic features: the absorption at 3300 cm^{-1} is due to the stretching of the acetylenic C—H bond, and that at 2120 cm^{-1} is due to the stretching of the C≡C bond. Another prominent absorption in both of these spectra occurs at around 1200 cm^{-1}. This is characteristic of the stretching of the C—O (single) bond in the ester grouping. Again, both of these spectra show general absorption in the 7 μ region due to C—H bending (of $—CH_3$ and $—CH_2—$).

The spectrum shown in Figure 17-8 is that of a compound whose ester carbonyl group is not conjugated with the carbon-carbon double bond and thus appears at about 1740 cm^{-1}. The sharp peak at 2220 cm^{-1} is due to the C≡N stretching vibration. This should be compared with the C≡C stretching peak seen in the spectra of Figure 17-7 at 2120 cm^{-1}. It should be noted that this stretching vibration occurs at approximately the same frequency for C≡N and C≡C, the difference being chiefly due to difference in mass between carbon and nitrogen.

17-8 Ultraviolet (UV) absorption spectra. Electronic transitions

Electrons in the ground state of organic molecules occupy three principal kinds of orbitals:

Bonding σ (sigma) orbitals of single bonds
Bonding π (pi) orbitals of multiple bonds
Non-bonding *n* orbitals, occupied by the unshared electron pairs such as those on oxygen, nitrogen, sulfur, halogens

By absorption of light energy, electrons can be promoted from ground-state orbitals to higher-energy orbitals, vacant in the ground state but occupied in the

excited state. These are *antibonding* orbitals, described by the symbols σ^* (sigma star) and π^* (pi star). Since n electrons are not engaged in bonding, there are no corresponding antibonding (n^*) orbitals.

The electronic transitions effected by absorption of ultraviolet and visible light are written

$$\sigma \longrightarrow \sigma^*$$
$$n \longrightarrow \sigma^*$$
$$\pi \longrightarrow \pi^*$$

The $\sigma \rightarrow \sigma^*$ *transitions* involve the promotion of electrons that are tightly bound between atomic nuclei. Thus electrons in σ^* orbitals are of much higher energy than those in the very stable σ orbitals; to attain them requires light of high energy (and thus very short wavelength). Such simple molecules as methane and ethane, which contain only σ bonds, show $\sigma \rightarrow \sigma^*$ transitions in the very-short-wavelength ultraviolet regions, at about 130 nm. Since only highly specialized instrumentation whose optical systems operate in a vacuum can be used in these far-UV regions, and since $\sigma \rightarrow \sigma^*$ transitions are seldom of informative value, this region of the spectrum is not often used in structural studies.

The $n \rightarrow \sigma^*$ *transitions* are shown by molecules containing oxygen, nitrogen, sulfur, and halogen atoms; they require lower energy than $\sigma \rightarrow \sigma^*$ transitions. Such compounds as methanol, methylamine, and methyl iodide have ultraviolet spectra with absorption peaks of low intensity, usually in the region near 200 nm. Most compounds with unshared electrons but without structural features that produce high-intensity absorption above 200 nm show increasing but non-specific (and not very informative) absorption near the 200 nm region. This is called *end absorption*, and has little diagnostic value.

Transitions to π^* orbitals require the presence of π orbitals in the molecule, and thus are seen in molecules containing multiple bonds: C=C, C=O, and so on. The $n \rightarrow \pi^*$ *transitions* are of relatively low intensity, but $\pi \rightarrow \pi^*$ *absorption bands* are strong. The energy of the $\pi \rightarrow \pi^*$ transition is not greatly different, for C=C, C≡C, and C=O. Acetone shows a λ_{max} at 189 nm, ethylene at 175 nm, 2-octyne at 178 nm.

Since the C=O group contains the π orbital as well as unshared (non-bonding) n electrons on oxygen, it has been found that acetone, acetaldehyde, and other saturated aldehydes and ketones show two principal absorption bands: a high-intensity band at about 185 nm ($\pi \rightarrow \pi^*$) and a low-intensity band at about 285 nm ($n \rightarrow \pi^*$). It should be noted that simple olefins such as ethylene, which do not possess unshared (n) electrons, show only the short-wavelength, high-intensity absorption band.

17-9 Conjugated systems

Compounds containing "isolated" double bonds, for example $CH_2{=}CHCH_2CH_2CH{=}CH_2$ and $CH_2{=}CHCH_2CH_2COCH_3$, show UV absorption like that of the simple

olefins or carbonyl compounds, the absorption being the sum of those of the separate functional groups.

When the unsaturated centers are adjacent—that is, in conjugation—interaction of the two π orbitals brings into play a new set of circumstances. Even the simplest of such systems, 1,3-butadiene ($CH_2{=}CH{-}CH{=}CH_2$) and acrolein ($CH_2{=}CH{-}CHO$), have high-intensity absorption maxima at 217 and 208 nm, respectively; with increasing substitution, such systems show λ_{max} well into the useful UV region. For example, mesityl oxide (4-methyl-3-penten-2-one, $(CH_3)_2C{=}CHCOCH_3$) has λ_{max} at 237 and 310 nm. These two maxima are those of the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively.

Why does conjugation lower the energy required for the $\pi \rightarrow \pi^*$ transition? It will be remembered that a simple olefin such as ethylene has available only the π (ground state, bonding) and π^* (excited state, antibonding) orbitals. The energy difference between these is about 175 kcal/mole, corresponding to the short-wavelength λ_{max} at 175 nm.

Butadiene, however, with four π electrons, has available four π orbitals, two bonding (π_1 and π_2) and two antibonding (π_3^* and π_4^*). The π_1 bonding orbital encompasses all of the π electrons over the four-carbon-atom systems, and is somewhat more stable than a single π orbital (as in ethylene). The π_2 orbital is also a bonding orbital,

Table 17-4
Principal absorption maxima for some conjugated and nonconjugated olefinic and carbonyl compounds*

Compound	*Name*	λ_{max}(*nm*)	ϵ (*at* λ_{max})
carbonyl			
$(CH_3)_2C{=}O$	acetone	189	900
$CH_3CH{=}CHCHO$	crotonaldehyde	217	15,000
$CH_3CH{=}CH{-}CH{=}CH{-}CHO$	2,4-hexadienal	270	27,000
$CH_3(CH{=}CH)_3CHO$	2,4,6-octatrienal	312	40,000
olefinic			
$CH_2{=}CH_2$	ethylene	175	15,000
$CH_2{=}CH{-}CH{=}CH_2$	1,3-butadiene	217	21,000
$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH_2$	1,3,5-hexatriene	258	35,000
$CH_2{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH_2$	1,3,5,7,9-decapentaene	334	125,000
β-carotene	(11 conjugated double bonds)	465	125,000

* The quantity ϵ, the *molar extinction coefficient*, is a measure of the intensity of absorption; see Section 17-10.

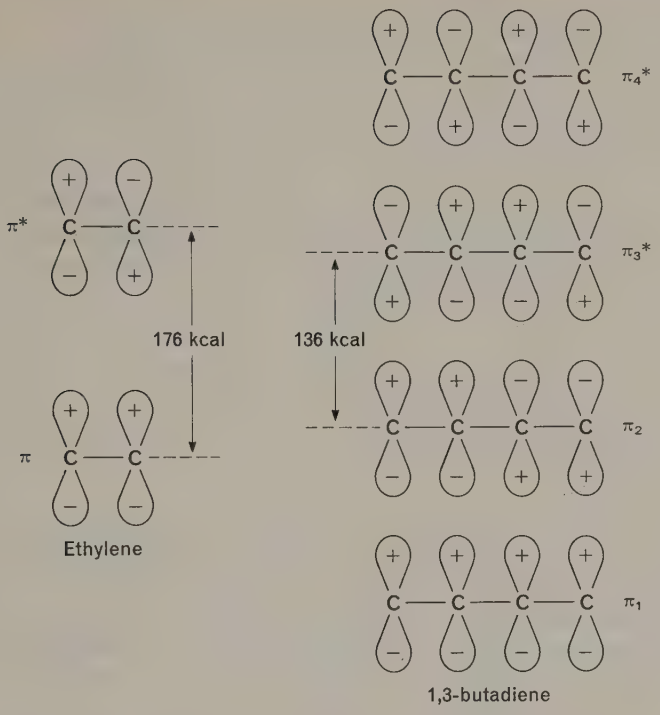


Figure 17-9
Schematic representation of electronic excitation energy levels in ethylene ($\lambda_{max} = 175$ nm) and butadiene ($\lambda_{max} = 217$ nm).

but is of higher energy than the π_1 orbital. The two π^* orbitals are, respectively, more stable (π_3^*) and less stable (π_4^*) than the π^* orbital of ethylene.

Energy absorption, with the appearance of an absorption band, can thus occur by a π_2 (bonding) $\rightarrow \pi_3^*$ (antibonding) transition, the energy difference of which (136 kcal/mole) is less than that of the simple $\pi \rightarrow \pi^*$ transition of ethylene (176 kcal/mole), giving a λ_{max} at a longer wavelength (217 nm). These remarks are summarized schematically in Figure 17-9.*

It is to be expected that the greater the number of bonding π orbitals, the lower will be the energy between the highest bonding π orbital and the lowest excited π^* orbital. The obvious extension of this in terms of λ_{max} is that *the greater the number of conjugated double bonds, the longer the wavelength of absorption.*

It can be seen by inspecting the data of Table 17-4 and referring to Table 17-2 that β-carotene, a conjugated system of 11 carbon-carbon double bonds, is a deeply colored orange-red compound. The polyene aldehyde $CH_3(CH{=}CH)_7CHO$ has λ_{max} 415 nm (ϵ 63,000), and is a yellow compound.

---

* The use of + and − in the relevant *p* orbitals is a convention that indicates only the sign of the wave functions that these diagrams represent, and has no reference to charges.

17-10 Quantitative expression of spectral measurements

The fraction by which the intensity of a beam of incident light is reduced in passing through an absorbing substance depends upon a number of factors: one factor is the molecular structure of the absorbing compound; another is the number of molecules of the absorbent in the light path. The number of molecules depends upon c, the concentration of the compound, and l, the length of the light path (the thickness of the sample cell). The relationship, known as the Beer-Lambert law, is

$$\log(I_0/I) = kcl$$

where

I_0 = intensity of incident light at a given wavelength
I = intensity of transmitted light
c = concentration
l = path length
k = an absorption coefficient, characteristic of the absorbing substance

The quantity c is ordinarily expressed in gram moles/liter, and l in centimeters, in which case k is the *molar extinction coefficient*, designated ϵ. Thus the usual expression is $\log(I_0/I)$ = optical density = ϵcl. Since *optical density* is the form in which the absorption of light by a sample is measured by most instruments, the molar extinction coefficient is easily calculated by the equation

$$\epsilon = \text{O.D.}/cl$$

For various reasons beyond the scope of this discussion, extinction coefficients are not easily measured with IR instruments, so that IR spectra are usually recorded as a graph of transmission versus wavelength.

UV spectra are conveniently recorded as a plot of ϵ against wavelength (in nm). Since ϵ values range in practice from as low as 10 to as high as 100,000, it is convenient to use log ϵ as the abscissa of UV spectra.

Most spectra (UV, visible, and IR) are measured with the sample dissolved in a solvent that is selected because of its transparency over the range of interest. For UV spectra, ethanol, methanol, hexane, and water are commonly used. IR spectra may be determined with solutions in chloroform, carbon disulfide, or carbon tetrachloride; with thin films of the pure compound; or with uniform suspensions of the finely ground sample in an inert medium such as solid potassium bromide or mineral oil.

17-11 Diagnostic uses of UV absorption spectra

To the organic chemist, the principal uses of UV and visible absorption spectra are:

1. As a means of measuring the concentration of a known compound in solution. Since the molar extinction coefficient (ϵ) is known and the optical density (O.D., also

called *absorbance*, A) can be measured at a selected wavelength (usually at λ_{max}), the expression $\epsilon = A/cl$ can be used to determine the concentration c when a cell of known path length l is used.

2. As a means of identifying a compound by comparing its UV spectrum with that of a known substance.

3. By far the most useful application of UV spectroscopy is to the identification of the structural unit, or *chromophore*, that is responsible for characteristic absorption bands. For instance, if the structure of an unknown unsaturated ketone could be, from other evidence, either (*a*) $CH_2{=}CHCH_2CH_2COCH_3$, (*b*) $CH_3CH{=}CHCH_2COCH_3$, or (*c*) $CH_3CH_2CH{=}CHCOCH_3$, the UV spectrum would give an unequivocal answer if it showed an intense (ϵ about 10,000) absorption band at about 225 nm. Only compound (*c*) could have this spectrum. If such an absorption band were absent, the compound could be (*a*) or (*b*), and other evidence would be required to choose between these possible structures.

It would not be profitable to give here a detailed description of the numerous chromophoric groupings of organic compounds, for there are many excellent monographs that provide this information.* Applications of UV spectroscopy pertinent to the structure, properties, and chemical behavior of organic compounds will be found in other chapters.

17-12 Auxochromic groups. Effects on UV and IR absorption

It is observed that many functional groupings, themselves with no useful UV or IR absorption characteristics, have a profound effect upon chromophoric systems to which they are attached. Such groupings are termed *auxochromes*. In general, an auxochrome is a group that deepens color; its presence causes a shift in the UV or visible absorption maximum to a longer wavelength.

The most conspicuous property of auxochromic groupings is their ability to provide additional opportunity for charge delocalization, and thus to provide for smaller energy increments for transition to excited states. Typical auxochromic groups are amino (and substituted amino) groups (—NH_2, —NHR, and —NR_2), hydroxyl (—OH), and alkoxyl groups (—OR).

It will be apparent that a charge delocalization indicated by the contributing structures

$$C{=}C{-}C{=}O \longleftrightarrow \overset{+}{C}{-}C{=}C{-}O^-$$

* One that can be recommended is J. R. Dyer, *Applications of Absorption Spectroscopy of Organic Compounds*, Prentice-Hall, Englewood Cliffs, New Jersey (1965), available in a paperback edition. This book deals with UV, IR, and NMR (Chapter 26 of this textbook) spectroscopy.

Table 17-5
The effect of the auxochromic amino group upon the UV absorption of the C=C—C=O system

Compound	λ_{max}	log ϵ
$CH_3CH_2CH_2CH{=}CHCOCH_3$	228	4.0
$Et_2NCH{=}CHCOCH_3$	307	4.4
$CH_3{-}\overset{\displaystyle CH_3}{\overset{\vert}{C}}{=}CHCOOEt$	217	4.1
$CH_3{-}\overset{\displaystyle NMe_2}{\overset{\vert}{C}}{=}CHCOOEt$	284	4.5

is greatly enhanced by the presence of the electron-donating $-NR_2$ group:

$$R_2\ddot{N}{-}C{=}C{-}C{=}O \longleftrightarrow R_2\ddot{N}{-}\overset{+}{C}{-}C{=}C{-}O^- \longleftrightarrow R_2\overset{+}{N}{=}C{-}C{=}C{-}O^-$$

The added opportunity for stabilization of the π^* excited state brings the lowest excited state closer to the highest ground state and thus permits a lower energy (longer wavelength) of absorption.

In Table 17-5, each pair of compounds includes one with a fundamental chromophore and another with the same chromophore attached to an auxochromic group.

Exercise 2

Which compound of each of the following pairs would have the longer wavelength λ_{max}? Explain.

(*a*) $CH_3CH{=}CHCH_2CH_2CHO$ and $CH_3CH_2CH{=}CHCHO$

(*b*) $H_2NCH{=}CHCOCH_3$ and $H_3\overset{+}{N}CH{=}CHCOCH_3$

(*c*) $CH_3OCH_2CH{=}CHCOCH_3$ and $CH_3OH{=}CHCOCH_2CH_3$

(*d*) $(CH_3)_2NCH{=}CHCH{=}CHCOOEt$ and $(CH_3)_2NCH{=}CHCOOEt$

(*e*) $(CH_3)_3\overset{+}{N}CH_2CH_2CH{=}CHCOCH_3$ and $(CH_3)_3\overset{+}{N}CH_2CH_2CH_2CH{=}CHCOCH_3$

The effects of auxochromic groups on IR absorption are less dramatic, but nevertheless significant and revealing. These have been discussed earlier (Section 17-6) and should be reviewed here in the light of the foregoing discussion.

18

Carbonyl compounds I: Properties and preparative methods

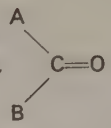
This chapter is the first of several that present the chemistry of one of the principal functional classes of organic compounds, carbonyl compounds. The spectroscopic characteristics of aldehydes and ketones provide excellent examples of how chemical structure and properties can find expression in UV and IR spectral data.

The considerable importance of aldehydes and ketones is reflected in the wide variety of synthetic methods available for their preparation. Those methods described in this chapter find practical application in everyday laboratory investigations and in industrial production. Many aldehydes and ketones are important articles of commerce, finding many uses in direct industrial applications and as starting materials for the preparation of other compounds.

18-1 Classes of carbonyl compounds

Compounds containing the functional group called the *carbonyl group* are a large and important class of substances. This includes compounds of a wide variety of types: aldehydes, ketones, carboxylic acids, and derivatives of carboxylic acids, including esters, amides, halides, and anhydrides. They will first of all be discussed

Table 18-1

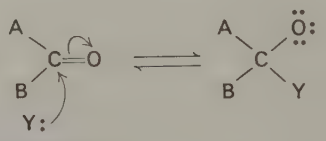
Types of carbonyl compounds, 

A	B	*Compound type*
H	H	formaldehyde*
R	H	aldehyde
R	R′	ketone
R	OH	carboxylic acid
R	OR′	ester
R	X (halogen)	acyl halide
R	OCOR	acid anhydride
R	NH_2, NHR′, NR'_2	amide

* Formaldehyde is a special example of the class of aldehydes, since it is the only compound in which A = B = H.

as a single class because the functional mode of their characteristic reactions is in all cases the same: attack of a nucleophilic agent upon the electron-deficient carbon atom of the  group.

Aldehydes and ketones are distinguished from derivatives of carboxylic acids in the events subsequent to the initial phase of their reactions, but it should always be borne in mind that the primary stage of their reactions can be represented by



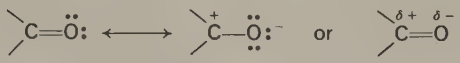
(Nucleophile) (1)

The rate and equilibrium of this initial reaction and events subsequent to it are governed by the nature of the groups A and B attached to the carbonyl carbon atom.

18-2 The carbonyl group

The sharing of four electrons between carbon and oxygen constitutes the carbon-oxygen double bond. The bond angles H—C—O and C—C—O in formaldehyde, acetaldehyde, and acetone are found to be close to 120°, indicating a trigonal planar

configuration. The C=O bond may be compared to the C=C bond; like the latter, it is made up of a two-electron σ orbital and a two-electron π orbital. The bond hybridization is thus sp_2. The principal distinction between the C=O bond and the C=C bond is that (*a*) in the former oxygen possesses two pairs of unshared electrons and (*b*) because of the greater electronegativity of oxygen, the electrons in the C=O bond are unsymmetrically shared, with oxygen the negative end of a C—O dipole:



(2)

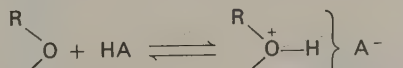
This charge dissymmetry can be seen in the dipole moment of some typical aldehydes and ketones:

	Compound	*Dipole moment (Debye units)*
	$HCHO$	2.3 D
	CH_3CHO	2.7 D
	CH_3COCH_3	2.9 D
compare	$CH_3CH{=}CH_2$	0.3 D
	$(CH_3)_3\overset{+}{N}{-}\overset{-}{O}$	5.0 D

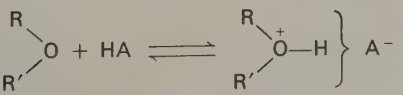
These figures show a definite charge separation in the C=O bond and account for the most characteristic properties of the carbonyl group, namely, *the electrophilic character of the carbon atom, and the ability of the carbonyl group to accept a proton, or coordinate with a Lewis acid, on oxygen.*

18-3 The basic character of the carbonyl group

The unshared electrons on the oxygen atom of the carbonyl group confer (weakly) basic properties upon carbonyl compounds. They may be compared qualitatively with alcohols and ethers, which undergo protonation with strong acids:



(3)



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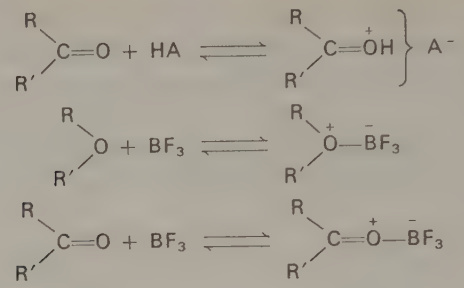


(5)

(6)

(7)

Because of the inherently weak basic character of oxygen (compare water and ammonia as bases), these oxygen-containing compounds are extremely weak bases; nevertheless, as will be seen in what follows, the protonated species is present in acid solutions *and is in many cases the reactive form of the aldehyde, ketone, ester, and so on.*

It should be noted that a protonated ketone is a resonance hybrid in which the positive charge is delocalized over the C—O bond:

(8)

Since the energy of a charged species is lowered by dispersal of charge, it could be anticipated that when one or both of the groups attached to the carbonyl group can accommodate the positive charge, the basicity (ease of protonation) is enhanced. This is illustrated in the following section.

18-4 Spectral characteristics of carbonyl compounds: Infrared spectra

Evidence for the degree of charge delocalization in carbonyl compounds is found in their infrared spectra. The C=O stretching frequencies of a number of carbonyl compounds are given in Table 18-2.

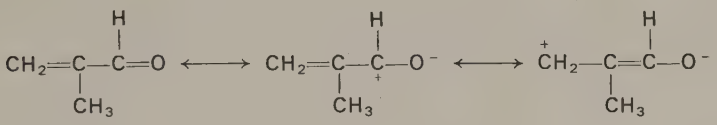
Table 18-2
Infrared C=O stretching frequency of some aldehydes and ketones

Compound	C=O *stretching frequency* (cm^{-1}, *in* CCl_4)
HCHO	1745
CH_3CHO	1733
$(CH_3)_2CHCHO$	1729
CH_3COCH_3	1719
$(CH_3)_2CHCOCH_3$	1719
$(CH_3)_3CCOCH_3$	1711
$(CH_3)_3CCOC(CH_3)_3$	1686

It should be noted that aldehydes have higher C=O frequencies than ketones, with formaldehyde the highest. In formaldehyde, the structure $H_2\overset{+}{C}—\overset{-}{O}$ represents the only dipolar form that can be written. In acetone, however, the positive charge on the carbonyl carbon atom can be further dispersed by participation of the methyl groups, consequently increasing the single-bond character of the C=O bond. (This may be compared with charge dispersal in the *t*-butyl carbonium ion.)

This is more effectively shown when charge dispersal is strongly enhanced by conjugation or the presence of electron-donating groups. Table 18-3 gives some values for C=O absorption that illustrate this.

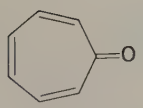
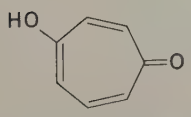
The lowered C=O frequencies for the unsaturated ketones indicate the *enhanced single-bond character* of the C=O bond. This can be attributed to charge dispersal of the following kind:



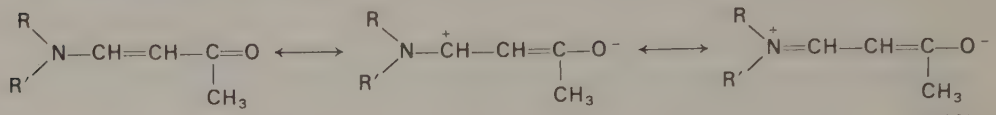
(9)

When the dialkylamino group is present to provide for further charge delocalization,

Table 18-3
Infrared C=O stretching frequencies of some carbonyl compounds

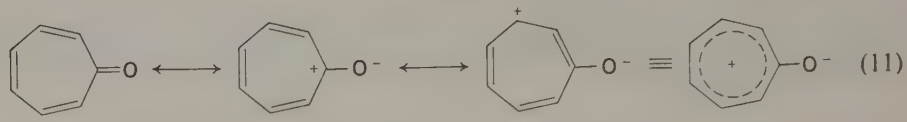
Compound	C=O *stretching frequency* (cm^{-1})
n-alkyl-$COCH_3$	1715–1720
CH_2=$CHCOCH_3$	1689
Et_2NCH=$CHCOCH_2CH_3$	1664
$Et_2NC(CH_3)$=$CHCOCH_3$	1643
 tropone	1638
 4-hydroxytropone	1600

a further decrease in the C=O frequency as seen, indicating a further enhancement of C=O single-bond character:

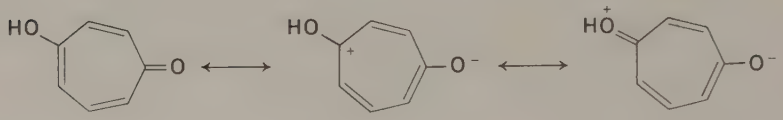


(10)

Tropone and 4-hydroxytropone (Table 18-3) illustrate this even more dramatically:*



(11)

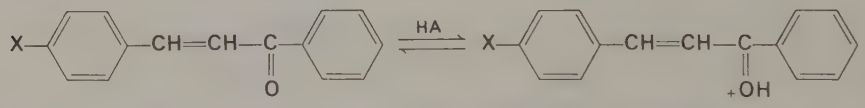


(12)

Exercise 1

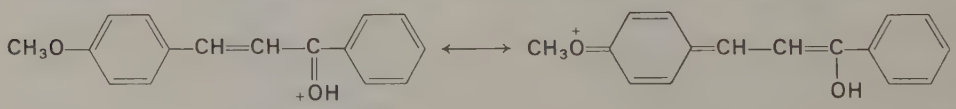
Would the C=O stretching frequency of 4-aminotropone be higher or lower than that of 4-hydroxytropone? Why?

Although the base strengths (that is, the pK_a of the $\rangle C{=}\overset{+}{O}H$ species) of ketones have not been measured extensively, studies have shown a correlation between C=O stretching frequency and ease of protonation. For example,



(13)

When X = $-OCH_3$, this compound is a stronger base than when X = H, because of participation of $-OCH_3$ in delocalization of the + charge upon protonation:



(14)

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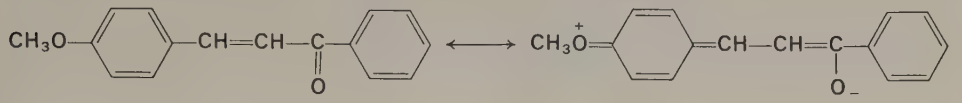
* Not all of the possible contributing structures that can be written are shown in these formulations.

The methoxy compound also has the lower C=O stretching frequency by virtue of the participation of the CH_3O— group in C=O bond lengthening:



(15)

Indeed tropone, the C=O stretching frequency of which shows a pronounced degree of charge delocalization, forms stable and isolable salts with strong acids.

18-5 Spectral characteristics of carbonyl compounds: Ultraviolet spectra

Simple aldehydes and ketones such as acetaldehyde, acetone, and cyclohexanone, in which no unsaturated functional groups are attached to the carbonyl group, show only weak absorption in the ultraviolet region. A low-intensity ($n \rightarrow \pi^*$) absorption is seen in the 280-nm region, but this provides but little useful structural information. Spectral characterization of compounds of this kind is best accomplished by examination of their infrared spectra.

Carbonyl compounds in which π-electron functionality is found attached to the carbonyl group show highly characteristic and diagnostically valuable ultraviolet spectra. In Table 18-4 are given the ultraviolet absorption maxima for a number of unsaturated aldehydes and ketones.

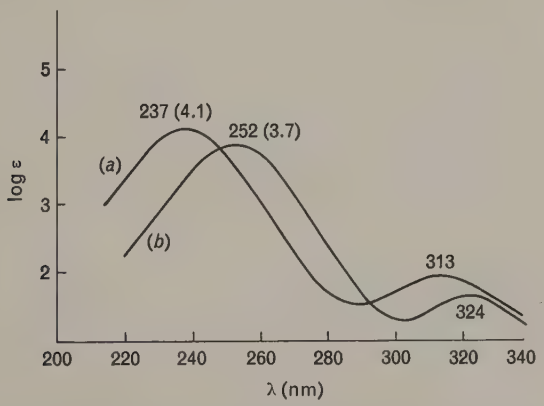


Figure 18-1
Ultraviolet spectra of the α,β-unsaturated ketones (*a*) mesityl oxide (4-methyl-3-penten-2-one) and (*b*) pulegone.

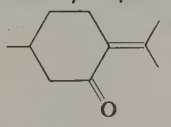
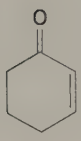
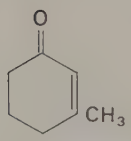
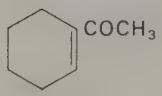
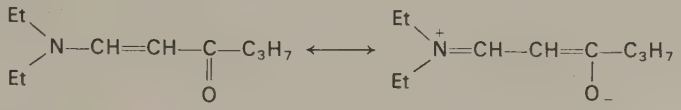


Table 18-4
Ultraviolet absorption maxima (for $\pi \rightarrow \pi^*$ transitions) for some selected α,β-unsaturated carbonyl compounds in ethanol solution. Extinction coefficients are omitted; all are in the range ϵ = about 10,000.

Compound	λ_{max} (*nm*)
$CH_2{=}CHCHO$	208
$CH_2{=}CHCOCH_3$	219
$CH_2{=}C(CH_3)COCH_3$	220
$CH_3CH{=}C(CH_3)COCH_3$	230
$CH_3C(CH_3){=}CHCOCH_3$	237
$CH_3C(CH_3){=}C(CH_3)COCH_3$	247
	225
	235
	232
$Et_2NCH{=}CHCOCH_2CH_2CH_3$	307
$CH_3C(CH_3){=}CHCOOEt$	217
$CH_3C(NMe_2){=}CHCOOEt$	284

It should be noticed that the UV maxima range from 208 nm for the simplest (acrylaldehyde) to 247 nm for 3,4-dimethyl-3-penten-2-one. The large effect upon the position of the maximum caused by the introduction of the diethylamino group (307 nm for 1-diethylamino-1-hexen-3-one) can be attributed to the electron-donating property of the amino nitrogen atom, which contributes to electron delocalization in the following way:



(16)

A similar increase in the λ_{max} of unsaturated carbonyl compounds is seen in poly-unsaturated aldehydes and ketones, in which there is increased opportunity for charge delocalization (Table 18-5).

Table 18-5
Ultraviolet absorption maxima ($\pi \rightarrow \pi^*$ transitions only) for unsaturated aldehydes and ketones, showing the bathochromic effect of extended conjugation (λ_{max} in nm)

Compound	$\lambda_{max}(\epsilon)$
$(CH_3)_2C{=}O$	189 (900)
$CH_3CH{=}CHCHO$	217 (15,000)
$CH_3CH{=}CH{-}CH{=}CHCHO$	270 (27,000)
$CH_3(CH{=}CH)_3CHO$	312 (40,000)

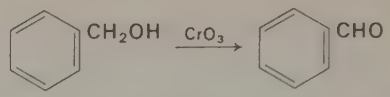
UV absorption spectra for two representative α,β-unsaturated ketones are shown in Figure 18-1. It should be noted that a second, low-intensity maximum is seen at about 310–325 nm ($n \rightarrow \pi^*$ transition). The appearance of this absorption peak is often of value in the spectral characterization of α,β-unsaturated ketones.

18-6 Synthesis of aldehydes and ketones

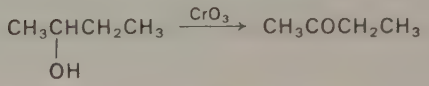
The introduction of the carbonyl group is usually accomplished by modifying an existing functional group.

Oxidation of alcohols. Oxidation and oxidizing agents will be dealt with in detail in a later chapter (Chapter 36). Primary alcohols can be oxidized to aldehydes; secondary alcohols can be oxidized to ketones. Tertiary alcohols are resistant to oxidation, but under vigorous conditions may be oxidized with fragmentation or rearrangement of the molecule.

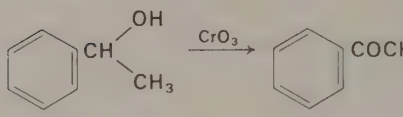
$$CH_3CH_2OH \xrightarrow{CrO_3} CH_3CHO \qquad (17)$$



(18)



(19)



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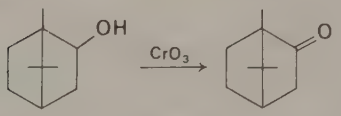

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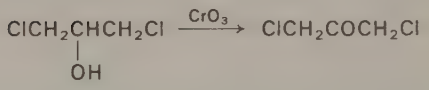
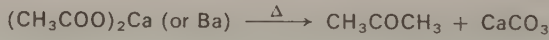


(22)

Exercise 2

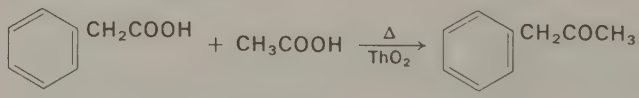
Using acetaldehyde as one starting material, and any other necessary reagents, show how you could synthesize (*a*) 3-methyl-2-butanone, (*b*) methyl phenyl ketone, (*c*) acetylcyclohexane, (*d*) 2-heptanone, and (*e*) 4-penten-2-one.

Carboxylic acids. Although not a widely used procedure, the pyrolysis of metal salts of carboxylic acids can be a convenient route to ketones.



(23)

"Mixed" ketones can be prepared in this way by the pyrolysis of mixtures of carboxylic acid salts. Dicarboxylic acids give cyclic ketones:*



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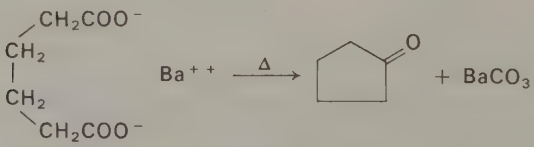

(25)

The method is not generally applicable to the preparation of cyclic ketones of less than 5- or more than 6-membered rings.

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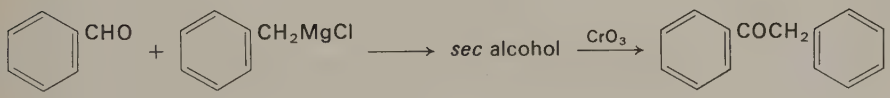
* This reaction may be performed by passing the vaporized acid or mixture of acids through a heated tube containing a heavy metal oxide. When two acids are used, there is formed a mixture of three ketones, which must be separated by usual methods (distillation, crystallization, and so on).

The oxidation of primary alcohols to aldehydes is often unsatisfactory because of the sensitivity of the aldehyde to further oxidation to the acid, but special methods have been devised in recent years to make this method practicable. Secondary alcohols can be oxidized to ketones without difficulty, and the reaction is ordinarily carried out with the use of chromic acid (Cr^{VI}) in aqueous solution, or in acetic acid, acetone, or pyridine as the solvent medium. Under the mild conditions ordinarily used (that is, at room temperature) further oxidation of the resulting ketone does not usually occur, and good yields are obtained. Because of the ease of preparation of secondary alcohols by the Grignard reaction, ketones of many structural types are readily accessible; for example:

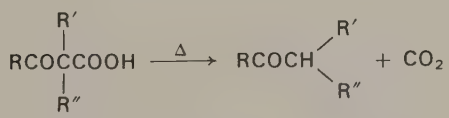
$$CH_3CH_2CHO + (CH_3)_2CHMgBr \longrightarrow CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH(CH_3)_2 \xrightarrow{CrO_3} CH_3CH_2COCH(CH_3)_2 \qquad (26)$$



(27)

Decarboxylation of β-keto acids. β-Keto carboxylic acids readily lose carbon dioxide upon moderate heating (for example, at the melting point) to form ketones:

$$RCOCH_2COOH \xrightarrow{\Delta} RCOCH_3 + CO_2 \qquad (28)$$



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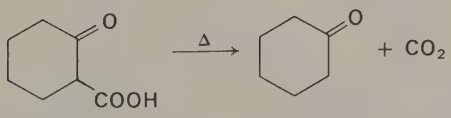

(30)

When the required β-keto acids can be readily prepared (see Chapter 24), this reaction is a convenient and efficient route to ketones of many kinds.

The biological decarboxylation of β-keto acids plays an important role in many metabolic processes. The formation of excessive amounts of acetone in persons suffering from diabetes is the result of a metabolic derangement in which β-ketobutyric (acetoacetic) acid accumulates and undergoes decarboxylation (under the catalytic influence of an enzyme):

$$CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOH \xrightarrow{-2H} CH_3COCH_2COOH \xrightarrow{-CO_2} CH_3COCH_3* \qquad (31)$$

Many methyl ketones occur in nature as the products of metabolism in higher plants. It has been demonstrated in many cases, and is a reasonable presumption in many others, that these compounds arise by the biological decarboxylation of a β-keto acid precursor. The β-keto acid (and the final ketone) may be formed by a series of reactions such as the following:†

$$RCH_2CH_2COOH \xrightarrow{-2H} RCH{=}CHCOOH \xrightarrow{+H_2O} R\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOH \xrightarrow{-2H} RCOCH_2COOH \xrightarrow{-CO_2} RCOCH_3 \qquad (32)$$

or it may be produced by a reaction of the following kind:

$$\underset{\text{Acyl coenzyme A}}{RCO{-}SCoA} + \underset{\text{Acetyl CoA}}{CH_3CO{-}SCoA} \longrightarrow RCOCH_2CO{-}SCoA + CoA{-}SH$$
$$\Big\downarrow \text{hydrolysis} \qquad (33)$$
$$RCOCH_2COOH + CoA{-}SH$$

The chemistry of acyl-CoA esters will be considered in Chapter 23.

Organometallic compounds. Grignard reagents can add to the cyano group of nitriles to yield imino compounds that, as Schiff bases (Section 19-8), are readily hydrolyzed to ammonia and the ketones:

$$RC{\equiv}N + R'MgX \longrightarrow R{-}\underset{\displaystyle R'}{\underset{|}{C}}{=}NMgX \xrightarrow{H_2O} R{-}\underset{\displaystyle R'}{\underset{|}{C}}{=}NH \xrightarrow[H^+]{H_2O} RCOR' + NH_4{}^+ \qquad (34)$$

Methyllithium reacts with carboxylic acids to yield methyl ketones. It is to be noted that the relatively less reactive Grignard (organomagnesium) reagents do not react with carboxylic acids past the initial unproductive step of formation of the halomagnesium salt:

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* The biological dehydrogenation has been discussed earlier (Chapter 11). The decarboxylation is catalyzed by a specific enzyme called a decarboxylase.

† In the actual metabolic process the acid is in the form of its coenzyme-A ester; the final steps involve hydrolysis of the ester, followed by decarboxylation.

$$RCOOH + R'MgX \longrightarrow RCOOMgX + R'H^{*} \quad (35)$$

$$RCOOMgX + R'MgX \longrightarrow \text{no further reaction} \quad (36)$$

It is for this reason that carboxylic acids can be synthesized successfully by the reaction of Grignard reagents with carbon dioxide:

$$RMgX + CO_2 \longrightarrow RCOOMgX \xrightarrow[H^+]{H_2O} RCOOH + Mg^{++} \text{ salts} \quad (37)$$

With the more reactive methyllithium, the reaction of CH_3Li with RCOOLi leads to the addition product:

$$RCOOLi + CH_3Li \longrightarrow RC(OLi)_2CH_3 \quad (38)$$

At low temperatures the addition product is stable and does not break down into Li_2O and $RCOCH_3$ (in which case further addition to $RCOCH_3$ would yield a tertiary alcohol). Hydrolysis leads to the methyl ketone:

$$RC(OLi)_2CH_3 \xrightarrow[H^+]{H_2O} RCOCH_3 + Li^+ \text{ salts} \quad (39)$$

Organocadmium compounds are relatively unreactive toward most types of carbonyl compounds, but react readily with acyl halides to yield ketones. The method is versatile, for R_2Cd compounds are readily prepared by the reaction of Grignard reagents with anhydrous cadmium chloride ($CdCl_2$) in ether solution:

$$2RMgX + CdCl_2 \longrightarrow R_2Cd + 2MgX_2 \quad (X = Br, Cl, \text{ or } I) \quad (40)$$

The reaction with an acyl chloride proceeds as follows:

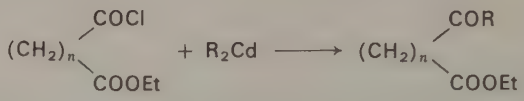
$$2RCOCl + R'_2Cd \longrightarrow 2RCOR' + CdCl_2 \quad (41)$$

The method has the special advantage of permitting the use of acid chlorides whose structures include additional functional groups that, although reactive toward organomagnesium compounds, are not attacked by dialkylcadmiums:

$$\begin{matrix} CH_2CH_2COCl \\ | \\ CH_2CH_2COOEt \end{matrix} + Et_2Cd \longrightarrow \begin{matrix} CH_2CH_2COEt \\ | \\ CH_2CH_2COOEt \end{matrix} \quad (42)$$

* Grignard reagents react with compounds containing ionizable (acidic) hydrogen to form the hydrocarbon RH, corresponding to RMgX. Acids, alcohols, amines, phenols, and even some hydrocarbons (for example, acetylenes) behave in this manner. The Zerewitinov determination of "active hydrogen" depends upon this reaction. Treatment of a measured amount of the compound to be analyzed with a measured amount of a standardized methylmagnesium iodide solution is followed by measurement of the volume of methane evolved.

or in general,



(43)

Aldehydes can be prepared by the reaction of Grignard reagents with orthoformic esters:

$$RMgX + HC(OEt)_3 \longrightarrow RCH(OEt)_2 + EtOMgX \qquad (44)$$

The immediate product of this reaction is an acetal, which is readily hydrolyzed under acidic conditions to yield the aldehyde.

Variants of this process, such as the use of ethoxymethyleneaniline ($EtOCH{=}NC_6H_5$) instead of the orthoester, are also useful.

Exercise 3

Write the sequence of steps through which the reaction of a Grignard reagent with ethyl orthoformate, $HC(OEt)_3$, proceeds. HINT: The initial stage is coordination of RMgX with the oxygen atom of one of the —OEt groups.

Exercise 4

Formulate the reaction of phenylmagnesium bromide with $EtOCH{=}NC_6H_5$, and the succeeding steps leading at length to benzaldehyde. NOTE: The —CH=N— grouping may be regarded as an analog of the carbonyl group.

Other methods. A variety of methods applicable to the synthesis of aldehydes and ketones have been or will be encountered in various parts of the text. Among these are:

(*a*) The hydration of alkynes (Chapter 10).
(*b*) The Friedel-Crafts and related reactions for the preparation of alkyl aryl ketones and aromatic aldehydes (Chapter 28).
(*c*) The rearrangement of 1,2-glycols (Chapter 13).
(*d*) The ozonolysis of alkenes (Chapter 10).
(*e*) The hydrolysis of 1,1-dihalides.
(*f*) The preparation of acetone from cumene hydroperoxide (Chapter 34).
(*g*) The Oppenauer oxidation, which involves the transfer of hydrogen from an alcohol to a ketone under the catalytic influence of an aluminum alkoxide. This is a reversal of the Meerwein-Ponndorf-Verley reaction (Chapter 11).

Problems

1. Account for the fact that although the C=O stretching frequency (IR) of acetaldehyde is 1733 cm^{-1}, that of trichloroacetaldehyde (Cl_3CCHO) is 1768 cm^{-1}.

2. Simple ketones of the class $R(CH_2)_nCOCH_3$ show IR absorption (C=O band) at about 1715 cm^{-1}. Would you expect to find the C=O absorption of an amide $R(CH_2)_nCONH_2$ at a higher or lower frequency (that is, wave number)? Why?

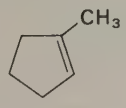
3. The IR absorption (C=O band) of $(CH_3)_2NCH{=}CHCOCH_3$ is at 1664 cm^{-1}. What would you expect that of the corresponding quaternary ammonium compound, $CH_3COCH{=}CHN(CH_3)_3{}^+Br^-$, to be?

4. A neutral compound, C_5H_9NO, showed strong IR absorption at about 1690 cm^{-1}, but no significant UV absorption above 200 nm. Write a structure that agrees with these observations.

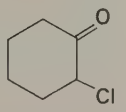
5. A compound (A), C_6H_8O, showed a UV maximum at 217 nm ($\log \epsilon = 4.3$). Upon catalytic hydrogenation it absorbed 2 moles of hydrogen to give (B), $C_6H_{12}O$. B showed no significant UV absorption above 200 nm and had an IR absorption peak at about 1730 cm^{-1}. Write structures for A and B that are in accord with these results.

6. Show the steps and reagents by which the following overall transformations can be carried out. More than one step will be needed; in (*a*), (*c*), and (*d*) the starting compound given is the only organic reagent to be used.

(*a*) $CH_3CH_2OH \dashrightarrow CH_3COCH_2CH_3$

(*b*) $HOOC(CH_2)_4COOH \dashrightarrow$ 

(*c*) $(CH_3)_2CHBr \dashrightarrow CH_3{-}\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}{-}CH(CH_3)_2$

(*d*) cyclohexene $\dashrightarrow$ 

(*e*) $(CH_3)_2C{=}CH_2 \dashrightarrow (CH_3)_2CHCH_2COCH_3$

(*f*) $CH_3COCOCH_3 \dashrightarrow (CH_3)_3CCOCH_3$

19

Carbonyl compounds II: Addition reactions

This chapter presents the most characteristic aspect of the chemical reactivity of carbonyl compounds: addition to the carbonyl group. This general reaction takes a great many forms, which, however disparate they may appear, will all be seen to be expressions of the electrophilic character of the carbonyl carbon atom. The representative examples described here include reactions used in synthesis, in characterization, in identification, and in separation and purification.

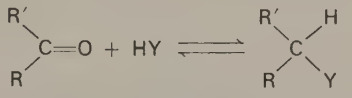
The rate and equilibria of carbonyl addition reactions are greatly influenced by the nature of the substituents R and R′ (in the general expression R—CO—R′). We shall see that similar substituent effects, both steric and electronic in nature, influence the reactivity of carbonyl compounds other than aldehydes and ketones. Attention will be directed to these in chapters to follow.

Many reactions that occur in biological systems involve addition to carbonyl groups; understanding the factors that influence the rates and equilibria of these reactions (for example, the transamination reaction described in this chapter) is valuable for recognizing the principles that govern many cellular processes.

19-1 Addition to the carbonyl group. Nucleophilic attack

The dipolar character of the carbonyl group, induced by the electronegativity of oxygen, *confers electrophilic character upon the carbonyl carbon atom* and renders it

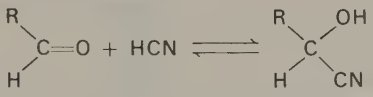
susceptible to nucleophilic attack. The overall process, in which the nucleophile is the conjugate base, $Y:^-$, of the compound H:Y, can be seen to be *an addition to the carbon-oxygen double bond*:



(1)

Reactions of this kind are commonly referred to as *carbonyl addition reactions*, although, as will be seen shortly, the initial product of nucleophilic attack may undergo further changes other than simple acceptance of a proton.

A well-studied case of the simple addition reaction is the addition of hydrogen cyanide, HCN, to an aldehyde or ketone:



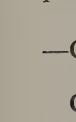
(2)

The formation of the final product, called a cyanohydrin, is acid-base catalyzed. That is, it depends upon conditions of pH that provide both for the presence of the cyanide ion, CN^-, and for proton donors. At very low pH the concentration of CN^- is small because of the suppression of the ionization

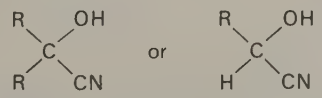
$$HCN \rightleftharpoons H^+ + CN^- \tag{3}$$

and at high pH, the intermediate anionic addition product will not be protonated to form the cyanohydrin. Studies of this reaction have shown that the *rate of formation* of the cyanohydrin is governed by the rate of the initial step, in which cyanide ion adds to the carbonyl carbon atom. Consequently, the preparation of cyanohydrins is carried out in a buffered medium in the intermediate pH range of about 5, in which both CN^- and a proton donor (for example, HCN itself) are present.

The addition of HCN is a reversible reaction, which is often utilized in the preparation of ketones. That is to say, if a compound containing the structural unit

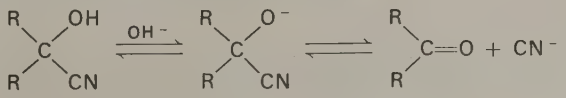


can be prepared (by any means), it is subject to the reversibility expressed in (2). Thus, the cyanohydrins



(4)

readily yield the corresponding carbonyl compounds, the equilibrium being displaced in this direction by the use of alkali (high pH):



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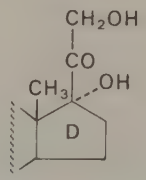
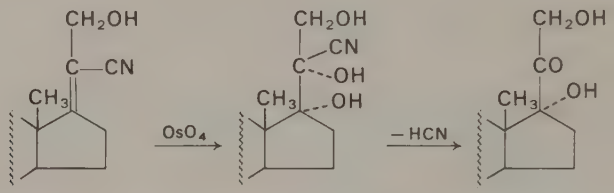
An example of this is found in the field of steroid synthesis. The corticosteroids are characterized by their possession of a D-ring with the structure



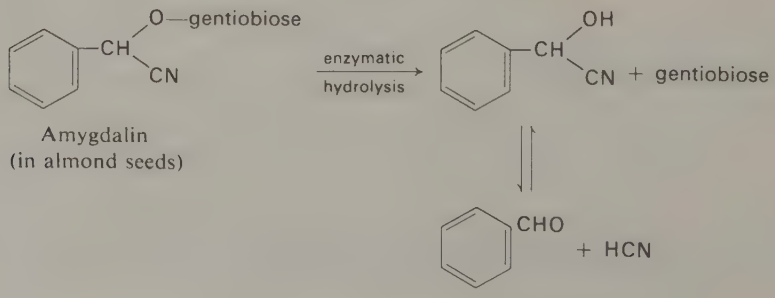
The introduction of the tertiary —OH group and formation of the carbonyl group has been accomplished by the following reactions:



(6)

It will be recognized that the intermediate compound, formed by hydroxylation of the carbon-carbon double bond with osmium tetroxide, is the cyanohydrin of the final ketone. In this case (and in most cases) the ketone ⇌ cyanohydrin equilibrium is to the side of (ketone + HCN); it can be made complete, with liberation of the ketone, by raising the pH to alkaline values.

Another example of the reversibility of the cyanohydrin reaction is found in a group of naturally occurring compounds known as "cyanogenetic" glycosides.* These compounds are *O*-glycosides of cyanohydrins. When the sugar residue is removed, usually by enzymatic hydrolysis, the resulting aglycon is a ketone or aldehyde cyanohydrin, and is a source of free HCN by virtue of the carbonyl ⇌ cyanohydrin equilibrium:



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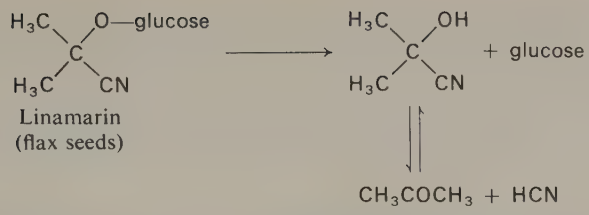
* Cyanogenetic means cyanide generating.

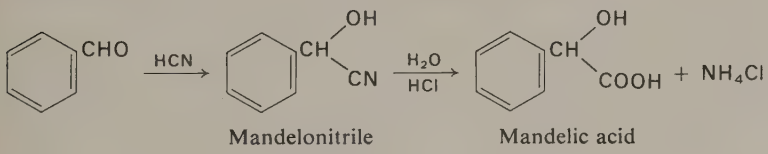


(8)

Cyanogenetic glycosides are found in some forage plants; they are responsible for serious losses of stock, in which death is due to cyanide poisoning by ingestion of the plants.

The controversial anti-cancer drug "laetrile" (which many medical authorities believe ineffective) is a crude cyanogenetic glycoside, whose putative activity is said to stem from its potential ability to release HCN *in vivo*.

Cyanohydrins are useful synthetic intermediates. They can be hydrolyzed with mineral acids to yield α-hydroxy acids, reduced (with $LiAlH_4$, or catalytically) to amino alcohols, or dehydrated to unsaturated nitriles:



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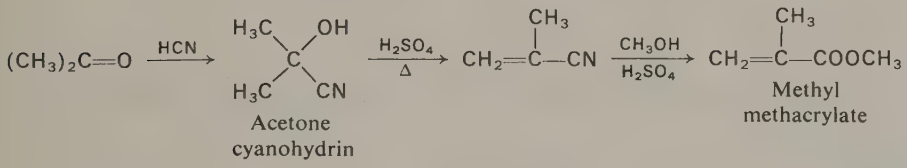

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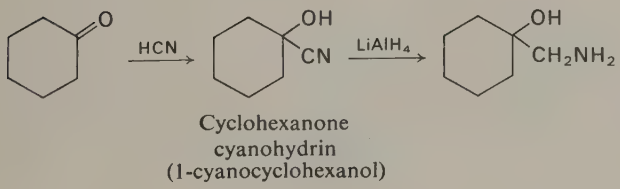
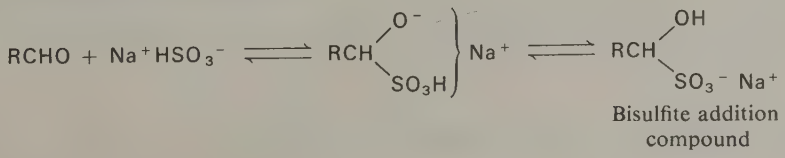


(11)

19-2 Bisulfite addition compounds

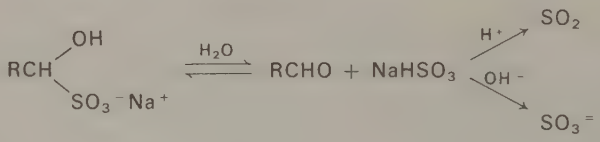
Most aldehydes, and simple ketones such as acetone, 2-butanone, and cyclohexanone, add sodium bisulfite in the reaction



(12)

The final addition product, which is water-soluble, is usually precipitated as the crystalline sodium salt when saturated aqueous sodium bisulfite is used. The formation of a bisulfite addition compound is a valuable diagnostic indication of the character of the carbonyl compound, for ketones RCOR in which neither of the R groups is methyl do not form the addition product in useful amount, owing to an unfavorable equilibrium.

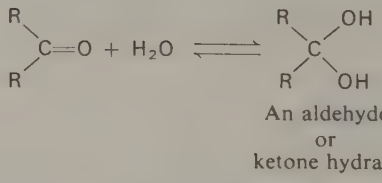
The principal uses of the bisulfite addition reaction are (*a*) for the characterization of aldehydes, low-molecular-weight methyl ketones, and cyclohexanones and (*b*) for the separation of mixtures. For example, if a mixture of benzaldehyde and acetophenone is shaken with a saturated aqueous solution of $NaHSO_3$, the bisulfite addition compound of benzaldehyde will separate in crystalline form; the acetophenone, which does not form a bisulfite compound, can be separated by filtration. The crystalline benzaldehyde bisulfite addition compound, washed with ether (in which, as a salt, it is insoluble) to remove traces of contaminants, can be converted into benzaldehyde by treatment with acid or base. Since the bisulfite addition reaction is reversible, raising or lowering the pH regenerates the carbonyl compound by destroying the bisulfate ion:



(13)

19-3 Addition of water and alcohols. Hydrates and hemiacetals

The equilibrium

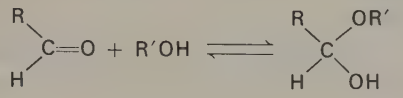


(14)

is real, and aqueous solutions of most aldehydes and ketones may be assumed to contain some of the hydrated form. In fact, however, the degree of hydration is extremely small for any but the simplest aldehydes, and stable hydrates are rare.* Formaldehyde is hydrated in aqueous solution, in which it exists largely as the hydrate $CH_2(OH)_2$; but the percentage of hydrate in the equilibrium formulated above is in most other cases very small.

* Except for the special examples discussed in Section 19-6.

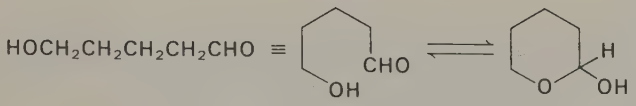
Alcohols add to the carbonyl group in the same way, giving the *hemiacetal*:



(15)

As in the case of hydration, the hemiacetal formation equilibrium is usually far to the left, and few acyclic hemiacetals are known as isolable substances.

Important exceptions to these generalizations about hemiacetal formation are the cyclic hemiacetals having 5- and 6-membered rings. In cases such as the following, the equilibrium is largely to the right—the cyclic hemiacetal is the principal component of the equilibrium mixture:



(16)

In *cyclic* hemiacetal formation the entropy factor for reaction is highly favorable, for the reacting groups (—OH and —CHO) are so disposed as to maximize the opportunities for interaction. In the case of the reaction of an alcohol and an aldehyde as separate molecules, one requirement for interaction is the decrease in entropy of the system necessary to bring the alcohol and aldehyde from a random relationship to the specific arrangement necessary for the nucleophilic attack of the alcoholic hydroxyl group upon the carbonyl carbon atom.

The best known examples of cyclic hemiacetals are those of the sugars, which have been discussed in Chapter 14. It will be recalled that an aldose—for example, glucose—exists largely in the cyclic (pyranose or furanose) form. The percentage of the "free" aldehyde form in solution is very small (usually only a few percent). It will also be recalled, moreover, that sugars such as glucose, fructose, ribose, and so on react to give derivatives of the "free" aldehyde form (oximes, osazones, and so on). The small amount of the aldehyde form in equilibrium reacts as such, the open-chain $\rightleftharpoons$ pyranose equilibrium providing more aldehyde as it is consumed in the reaction.

19-4 Acetal formation

The mechanism of acetal formation has been discussed in Chapter 12. Acetals are important derivatives of carbonyl compounds: it will be recalled that the acetal grouping is stable under alkaline conditions but is readily hydrolyzed by water with acid catalysis. Thus, "protection" of the carbonyl group by acetal formation is a device often useful in synthetic manipulations.

Although acetals of aldehydes are readily prepared, the formation of acetals

between monofunctional alcohols (such as methanol or ethanol) and most ketones is difficult to accomplish in good yield, for the equilibrium is unfavorable. The use of the bifunctional alcohol ethylene glycol overcomes this unfavorable equilibrium (for reasons related to those that permit the formation of stable cyclic hemiacetals), and good yields of the cyclic acetals or ketals are readily obtained.

Exercise 1

Formulate all the steps in the formation of the cyclic acetal by the acid-catalyzed reaction between acetone and ethylene glycol.

Exercise 2

An optically active compound (A), $C_7H_{14}O_2$, is unaffected by aqueous alkali. When its solution in dilute aqueous HCl is distilled, a compound (B), C_3H_6O, is found in the distillate. Compound B does not reduce Tollens' reagent or Fehling's solution (oxidizing test reagents, see next section). The aqueous solution after distillation of B is still optically active, but after the addition of sodium periodate the optical activity disappears. Write a structure for A that accounts for these observations.

19-5 Tests for aldehydes and ketones and differentiation between them

The addition of bisulfite and HCN is not a property of aldehydes only, but of certain kinds of ketones (for example, R—$COCH_3$) as well. Thus, the classification of an unknown carbonyl compound as an aldehyde cannot safely be based solely upon the observation that it forms a cyanohydrin or a bisulfite addition compound. On the other hand, a carbonyl compound that does not react in either of these ways is probably not an aldehyde. The clearest distinction between aldehydes and ketones lies in the ease with which aldehydes can be oxidized to acids with certain reagents, and the stability of ketones to these reagents. Two oxidizing agents that are commonly used for such tests are Tollens' reagent and Fehling's solution (or the very similar Benedict's reagent). Tollens' reagent is an ammoniacal solution of the silver-ion/ammonia complex; it is readily reduced by easily oxidized compounds to form metallic silver (as a black precipitate or a silver mirror):

$$Ag^+(NH_3)_2 + RCHO \longrightarrow RCOOH + \underline{\underline{Ag}} \qquad (17)$$

The criterion of a positive test is the appearance of metallic silver; the organic products of the oxidation are usually not demonstrated as the test is ordinarily performed.

Fehling's solution and Benedict's reagent are both cupric complexes, and a readily oxidized compound reduces the cupric ion to the cuprous state, with the formation of an orange to red precipitate of cuprous oxide (Cu_2O).

Neither Tollens' reagent nor Fehling's solution is specific for aldehydes, since other easily oxidized compounds also give positive tests. But if it is a matter of distinguishing between simple aldehydes and ketones, only aldehydes will give positive tests, while ketones will not. In Chapter 14 it was noted that the sugar fructose reduces Fehling's solution and Tollens' reagent. Fructose is a hydroxy ketone, containing the grouping —CO—CH(OH)—; it has been found that Fehling's solution also oxidizes other compounds with this structure. For example, acetoin, $CH_3COCHOHCH_3$, gives a positive Fehling's test. Simple dialkyl ketones, however, do not.

Aldehydes can also be recognized by their ability to react with Schiff's reagent. This reagent is formed by adding sulfur dioxide to a solution of a magenta dye called *fuchsin*, which causes the decolorization of the dye. Aldehydes react with the solution of the decolorized dye in a complex reaction that results in the reappearance of a magenta color (not identical to the original dye). Ketones do not restore the color.

Exercise 3

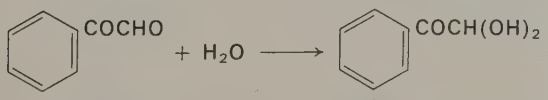
Prepare a summary, in tabular form, of the behavior of aldehydes and ketones with the diagnostic and derivative-forming reagents that have been discussed.

19-6 Stable hydrates of carbonyl compounds

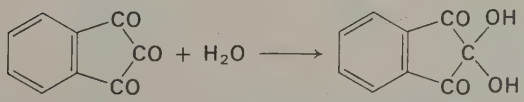
Certain aldehydes and ketones not only add the elements of water rapidly but form stable hydrates that can be isolated as distinct compounds. The following are some compounds that show this behavior:

$$Cl_3CCHO + H_2O \longrightarrow Cl_3CCH(OH)_2 \quad (18)$$

Chloral hydrate

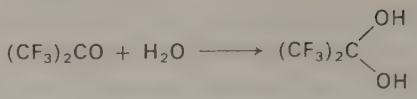


(19)



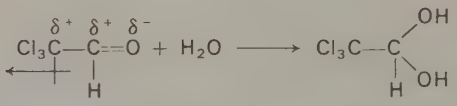
(20)

Ninhydrin



(21)

Note that all of these compounds possess a feature in common: one or both of the groups attached to the hydrated carbonyl group (—CCl_3, —CF_3, —CO—) are strongly electron-attracting. The reason for the favorable equilibrium in these hydration reactions is that in the free carbonyl compound there exist dipole interactions due to the positive charges on the contiguous carbon atoms. Addition of water to the carbonyl group of chloral is favored, even more than addition to the carbonyl group of acetaldehyde itself, for the destabilizing effect of the contiguous positive charges is diminished on hydration:



(22)

Inductive effect of chlorine

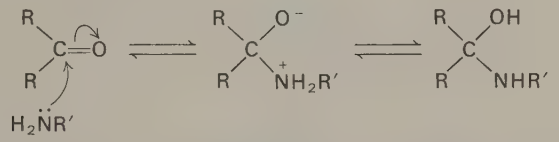
The infrared data in Table 19-1 show that compounds like chloral and hexafluoroacetone have greatly diminished single-bond character in the C=O group, an indication that the form $R\overset{+}{C}H—O^-$ makes a smaller contribution to the hybrid when the substituents on R are electron withdrawing. In particular, the data indicate that the structure $Cl_3C\overset{+}{C}H—\overset{-}{O}$ makes a smaller contribution than does the structure $CH_3\overset{+}{C}H—\overset{-}{O}$ in the respective aldehydes.

Table 19-1
C=O stretching frequencies in the infrared for some α-halogenated aldehydes and ketones, compared with acetaldehyde and dimethyl ketone

Compound	C=O *stretching frequency* (cm^{-1} *in* CCl_4)
(CH_3CHO)	(1733)
$ClCH_2CHO$	1742
Cl_2CHCHO	1748
Cl_3CCHO	1768
(CH_3COCH_3)	(1719)
F_3CCOCF_3	1780
$CH_2=CHCH_2COC_3F_7$	1773

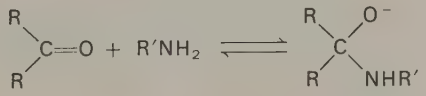
19-7 Addition of ammonia and amines

The better the nucleophile the more complete the addition to the carbonyl group; that is, the equilibrium in the addition reaction is more favorable to product than to reactants. Amines are effective nucleophiles, a property that reflects their basicity. Simple addition of ammonia or an amine to an aldehyde or ketone occurs by way of a nucleophilic attack identical in kind with that described as the fundamental mechanism of the carbonyl addition reaction:



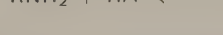
(23)

This addition reaction, like those involving hydrogen cyanide and sodium bisulfite, is strongly pH dependent: it is very slow at low pH, when the amine is largely protonated (RNH_3^+) and thus not nucleophilic; and it does not lead to the final addition product at high pH, where the equilibrium can be written



(24)

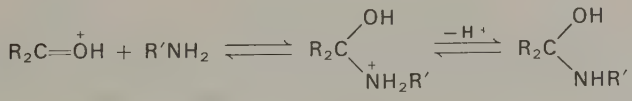
At intermediate pH (say, in the region 4 to 6), both the nucleophilic species RNH_2 and the proton-donating species RNH_3^+ are present in the acid-base equilibrium



(25)

and the reaction proceeds to give the addition product. Since protonation of the carbonyl oxygen atom, which can occur at intermediate pH, increases the electrophilic character of the carbonyl carbon atom, the separate expressions given above can be summarized in more explicit terms:

(26)

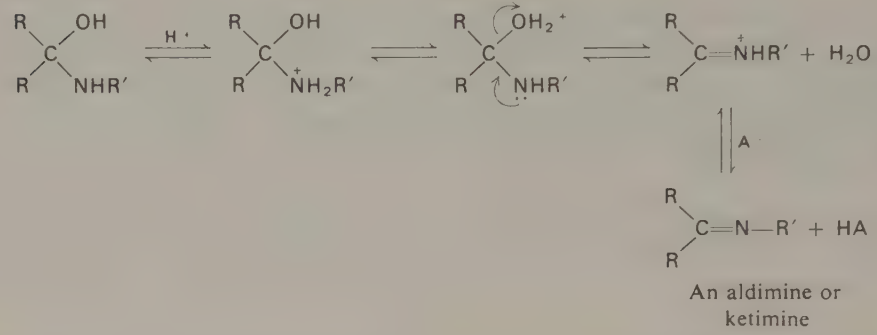


(27)

19-8 Schiff bases. Ketimines and aldimines

Relatively few carbonyl-group amine adducts are stable in the hydroxyamino form; in most cases they undergo loss of the elements of water to generate a C=N bond.

This dehydration step under the mildly acidic conditions of the addition reaction may be pictured as follows:



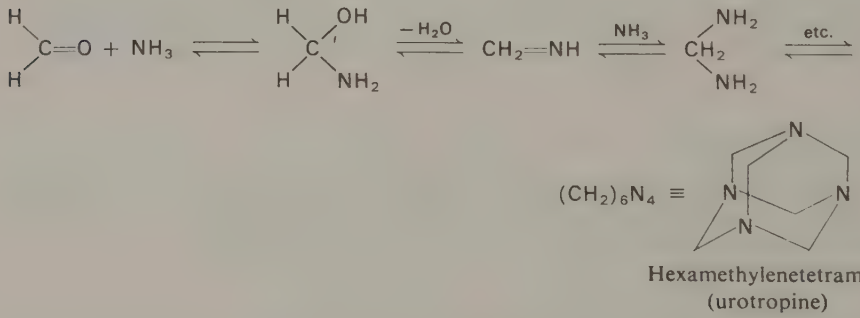
(28)

An aldimine or ketimine

The overall rate of formation of the final product as a function of the pH of the reaction mixture is shown graphically in Figure 19-1.

Compounds having the general structures RCH=NR′ and R_2C=NR′ are called, respectively, *aldimines* and *ketimines*; they are commonly referred to as *Schiff bases.*

Schiff bases of lower-molecular-weight aldehydes are usually unstable and polymerize in solution, probably by continued addition of the amine to the C=N linkage. The simplest Schiff base, that derived from formaldehyde and ammonia, is an intermediate in a reaction that yields a compound derived from six CH_2O and four NH_3:



(29)

Hexamethylenetetramine (urotropine)

The product of this reaction, hexamethylenetetramine, also called *methenamine* or *urotropine*, is a useful medicinal agent, effective as a urinary tract antiseptic. Under the slightly acidic conditions of the urinary tract it slowly decomposes (by hydrolytic reversal of its formation) to produce formaldehyde. Since urotropine is an amine, it forms salts with carboxylic acids. The usual medicinal form is the salt of urotropine with mandelic acid.

Schiff bases of aromatic aldehydes are usually stable, and are often crystalline compounds useful in characterization and identification. The special classes of Schiff

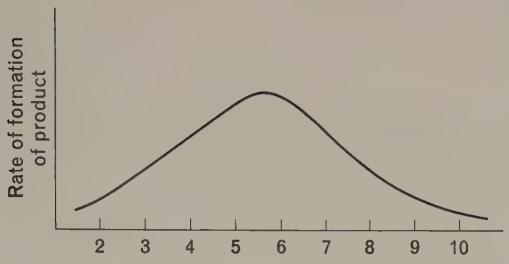


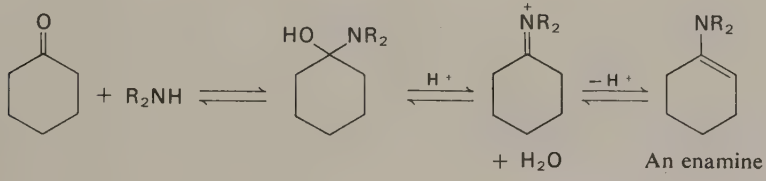
Figure 19-1
Effect of pH on the formation of the product in the reaction

$$R_2C{=}O + R'NH_2 \rightleftharpoons R_2C{=}NR' + H_2O$$

bases prepared from derivatives of ammonia such as X—NH_2, where X = OH, RNH—, and other substituents, are described in Section 19-11.

19-9 Reaction of carbonyl compounds with secondary amines

An aldehyde or ketone cannot yield a Schiff base by reaction with a secondary amine, for the initial adduct $-\overset{\displaystyle NR_2}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-$ cannot lose the elements of water to form a C=N bond. In the presence of an acid catalyst, however, the adduct can lose the elements of water in another way to form an unsaturated amine called an *enamine*:



(30)

The overall reaction as shown here consists of a series of related equilibria, but can be brought to practical completion by removing the water from the reaction mixture. This can be accomplished by refluxing a mixture of, for example, cyclohexanone, dimethylamine, and toluene with a small amount of a sulfonic acid. The water formed in the reaction is azeotropically distilled and collected in a trap where its volume can be measured. After the theoretical amount of water has been collected the enamine can be isolated by distillation.

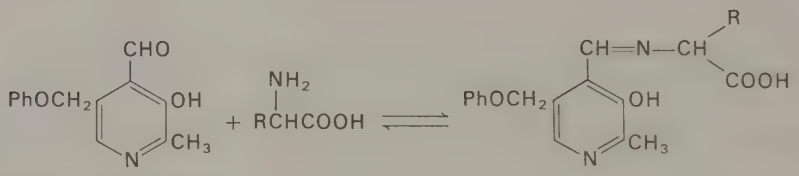
Enamines are valuable reagents for synthesis. Their use in carbon-alkylation and -acylation reactions is discussed in Chapter 23.

Exercise 4

Write equations for the formation of the enamines prepared from (*a*) diethyl ketone and pyrrolidine; (*b*) acetone and diethylamine; and (*c*) cyclopentanone and piperidine.

19-10 Schiff bases in biological transformations

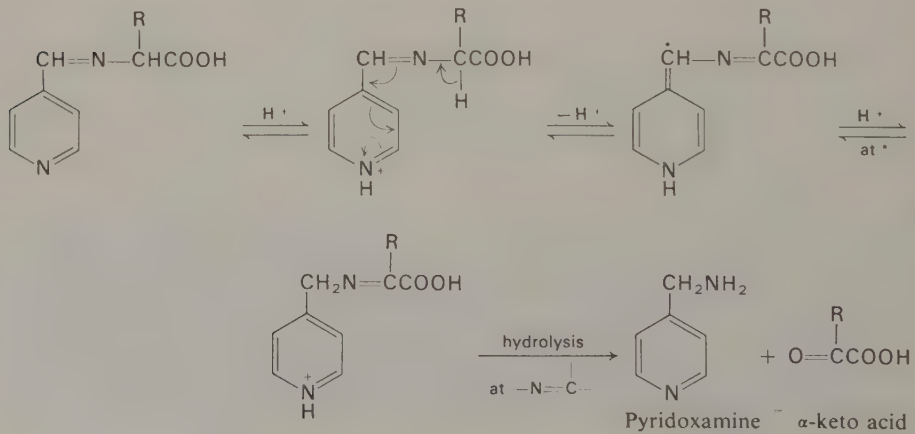
A number of transformations of α-amino acids occurring in biological systems proceed through the intermediate formation of a Schiff base between the $—NH_2$ group of the amino acid and the formyl group (—CHO) of an enzyme prosthetic group, *pyridoxal phosphate*:



(31)

Pyridoxal phosphate
(PhO = phosphate)

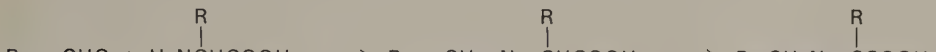
Protonation of the resulting Schiff base on the pyridine nitrogen atom now provides a pathway for the proton exchange shown in the following scheme:*



(32)

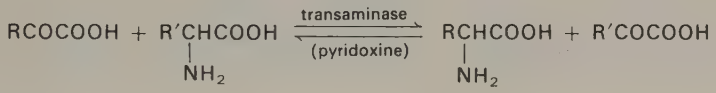
* The substituents $—CH_2OPh$, —OH, and $—CH_3$ are omitted here for clarity in the formulations.

The overall process involves the establishment of an equilibrium between two Schiff bases, represented as follows:



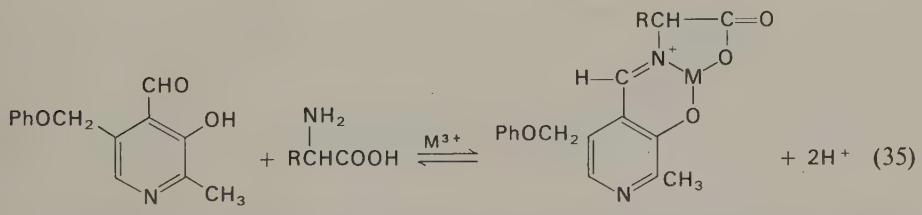
(33)

(Pyr— represents the pyridine ring of pyridoxine/pyridoxal). Because Schiff-base formation is reversible by hydrolysis to the aldehyde (or ketone) and the amine, the whole process provides for the transfer of an amino group from one α-keto acid to another:



(34)

This reaction, known as *transamination* and catalyzed by enzyme systems called *transaminases*, is one of the most important biochemical transformations; it represents the manner in which most of the natural amino acids are formed. The reactions described above can be carried out *in vitro* in the absence of the specific proteins that constitute the natural transaminases; but the non-enzymatic *in vitro* reaction requires the presence of a polyvalent metal cation, which presumably forms a chelate complex:

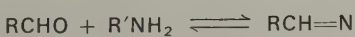


(35)

It is not certain whether the natural enzymatic reactions involve a metal ion at the site of reaction.

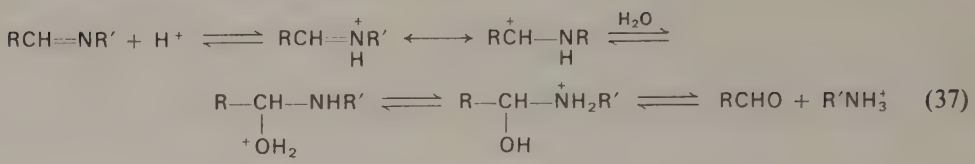
It is implicit in the above that Schiff base formation, like the other carbonyl addition reactions so far discussed, is reversible, and that Schiff bases can be hydrolyzed to their initial components. The hydrolysis can be made irreversible with excess acid (that is, at low pH), for the amine becomes protonated and thus is no longer able to re-form the Schiff base:

(*a*) Formation of Schiff base



(36)

(*b*) Hydrolysis of Schiff base



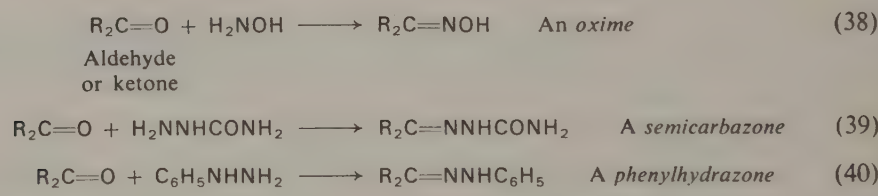
(37)

19-11 Carbonyl derivatives. Characterization and identification of carbonyl compounds

The most useful derivatives of ammonia in the chemistry of carbonyl compounds are those that combine with carbonyl compounds to form crystalline derivatives, the melting points of which can be used to establish the identity of the aldehydes or ketones. The principal derivative-forming reagents of this type are the following:

H_2NOH	$H_2NNHCONH_2$	$NHNH_2$
Hydroxylamine	Semicarbazide	Phenylhydrazine*

In all of these reagents the terminal $—NH_2$ group is sufficiently nucleophilic to form Schiff-base-like products with aldehydes and ketones. These are known by special names:



(38)

(39)

(40)

Of these, the 2,4-dinitrophenylhydrazones are most often used for characterization and identification, for they are nearly always nicely crystalline compounds with well-defined melting points.

19-12 Girard's reagents

The separation of aldehydes and ketones from non-carbonyl compounds is often difficult to accomplish by physical means (chromatography, distillation, crystalliza-

* In practice, substituted phenylhydrazines (for example, 2,4-dinitrophenylhydrazine) are more useful, because their derivatives have more satisfactory crystalline habits and melting points.

tion), and recourse to chemical methods is sometimes necessary. Most complex carbonyl compounds of high molecular weight do not form bisulfite addition compounds and thus cannot be dealt with in the ways that are useful with such simpler compounds as cyclohexanone, benzaldehyde, and acetone. Most aldehydes and ketones do, however, react with carbonyl-derivative-forming reagents and can be converted into oximes, semicarbazones, and so on. In some cases the resulting derivatives can be separated by crystallization, recrystallized to purity, and reconverted by hydrolysis into the desired ketones or aldehydes.

Certain reagents of this kind have the additional valuable property of forming carbonyl derivatives that are water-soluble and ether-insoluble. A *Girard's reagent*, shown in the following scheme, is a compound of the general class $RCONHNH_2$, whose terminal $—NH_2$ group reacts with carbonyl groups (of $R'_2C{=}O$) to form derivatives of the type $RCONHN{=}CR'_2$. In Girard's reagent-T, the R group has the structure $\bar{Cl}(CH_3)_3\overset{+}{N}CH_2—$; as ammonium salts, the reagent and its derivatives are water-soluble and ether-insoluble.

Suppose it is desired to separate a high-molecular-weight ketone $R_2C{=}O$ from a mixture with the corresponding alcohol, R_2CHOH (or other non-ketonic compounds). Treatment of the mixture with a Girard's reagent proceeds as follows:

$$\left.\begin{matrix} R_2C{=}O \\ + \\ R_2CHOH \end{matrix}\right\} + Cl^-(CH_3)_3\overset{+}{N}CH_2CONHNH_2 \longrightarrow \left\{\begin{matrix} Cl^-(CH_3)_3\overset{+}{N}CH_2CONHN{=}CR_2 \\ + \\ \text{unchanged } R_2CHOH \end{matrix}\right. \xrightarrow[\text{and water}]{\text{add ether}}$$

Girard's reagent-T

ether layer: R_2CHOH

water layer: $R_2C{=}NNHCOCH_2\overset{+}{N}(CH_3)_3Cl^- \xrightarrow[(H_2O/H^+)]{\text{hydrolyze}}$

$$R_2C{=}O + (CH_3)_3\overset{+}{N}CH_2COOH + NH_2NH_2 \longrightarrow \text{extract with ether, recover } R_2CO \quad (41)$$

Girard's reagents have found extensive use in studies of steroid metabolism. Many steroidal hormones are ketones, and can be separated from non-ketonic material (for example, in urine) by means of these reagents.

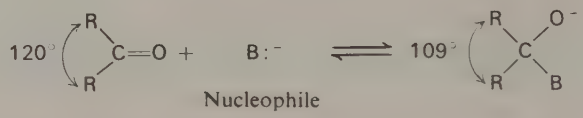
Exercise 5

How could one accomplish by chemical means the complete separation of a mixture of di-isopropyl ketone, pentanal, and 3-pentanol?

19-13 Effect of structure on rate and equilibrium in carbonyl addition reactions

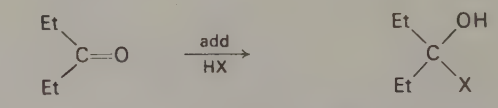
Addition to the carbonyl group of aldehydes and ketones is strongly influenced by the nature of the substituents attached to the carbonyl group. As the R groups in R_2CO become more complex, as in the series R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, and $C(CH_3)_3$, the rate of the addition reaction decreases and the position of equilibrium tends to lie more on the side of reactants than of products. Both steric (bulk and complexity of the R groups) and electronic (electron-donating or -withdrawing properties of the R groups) effects play a part.

In the addition of a nucleophilic agent to the carbonyl group, the configuration of the carbonyl carbon atom changes from the trigonal planar arrangement (sp^2) to the tetrahedral arrangement (sp^3) in the addition product. The change in bond angles from about 120° (sp^2) to 109° (sp^3) necessarily involves a crowding of the R groups into closer proximity. This increase in intramolecular repulsive forces is reflected in the energy requirements for the reaction, both in the transition state (affecting rate) and in the final product (affecting equilibrium). It is clear that with large and bulky R groups in $R_2C{=}O$ a considerable increase in repulsive interaction will take place in the reaction



Nucleophile (42)

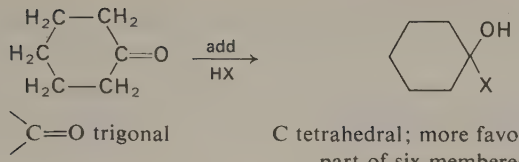
Cyclohexanone undergoes addition reactions much more readily than diethyl ketone, to which it is similar in the degree of substitution of the carbonyl carbon atom. This greater reactivity of cyclohexanone than of diethyl ketone has been explained in the following way: cyclohexane (all carbon atoms tetrahedral) is a nearly strainless compound, and so any departure of the bond angles from 109.5° would be expected to lead to strain, and thus to lower stability. In cyclohexanone one of the carbon atoms (the $-\overset{|}{C}{=}O$) is nearly trigonal (C—C=O angle 120°), and thus the formation of an addition compound, such as the cyanohydrin, would tend to bring this carbon atom back to the preferred tetrahedral configuration. Furthermore, since the carbon atoms are "tied back" in the ring, there would be no increase in the crowding of these atoms when addition occurred, as there would be in the case of diethyl ketone. In summary,



(43)

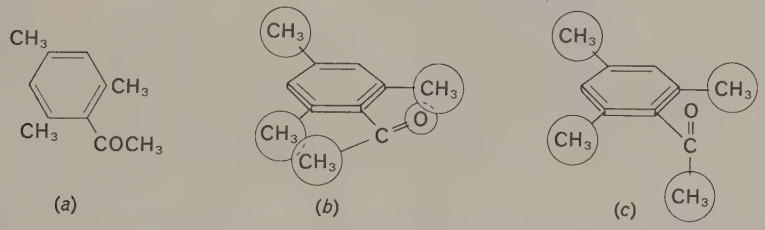
C=O trigonal

C tetrahedral; crowding of Et groups by change in bond angles

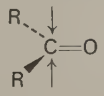


(44)

Steric effects can also affect the rate of an addition reaction by impeding the approach of the nucleophile to the carbonyl carbon atom. An instructive example is 2,4,6-trimethylacetophenone [(*a*) see below]. This compound is quite inert to carbonyl-addition reagents; it does not form an oxime or semicarbazone, and does not even form addition products with Grignard reagents. An examination of a model of this ketone will show that the $O{=}\overset{|}{C}{-}CH_3$ grouping cannot assume a position in which it is coplanar with the aromatic ring (*b*). Indeed, the configuration involving the least interaction between the substituents would be (*c*):



It is clear that the approach of a nucleophile to the carbonyl carbon atom must take place in a direction normal to the plane of the molecule



Approach of nucleophile normal to trigonal plane

and that if 2,4,6-trimethylacetophenone has the preferred conformation (*c*), a nucleophile attacking the carbonyl carbon atom would find its approach blocked by the 2- or 6-methyl group. This impedance is in fact so severe that the ketone is quite inert to addition to the carbonyl group.

Exercise 6

The C=O stretching frequency (IR) for acetophenone is 1692 cm^{-1}; for 2,4,6-trimethylacetophenone it is 1705 cm^{-1}. Comment on this, in view of the discussion of the chemical reactivity of the latter.

Similar, though less extreme, effects are seen in ketones in which the R groups in $R_2C{=}O$ are highly substituted. Hexamethylacetone, $(CH_3)_3CCOC(CH_3)_3$, for example, is slow to react with carbonyl reagents. Further examples of the effects of α substitution were discussed when esterification and saponification of esters were dealt with (Chapter 12).

The most carefully studied carbonyl addition reaction is semicarbazone formation. Table 19-2 gives relative rates of reaction of some variously substituted aldehydes and ketones with semicarbazide.

Table 19-2
Relative rates of semicarbazone formation

Compound	*Relative rate*
CH_3CHO	60
$(CH_3)_3CCHO$	3.3
CH_3COCH_3	1
$(CH_3)_3CCOCH_3$	0.01
C_6H_5CHO	0.3
cyclohexanone	6.0

It can be seen that when one of the substituents in $R_2C{=}O$ is H (aldehydes), the rate of reaction is high: trimethylacetaldehyde reacts faster than acetone, the simplest ketone. Substitution on the α carbon atom of acetone causes a sharp drop in the rate of reaction. Cyclohexanone, in which the cyclic structure holds the α carbon atoms "folded back," reacts faster than acetone.

Exercise 7

How could you account for the fact that benzaldehyde, C_6H_5CHO, reacts about one-tenth as fast as trimethylacetaldehyde?

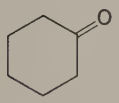
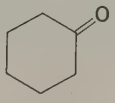
The final *equilibrium* in the carbonyl addition reaction is not always related to the *rate* of the reaction, for the stability of the product (for example, the semicarbazone) depends upon factors different from those that affect the initial attack of the nucleophile upon the carbonyl carbon atom. An instructive experiment is the following:

A mixture of one mole of cyclohexanone and one mole of benzaldehyde is allowed to react with one mole of semicarbazide. A rapid reaction ensues, and *cyclohexanone*

semicarbazone is formed almost exclusively. Thus, cyclohexanone reacts much more rapidly than benzaldehyde (Table 19-2). However, if the reaction mixture is allowed to stand for some time it is found that *benzaldehyde semicarbazone* is the product. Thus, the final equilibrium strongly favors the latter. In benzaldehyde semicarbazone the conjugation of the aromatic π electrons with the —CH=N— grouping provides for resonance stabilization that does not have a counterpart in the semicarbazone of cyclohexanone.

Table 19-3 summarizes some experimental results of studies of rate *vs.* equilibrium in semicarbazone formation.

Table 19-3
Rate of formation and equilibrium in semicarbazone formation

Rate of formation		*Equilibrium*	
fastest	CH_3CHO		forms most stable semicarbazone
		$CH_3COCOOH$	
	$(CH_3)_3CCHO$		
	$CH_3COCOOH$	$(CH_3)_3CCHO$	
	CH_3COCH_3	CH_3CHO	
			
		CH_3COCH_3	
	$(CH_3)_3CCOCH_3$	$(CH_3)_3CCOCH_3$	

Problems

1. Complete the following equations, using structural formulas throughout: (*a*) acetone + HCN, (*b*) acetaldehyde + $NaHSO_3$, (*c*) cyclohexanone + $NaHSO_3$, (*d*) isobutyraldehyde (2-methylpropanal) + hydroxylamine, (*e*) diethyl ketone

(3-pentanone) + hydrazine, (*f*) propanal + aniline, (*g*) benzaldehyde + phenylhydrazine, (*h*) 3-methyl-2-pentanone + semicarbazide, (*i*) Girard's reagent + cyclopentanone, (*j*) acethydrazide ($CH_3CONHNH_2$) + acetone.

2. 4-Aminobutanal is unstable, tending to lose the elements of water to form a compound C_4H_7N. What is the structure of this compound and how is it formed?

3. 2-Aminocyclohexanone readily changes into a compound $C_{12}H_{18}N_2$ with the loss of water, according to the equation $2C_6H_{11}NO \rightarrow C_{12}H_{18}N_2 + 2H_2O$. What is the structure of the product?

4. Write the structural formulas for: (*a*) 3-methylpentanal, (*b*) methyl vinyl ketone, (*c*) 2,3-dibromononanal, (*d*) 5-octanone, (*e*) trimethylacetaldehyde, (*f*) 3-buten-2-one, (*g*) 5-methyl-1-hepten-3-one, (*h*) bromal hydrate, (*i*) acetone dimethyl ketal, (*j*) cyclohexanone oxime.

5. Outline a scheme for separating into pure components a mixture of cyclohexanone, cyclohexanol, and 3-hexanone. Use chemical procedures, not distillation or other physical methods.

6. Arrange the following compounds in the order of their rate of reaction with sodium bisulfite: (*a*) acetaldehyde, (*b*) pinacolone, (*c*) 2-pentanone, (*d*) 3-pentanone, (*e*) formaldehyde, (*f*) 4-methyl-3-penten-2-one.

7. Write the structure of the most probable protonated form of 4-methoxy-3-buten-2-one ($CH_3OCH{=}CHCOCH_3$), showing the contributing structures of the resonance hybrid.

8. Reduction of cyclohexanone cyanohydrin with $LiAlH_4$ gives compound A, $C_7H_{15}NO$. When A is treated with nitrous acid, nitrogen is evolved and compound B, $C_7H_{12}O$, is formed. The IR spectrum of B shows a strong absorption band at 1710 cm^{-1}, and a low-intensity ($\log \epsilon = 1.1$) UV maximum at 281 nm. Write the structures of compounds A and B.

20

Carbonyl compounds III: Addition of organometallic compounds. Other addition reactions

The addition reactions discussed in Chapter 19 are for the most part reversible; even though the equilibrium may be such that product formation is essentially complete, the products (for example, cyanohydrins and oximes) are subject to ready hydrolysis, with regeneration of the original aldehyde or ketone.

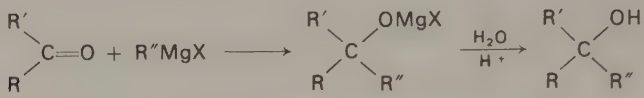
A class of addition reactions that lack the feature of reversibility is described in this chapter. These are reactions, typified by the Grignard reaction, that add organometallic compounds to carbonyl compounds. This and a number of closely related reactions are of enormous synthetic usefulness: they provide versatile and efficient routes to alcohols, ketones, carboxylic acids, aldehydes—products in which new carbon-carbon bonds have been formed.

The Grignard reaction, the Reformatsky reaction, the Wittig synthesis of olefins, and the addition of diazomethane to the carbonyl group are characterized by a common feature: the attack upon the electrophilic carbonyl carbon atom by a strongly nucleophilic carbon atom of the reagent.

20-1 Addition of Grignard reagents to aldehydes and ketones

The addition of organometallic compounds (Grignard reagents and organolithium compounds) to carbonyl compounds is a reaction of wide applicability and versatility.

It provides access to a wide variety of compounds:



(1)

R or R′ = H, alkyl, aryl, alkoxyl
R″ = alkyl, aryl, allyl, vinyl, alkynyl

The immediate products of such reactions are alcohols, which can serve as the starting materials for further transformations of many kinds; some of these have been described in Chapter 11. Although the use of Grignard reagents was introduced there, it is appropriate here to discuss further the formation of Grignard reagents and their reactions with carbonyl compounds in detail, and to add a description of organometallic reagents of other kinds.

20-2 Preparation and properties of organomagnesium (Grignard) reagents

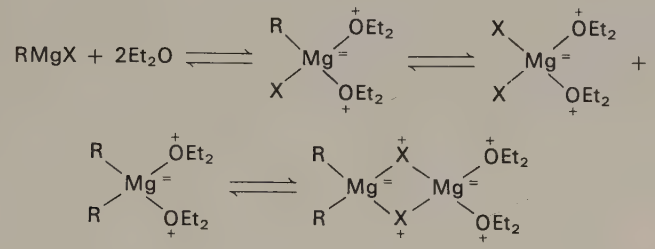
Grignard reagents are easily prepared from alkyl and aryl iodides and bromides by allowing the halide to react with metallic magnesium in ether. When tetrahydrofuran is used as the solvent, chlorides react satisfactorily. Reaction usually begins without delay; the magnesium dissolves, and the final ether solution is used as the reaction medium for the next step. Ethyl ether (or a cyclic ether such as tetrahydrofuran) is necessary because it participates actively in the formation of the organomagnesium compound by solvating it. The simple expression

$$RX + Mg \longrightarrow RMgX \qquad (2)$$

is an adequate representation for most practical considerations, but the reaction is somewhat more complex in detail.

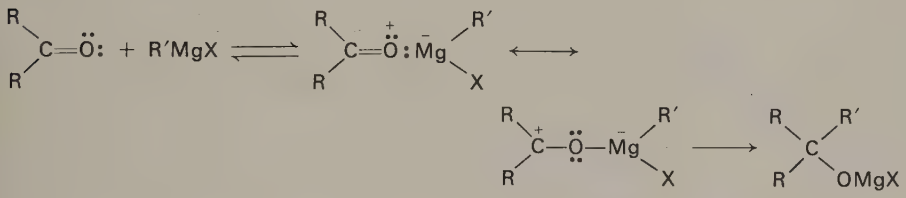
Although the expression RMgX (for example, CH_3CH_2MgBr for ethylmagnesium bromide) is satisfactory for most formulations of the reactions of Grignard reagents, the ether solution of RMgX is an equilibrium mixture of several species of ether-solvated magnesium compounds. It will be recalled that magnesium in its bivalent compounds has the capacity to accept two electron pairs from donor molecules to achieve a four-coordinated state. Ether, with unshared electrons on oxygen, can provide the additional coordination bonds, and thus solvate the organomagnesium compounds. In addition to this straightforward solvated complex, there is evidence

that various species consisting of combinations of R, Mg, X, and ether exist in the solution:



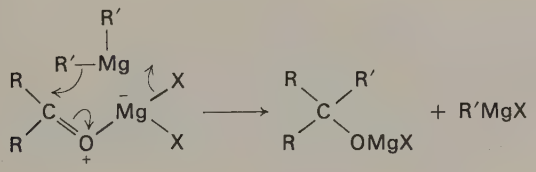
(3)

There is seldom a need, however, to give explicit consideration to these various species. Two facts should be kept in mind: (1) the Mg atom in RMgX, XMgX, or RMgR has unfilled orbitals and thus has the properties of a Lewis acid; and (2) these unfilled orbitals may be occupied by electron pairs of ether, *or by the electron pairs of the carbonyl oxygen atom.* Thus, an adequate picture of the reaction between RMgX and a ketone is



(4)

It is also possible to view the reaction as involving both MgX_2 and R_2Mg, in which case the reaction complex can be formulated as



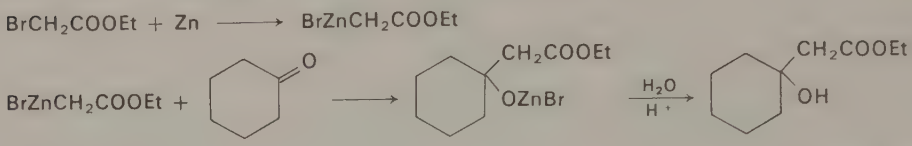
(5)

In either case, coordination of the magnesium atom with the carbonyl oxygen atom increases the electrophilic character of the carbonyl carbon atom and affords part of the driving force for the shift of R′ from magnesium to carbon.

Besides the preparation of alcohols (described in Chapter 11), other applications of organomagnesium and other organometallic compounds are the preparation of ketones from nitriles, carboxylic acids, and certain carboxylic acid derivatives. These will be described in chapters to follow.

20-3 Other organometallic reagents

Organometallic reagents of other metals are less widely used than those of magnesium and lithium, but the *Reformatsky reaction*, in which an organozinc compound is the reactive intermediate, is a useful synthetic procedure:



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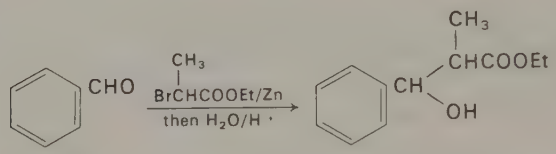
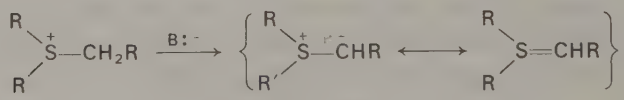


(7)

Although organolithium and organomagnesium compounds are usually prepared (in solution) in separate operations prior to the addition of the carbonyl compound, the Reformatsky reaction is carried out by adding both the bromoester and the ketone (or aldehyde) to metallic zinc in a suitable solvent. The bromozinc compound is formed and consumed *in situ*. Decomposition of the addition product with dilute aqueous acid yields the hydroxy ester and zinc salts.

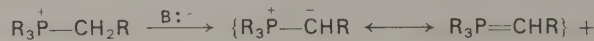
20-4 The Wittig synthesis of olefins. Reactions of phosphorus ylids with carbonyl compounds

An *ylid* is a compound formed by removal of a proton, by action of a base, from a carbon atom adjacent to a positively charged "hetero" atom. The best known ylids are those containing sulfur or phosphorus as the hetero atom. Both of these have available 3*d* orbitals and so are capable of expanding their octets, thus permitting delocalization of the negative charge on carbon. Typical ylids are those formed by removal of a proton adjacent to a sulfonium sulfur atom:



(8)

or a phosphonium phosphorus atom:



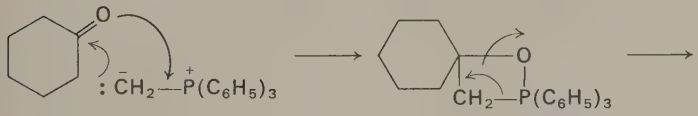
(9)

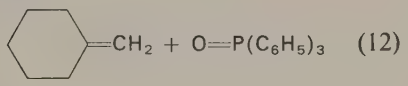
Phosphorus ylids have found extensive synthetic use in the *Wittig reaction.* Although the phosphorus ylid can be represented as the pentacovalent phosphorus compound, the relatively inefficient use of the phosphorus 3*d* orbitals gives it a strongly dipolar character, with anionic character in the carbon atom. *The phosphorus ylids are therefore stabilized carbon anions,* and are nucleophilic reagents capable of attacking the carbonyl carbon atom. An example of the formation of a phosphorus ylid (Wittig reagent) and its reaction with a carbonyl compound (cyclohexanone) is the following:

$$(C_6H_5)_3P: + CH_3Br \longrightarrow \{(C_6H_5)_3\overset{+}{P}—CH_3\}\ Br^- \tag{10}$$

(Compare $R_3N: + R'Br \rightarrow \{R_3\overset{+}{N}R'\}Br^-$)

$$(C_6H_5)_3\overset{+}{P}—CH_3Br^- + CH_3Li \longrightarrow \left\{\begin{array}{c}(C_6H_5)_3\overset{+}{P}—\overset{-}{C}H_2 \\ \updownarrow \\ (C_6H_5)_3P{=}CH_2\end{array}\right\} + CH_4 + LiBr \tag{11}$$





(12)

The first step (formation of the quaternary phosphonium salt) may be compared with the formation of a quaternary ammonium salt. The reaction is versatile, for phosphorus ylids of a wide range of structural types can be prepared with ease. The following examples suggest some of the synthetic applications of the method:

$$(C_6H_5)_3P + BrCH_2COOEt \longrightarrow (C_6H_5)_3\overset{+}{P}—CH_2COOEt\ Br^-$$

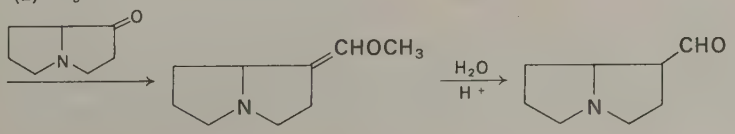
$$\downarrow OEt^-$$

$$(C_6H_5)_3\overset{+}{P}—\overset{-}{C}HCOOEt \xrightarrow{C_6H_5CHO} C_6H_5CH{=}CHCOOEt \tag{13}$$

$$C_6H_5CH{=}CHCH_2Cl \xrightarrow[(2)\ EtO^-]{(1)\ (C_6H_5)_3P} C_6H_5CH{=}CH—\overset{-}{\underset{\cdot\cdot}{C}}H—\overset{+}{P}(C_6H_5)_3$$

$$\xrightarrow{C_6H_5CHO} C_6H_5CH{=}CH—CH{=}CHC_6H_5 \tag{14}$$

$$CH_3OCH_2Cl \xrightarrow[(2)\ CH_3Li]{(1)\ (C_6H_5)_3P} CH_3O\overset{-}{\underset{\cdot\cdot}{C}}H—\overset{+}{P}(C_6H_5)_3$$



(15)

It should be noted that the strength of the base required to remove a proton from the phosphonium salt varies: in some cases sodium ethoxide can be used, in others the much more powerful methyllithium (CH_3Li) is required. When R′ in $R_3\overset{+}{P}—CH_2R'$ is electron-attracting, as in $(C_6H_5)_3\overset{+}{P}—CH_2COOEt$, the acidity of the protons on the $—CH_2—$ group is greatly enhanced, and deprotonation can be accomplished without alkyllithiums. Indeed, the acidity of phosphonium salts is often surprisingly high. Some pK_a values are given in Table 20-1.

Table 20-1
pK_a values for some phosphonium salts containing electron-attracting substituents

*Compound**	pK_a
$\phi_3\overset{+}{P}—CH_2CO$–  –NO_2	4.2
$\phi_3\overset{+}{P}—CH_2CO$– 	5.5
$(CH_3)_3\overset{+}{P}—CH_2CO$– 	8.7
$\phi_3\overset{+}{P}—CH_2CONH_2$	11.0

* ϕ stands for the phenyl group, C_6H_5.

20-5 Addition of diazomethane to carbonyl compounds

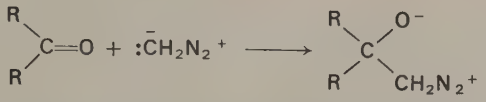
Diazomethane may be regarded as a special case, a stabilized nitrogen ylid. Most nitrogen ylids [for example, $(CH_3)_3\overset{+}{N}—CH_2:^-$] are unstable; the nitrogen atom cannot utilize additional orbitals to accommodate the negative charge [as in the structure $(CH_3)_3N{=}CH_2$]. While they are formed as highly reactive intermediates in some reactions, they are not Wittig reagents. In diazomethane, however, the negative charge on carbon can be stabilized by delocalization of the following kind:

$$:\overset{-}{C}H_2—\overset{+}{N}{\equiv}N: \longleftrightarrow CH_2{=}\overset{+}{N}{=}\overset{-}{\ddot{N}}: \qquad (16)$$

It can be seen that pentacovalent nitrogen is not present. Diazomethane is a stable compound, which can be prepared and preserved (usually in ether solution).

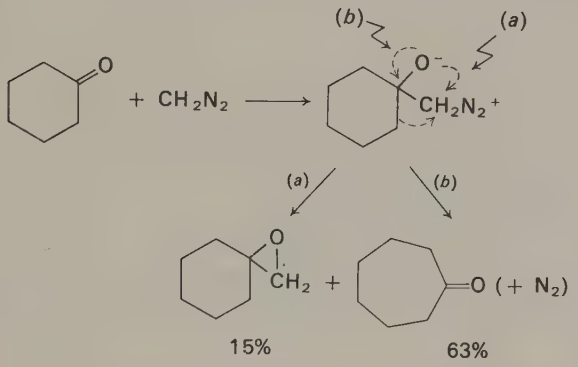
The attack of diazomethane upon an aldehyde or a ketone follows the pattern

of the addition reactions so far discussed, the nucleophilic carbon attacking the carbonyl carbon atom in the usual way:



(17)

The initial addition product may react further in several ways. Since $-N_2^+$ is a readily displaced group, leaving as the stable nitrogen molecule, two principal courses are followed. Taking cyclohexanone as a typical example, the principal products are (*a*) the epoxide and (*b*) the ring-enlarged ketone, cycloheptanone:



(18)

The reaction of cyclohexanone with diazomethane is a useful preparative method for cycloheptanone. Some cyclooctanone is formed as well.

Exercise 1

When benzaldehyde is allowed to react with diazomethane, one of the products formed is $C_6H_5CH_2CH(O)CH_2$. How can you account for this?

20-6 Other reactions involving organometallic reagents

Reactions of organomagnesium and other organometallic compounds with acid derivatives and with polyfunctional carbonyl compounds are of wide synthetic application. They are discussed in the chapters to follow, in which unsaturated aldehydes and ketones, polycarbonyl compounds, and acids and acid derivatives are introduced.

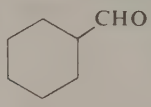
Problems

1. Using any reactions discussed to this point in the text, and including any organometallic or Wittig reagent, show how you could prepare each of the following compounds. Starting materials must include the compound specified in parentheses, and may include any other reagents regarded as reasonably available and inexpensive.

(*a*) $(CH_3CH_2)_2C{=}CH_2$ (propionic acid)

(*b*) $C_6H_5CH_2CH_2COOEt$ (benzaldehyde, C_6H_5CHO)

(*c*) $C_6H_5CH{=}CHCOOH$ (benzaldehyde)

(*d*)  (cyclohexanone)

(*e*) $C_6H_5COCH_2CH(CH_3)_2$ (benzaldehyde)

(*f*) $(CH_3)_2C{=}C(CH_3)_2$ (acetone)

(*g*) $CH_3CH_2CH_2COC_6H_5$ (propene)

(*h*) $C_6H_5CH_2CH{=}C(CH_3)_2$ (benzaldehyde)

(*i*) $CH_3COCH_2CH_2CH_3$ (2-butanol)

(*j*) $(CH_3)_2CHCH_2CH_2CH{=}CHC_6H_5$ (3-methylbutanoic acid)

21

Polyfunctional carbonyl compounds

In Chapters 19 and 20 the reactions of carbonyl compounds were described with attention to the functional group as an isolated unit, and with consideration of the influence of the substituents attached to the carbonyl group on the rate and equilibrium, but not the course, of a reaction.

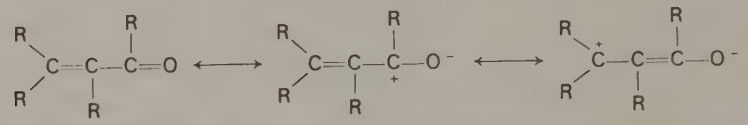
Carbonyl compounds that possess a second functional group—a carbon-carbon double bond, a second carbonyl group, a hydroxyl group—in an adjacent or nearby position often show unique properties and react in such a way that the second group modifies the behavior of the first or both participate in the reaction. The most important classes of such bifunctional carbonyl compounds are the unsaturated aldehydes and ketones, and those containing carbonyl groups in a 1,2, 1,3, or 1,4 relationship. Although in general much of the behavior of these compounds is that of carbonyl compounds as described in the foregoing chapters, they also display unique characteristics that deserve special attention. This chapter deals with some of the most prominent kinds of such special bifunctional reactivity.

It will be recalled (Chapter 18) that the UV and IR spectral characteristics of carbonyl compounds are greatly modified by the presence of conjugated carbon-carbon unsaturation. In this chapter some spectroscopic features of polyfunctional carbonyl compounds are mentioned.

21-1 Unsaturated carbonyl compounds

In unsaturated aldehydes, ketones, and acid derivatives in which the carbon-carbon double bond is not adjacent to the carbonyl group, the reactivities of the two functional groups, C=C and C=O, are in general little different from those of compounds in which these groupings are present alone. When the carbon-carbon double bond is adjacent (α,β) to the carbonyl group, however, special reactivity appears, in which the system C=C—C=O acts as a unit.

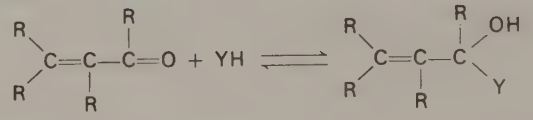
Because of the conjugation of the carbon-oxygen and carbon-carbon double bonds, the electrophilic character of the carbonyl carbon atom can be expressed at the carbon atom in the β position:



(1)

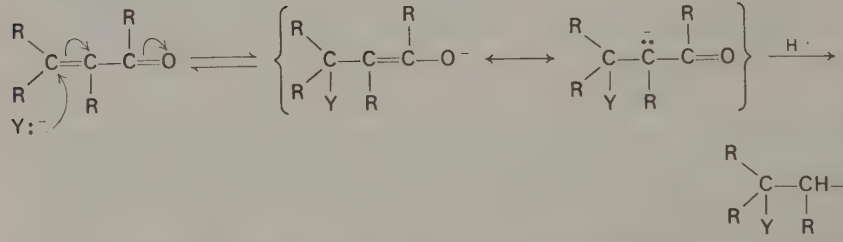
The α,β-unsaturated system can therefore undergo nucleophilic attack and addition in two ways:

(*a*) 1,2 addition



(2)

(*b*) 1,4 addition



(3)

In the overall process of addition of YH to the α,β-unsaturated system it is as if the addend, YH, had added to the carbon-carbon double bond. This is, however, usually referred to as "1,4 addition" because of the participation of the carbonyl group. Some specific examples of this kind of reaction are the following:*

$$CH_2{=}CHCOOCH_3 + (CH_3)_2NH \longrightarrow (CH_3)_2NCH_2CH_2COOCH_3 \qquad (4)$$

$$CH_2{=}CHCOCH_3 + CH_3OH \xrightarrow{CH_3O^-} CH_3OCH_2CH_2COCH_3 \qquad (5)$$

* The most widely used and important additions to α,β-unsaturated systems of this class are the additions of carbon anions. An example is the Michael reaction (Chapter 25).

$$C_6H_5CH{=}CHCOC_6H_5 + CH_3SH \longrightarrow C_6H_5\underset{\displaystyle SCH_3}{\underset{|}{C}}HCH_2COC_6H_5 \qquad (6)$$

$$2CH_2{=}CHCN + CH_3NH_2 \longrightarrow CH_3N(CH_2CH_2CN)_2 \qquad (7)$$

$$2CH_2{=}CHCOOCH_3 + H_2S \longrightarrow S(CH_2CH_2COOCH_3)_2 \qquad (8)$$

$$C_6H_5CH{=}CHCHO + 2NaHSO_3 \longrightarrow C_6H_5\underset{\displaystyle SO_3Na}{\underset{|}{C}}HCH_2C\overset{\displaystyle OH}{\underset{\displaystyle SO_3Na}{<}} \qquad (9)$$

$$CH_3CH{=}CHCOOEt + NaCN \xrightarrow{H^+} CH_3\underset{\displaystyle CN}{\underset{|}{C}}HCH_2COOEt \qquad (10)$$

The reader should examine each of these with care and relate them to the general mechanistic schemes presented in (2) and (3).

Addition of halogen acids to α,β-unsaturated carbonyl compounds is an acid-catalyzed reaction, and proceeds by addition of the halogen anion (for example, Br^-) to the protonated aldehyde or ketone.

$$CH_2{=}CH{-}CHO + HCl \rightleftharpoons CH_2{=}CH{-}CH{=}\overset{+}{O}H \longleftrightarrow \overset{+}{C}H_2CH{=}CH{-}OH \xrightarrow{Cl^-}$$
$$\{ClCH_2CH{=}CHOH\} \longrightarrow ClCH_2CH_2CHO \qquad (11)$$

When an α,β-unsaturated aldehyde is treated with hydrogen chloride in alcohol solution, the unsaturated acetal that would be formed by the usual reaction of the aldehyde carbonyl group is accompanied by the β-chloroacetal resulting from (*a*) 1,4-HCl addition, followed by (*b*) acetal formation:

$$CH_2{=}CHCHO \xrightarrow{HCl} ClCH_2CH_2CHO \xrightarrow{CH_3OH} ClCH_2CH_2CH(OCH_3)_2 \qquad (12)$$

The character of the product mixture in such cases depends upon the experimental conditions; for example, HCl-catalyzed addition of ethanol to acrolein (propenal) when HCl is present as a catalyst, but not in excess, yields the β-ethoxyacetal along with the unsaturated acetal:

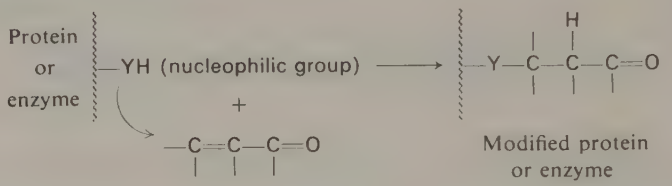
$$CH_2{=}CHCHO \xrightarrow[HCl]{EtOH} CH_2{=}CHCH(OEt)_2 + EtOCH_2CH_2CH(OEt)_2 \qquad (13)$$

21-2 Biological activity of α,β-unsaturated carbonyl compounds

The presence of the functional system C=C—C=O is often associated with marked physiological activity. Unsaturated ketones, esters, and lactones evoke a variety of

physiological responses: they may be lacrimatory, antibacterial, cytotoxic and antitumor, or vesicant and allergenic (causing dermatitis) in their actions. One of the simplest of the class is acrolein, a severe lacrimator; it is a product of the pyrolytic decomposition of glycerol, and is produced when cooking fats or oils are overheated.

These physiological responses cannot yet be described exactly in terms of the functional groups (that is, the specific biological nucleophiles) that are involved, but the general character of the process can be represented as follows:



(14)

A nucleophilic functional group commonly found in many proteins, and one that is known to be important to the activity of many enzymes, is the sulfhydryl group, —SH, which can be present in protein molecules in the peptide-linked cysteine, $HSCH_2CH(NH_2)COOH$. Other reactive functional groups capable of ready addition to an α,β-unsaturated carbonyl compound are amino groups, present in many proteins as side-chain substituents. The hydroxyl group of tyrosine (*p*-hydroxyphenylalanine) may also react. These possible ways of altering protein structure may be summarized as follows, where E represents the remainder of the protein macromolecule and, for illustration, the reactive α,β-unsaturated compound is acrylonitrile:

$$E—SH + CH_2=CHCN \longrightarrow E—SCH_2CH_2CN \tag{15}$$

$$E—CH_2NH_2 + CH_2=CHCN \longrightarrow E—CH_2NHCH_2CH_2CN \tag{16}$$

(17)

Although it is not possible to predict *a priori* the exact nature of the physiological consequences of such reactions, it is clear that the structure, and thus the function, of a protein or enzyme "alkylated" in this way will probably be profoundly altered. A related process, the acylation of the hydroxyl group of serine in esterases, with destruction of catalytic activity, will be described in Section 23-16.

21-3 Addition of Grignard reagents to α,β-unsaturated carbonyl compounds

The addition of a Grignard reagent to an α,β-unsaturated carbonyl compound can take place in a 1,2 or a 1,4 manner, depending upon the degree and kind of substitution on the conjugated system. In general, (*a*) structural features that reduce the reactivity

Table 21-1
1,2 and 1,4 addition in the reaction of Grignard reagents with α,β-unsaturated carbonyl compounds

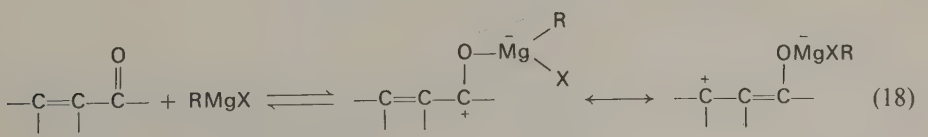
*Compound**	% 1,2 *addition*		% 1,4 *addition*	
	C_6H_5MgBr	EtMgBr	C_6H_5MgBr	EtMgBr
RCH=CHCHO	100	100	0	0
$RCH{=}CHCOCH_3$	88	40	12	60
$RCH{=}CHCOCH_2CH_3$	60	29	40	71
$RCH{=}CHCOCH(CH_3)_2$	12	0	88	100
$RCH{=}CHCOC(CH_3)_3$	0	0	100	100
$R_2C{=}CHCOR$	100	82	0	18
RCH=C(R)COR	0	0	100	100
$RC(CH_3){=}CHCOR$	76	79	24	21

* In all the compounds in this table, R = phenyl, C_6H_5—.

of the carbonyl group favor 1,4 addition; (*b*) substitution at the β carbon atom of the conjugated system tends to favor 1,2 addition; and (*c*) the lower alkylmagnesium halides tend to favor 1,2 addition, while more complex Grignard reagents lead to increased amounts of 1,4 addition. In many cases both addition products are formed, for the balance of these factors may be such that neither type of addition is totally suppressed. Table 21-1 shows results in some typical cases.

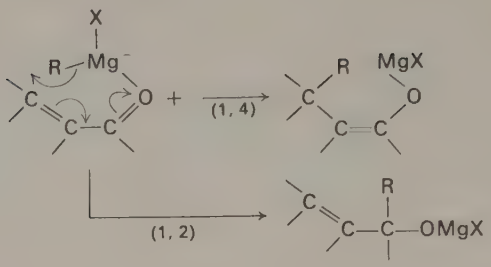
Two things are evident: the α,β-unsaturated aldehyde adds exclusively 1,2, and increasing substitution on the methyl group of —$COCH_3$ leads to decreasing 1,2 addition. This, it will be noted, is in accord with the earlier observation that increasing α substitution diminishes carbonyl group reactivity.

The addition of Grignard reagents to α,β-unsaturated carbonyl compounds can be looked upon as a Lewis acid–catalyzed addition reaction, for the coordination of RMgX with the carbonyl oxygen atom polarizes the system just as does protonation. The subsequent transfer of $R:^-$ from the magnesium to the electrophilic center can then occur at either of the two electrophilic positions. It has been suggested that a cyclic mechanism is involved, but there is no compelling evidence that this is a necessary course for the 1,4 addition:



(18)

Then:



The group R— that becomes attached to the β carbon atom may be derived from another RMgX molecule in an *inter*molecular transfer.

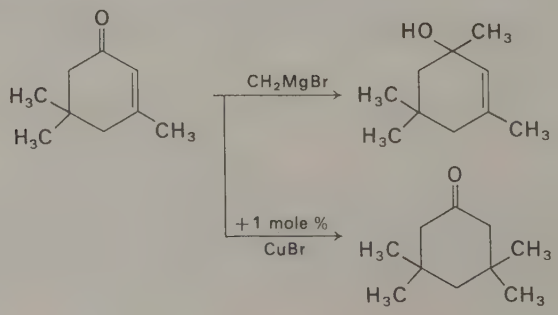
21-4 Experimental variations in the addition of Grignard reagents to α,β-unsaturated systems

Organolithium reagents tend to give a greater 1,2/1,4-addition-product ratio than organomagnesium compounds; if the 1,2 addition product is the one desired, the organolithium compound is the preferred reagent.

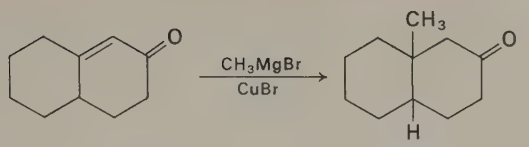
Preponderant or complete 1,4-addition occurs when a small amount of a cuprous salt (for example, CuCl or CuBr) is added to the Grignard reagent prior to or during the reaction with the carbonyl compound. It is probable that an intermediate organocopper compound is formed, which is the active reagent in the addition reaction. The exact character of the copper-containing intermediate is not known. It may be a compound of the following kind:

(19)

Some examples of this reaction are:



(20)



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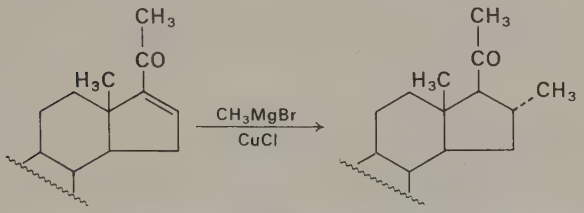
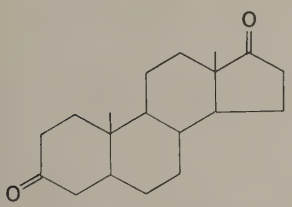


(22)

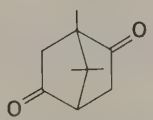
Variants of cuprous-salt/Grignard-reagent procedures include the use of cuprous salts with alkyllithiums.

21-5 Polycarbonyl compounds

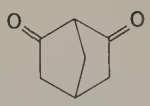
The presence of two or more carbonyl groups in the same molecule (in diketones, triketones, and so on) may or may not be attended by unique chemical behavior. When the two groups are widely separated in the molecule there is ordinarily no interaction between them, and both groups react quite independently in addition reactions, in the formation of carbonyl derivatives, and so on. Similar remarks apply to diketones in which the carbonyl groups, although not widely separated, are prevented from interacting for stereochemical reasons. Examples of these situations are found in such diketones as the following:



Androstane-3,17-dione



Bornane-2,5-dione
(5-ketocamphor)



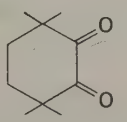
Norbornane-2,6-dione

21-6 1,2-Diketones. Nomenclature and physical properties

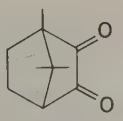
1,2-Diketones (also called α-diketones) are typified by the following examples (note that trivial names are sometimes used):

$CH_3COCOCH_3$

Butane-2,3-dione
(biacetyl)



3,3,6,6-tetra-
methylcyclohexane-
1,2-dione



Camphor
quinone

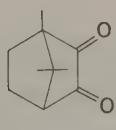
$C_6H_5COCOC_6H_5$

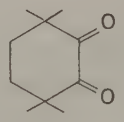
Benzil
(diphenyldiketone)

Because of interaction between the two $\overset{+}{C}—\overset{-}{O}$ dipoles, α-diketones tend, when this is structurally permissible, to assume conformations in which the two carbonyl groups are *trans* disposed. Under these circumstances the IR absorption is usually at somewhat higher frequencies than that of simple ketones. In general, however, the shifts are not large: aliphatic α-diketones may be expected to absorb at about 1725–1730 cm^{-1} (C=O stretching), compared with about 1710–1715 cm^{-1} for simple ketones.

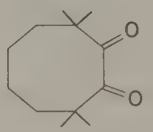
Many α-diketones are yellow in color, indicating absorption, usually of low intensity, in the region of 350–450 nm. This is in contrast to simple aliphatic and aromatic ketones, which are colorless and have only low-intensity absorption at ultraviolet wavelengths between 200 and 300 nm.

Some typical examples are the following:



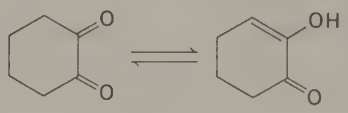


$((CH_3)_2CHCO)_2$



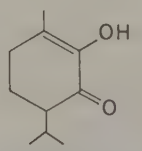
λ_{max}(nm)	264, 478	297, 380	285, 365	343
log ε	1.4, 1.6	1.5, 1.0	1.7, 1.3	1.3

Finally, some α-diketones exist largely in the enolic form. Cyclohexane-1,2-dione, for instance, is a tautomeric equilibrium mixture of the two forms



(23)

the second of which, the major constituent, is described by the generic term *diosphenol.* Diosphenol itself is a naturally occurring compound with the structure



Diosphenol (2-hydroxy-3-methyl-6-isopropylcyclohex-2-ene-1-one)

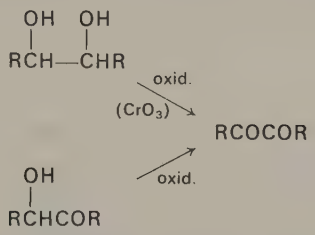
and the word is applied descriptively to compounds containing this cyclic structural unit. Simple open-chain (acyclic) aliphatic 1,2-diketones such as biacetyl and similar α-diketoalkanes are not enolic.

Exercise 1

Can you suggest why cyclohexane-1,2-dione exists nearly completely as the enolic tautomer, while the acyclic hexane-3,4-dione does not?

The preparation of α-diketones can be accomplished in a number of ways.

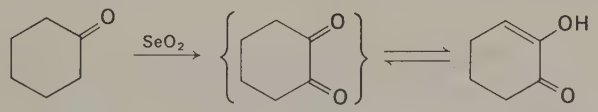
(*a*) By the careful oxidation of 1,2-glycols or of α-hydroxyketones:



(24)

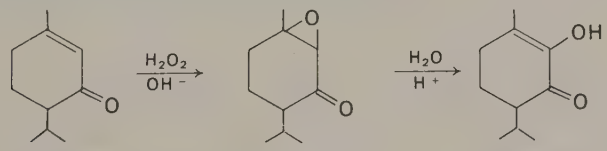
(25)

(*b*) By the oxidation with selenium dioxide (SeO_2) of ketones containing α-methylene groups (—CH_2CO—). For example, cyclohexane-1,2-dione:



(26)

(*c*) By the rearrangement of 1,2-epoxyketones. For example, diosphenol itself results when piperitone oxide is treated with acids:



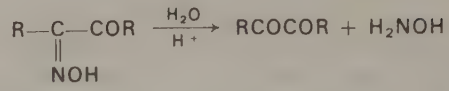
Piperitone Piperitone oxide Diosphenol

(27)

Exercise 2

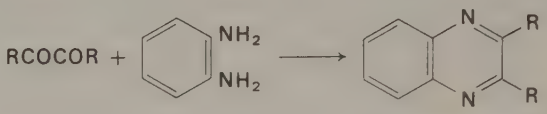
Suggest a reasonable mechanism for the acid-catalyzed isomerization of piperitone oxide into diosphenol. (HINT: What initial protonation step would be expected to lead to the product?)

(*d*) By the acid hydrolysis of α-oximinoketones:



(28)

1,2-Diketones react with carbonyl-derivative-forming reagents to give mono- or di-oximes, phenylhydrazones, and so on. An important diagnostic reaction that can be used to detect the presence of the 1,2-diketo grouping is the reaction with *o*-phenylenediamine:

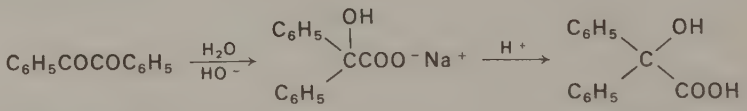


(29)

A quinoxaline

This reaction is quite general, and occurs with enolic α-diketones as well. The products, known as *quinoxalines*, are usually crystalline compounds suitable for identification purposes.

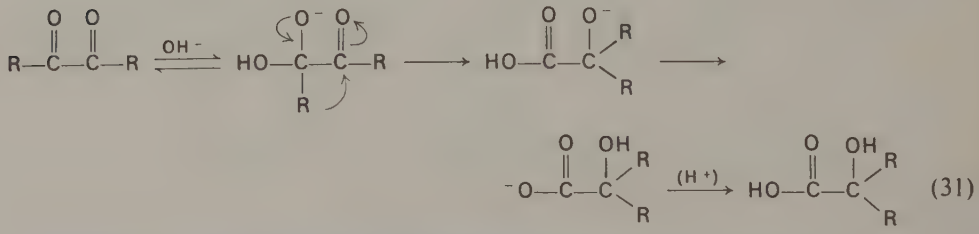
When 1,2-diketones are subjected to the action of strong alkalis, they undergo a characteristic rearrangement known by the general term "*benzilic acid rearrangement*," so called because the most familar example is the reaction of alkali with the aromatic α-diketone benzil:



(30)

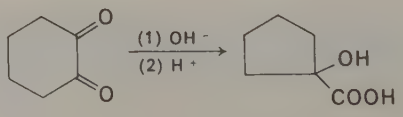
Benzil Benzilic acid

The course of this rearrangement can be represented by the general expression



(31)

Application of the reaction to cyclic diketones results in ring-contraction:



(32)

Exercise 3

Formulate the stepwise course of (32), the ring-contraction of cyclohexane-1,2-dione into 1-hydroxycyclopentanone carboxylic acid, by the mechanism in (31).

Another characteristic reaction of α-diketones is their smooth oxidative cleavage by alkaline hydrogen peroxide:

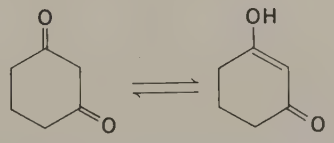
$$RCOCOR' \xrightarrow[OH^-]{H_2O_2} RCOOH + R'COOH \qquad (33)$$

21-7 1,3-Diketones (β-diketones)

The preparation and enolic properties of 1,3-dicarbonyl compounds will be considered separately in Chapter 22. 1,3-Diketones are usually mixtures of the tautomeric enol and keto forms:

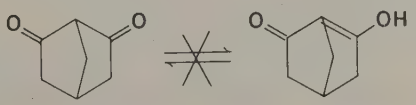
$$RCOCH_2COR \rightleftharpoons RC(OH)=CHCOR \qquad (34)$$

The position of equilibrium (that is, the proportion of enol) depends upon the nature of the R groups and the solvent. In certain cases this enolization is prohibited for steric reasons; certain cyclic 1,3-diketones are not enolic and are not readily converted into the enolate anion $\{-CO\ddot{C}HCO-\}^-$. For example, while cyclohexane-1,3-dione is a mixture of the diketo and ketoenol forms,



(35)

the bicyclic 1,3-diketone norbornane-2,6-dione is nonenolic:



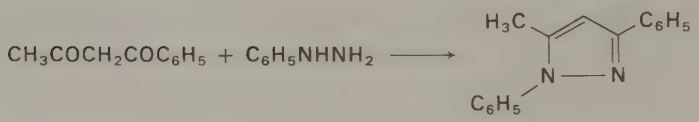
(36)

This is because the distortion of bond angles required for a double bond at the bridgehead is energetically so disadvantageous that the enolic structure is very unstable with respect to its diketonic tautomer. An early expression of this is embodied in *Bredt's rule*, which states that compounds having a double bond at a bridgehead cannot exist. In more recent years "exceptions" to this "rule" have been prepared, in which compounds containing larger rings have sufficient flexibility to accommodate a bridgehead double bond. Still, Bredt's rule is quite valid for smaller bicyclic systems such as norbornane-2,6-dione. At the time it was expressed the larger ring systems in which the rule was "violated" were not known.

Because of the 1,3 relationship of the carbonyl groups in β-diketones, they are capable of reacting with some carbonyl-derivative-forming reagents to form cyclic compounds:

(37)

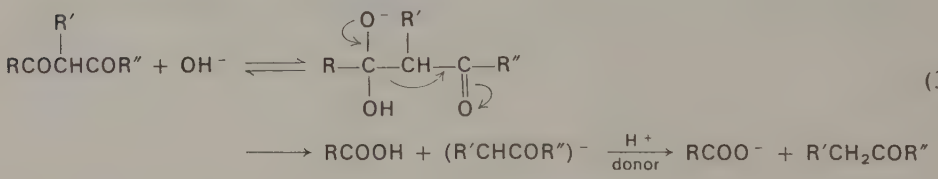
An isoxazole



(38)

A pyrazole

1,3-Diketones can be cleaved by alkali to yield a ketone and a carboxylic acid. The reaction begins by the characteristic attack upon the carbonyl carbon atom by the nucleophilic OH^- ion:



(39)

The cleavage reaction is brought to completion by protonation of the enolate anion $(R'CHCOR'')^-$ by the solvent medium (alcoholic alkali) and the formation of the carboxylate anion. Cleavage is made energetically possible in the first place by the fact that the fragment $(R'CHCOR'')^-$ can be displaced because of its inherent capacity for stabilization by delocalization of the negative charge. It will also be noted that if the attacking nucleophile is an alkoxide anion (for example, CH_3O^-) instead of OH^-, the reverse reaction represents one of the steps in a Claisen condensation (Chapter 24).

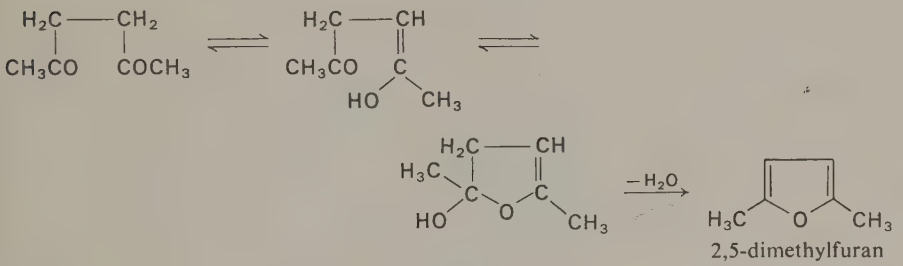
Exercise 4

While the 1,3-diketone $RCOCR_2COR$ can be cleaved by alkali as just described, the 1,4-diketone $RCOCR_2CH_2COR$ is not susceptible to alkaline cleavage. Why is the 1,4-diketone not cleaved?

21-8 1,4-Diketones, 1,5-diketones, and 1,6-diketones

1,4-Diketones, which can be prepared by the methods of general ketone synthesis, display many characteristics common to simple monoketones. The two carbonyl groups act independently in such reactions as the formation of oximes and semicarbazones.

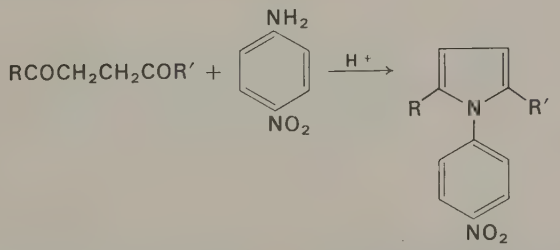
Cyclization reactions of 1,4-diketones are known. When heated with acids (or Lewis acids such as $ZnCl_2$) they form furan derivatives, a reaction that may be regarded as proceeding by way of the enolic tautomer:



(40)

2,5-dimethylfuran

Reaction of 1,4-diketones with amines results in the formation of pyrroles, as illustrated in the following example. When the amine is an aniline derivative, the pyrroles are often crystalline compounds that are useful for characterization and identification of the diketones:



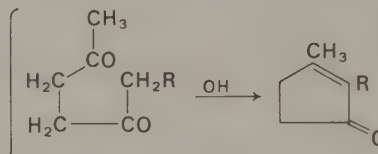
(41)

An *N*-*p*-nitrophenylpyrrole

1,5- and 1,6-diketones are not prone to undergo reactions of the above types.

A general reaction of appropriately constituted 1,4-, 1,5-, and 1,6-diketones is their cyclization by intramolecular aldol condensation (Chapter 22). Such condensations occur when one carbonyl group and a —CH_2CO— unit are so disposed that a 5- or 6-membered ring can form:

(1,4-diketones)



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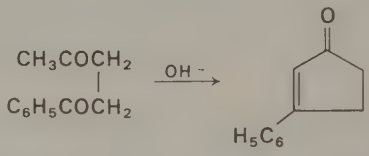
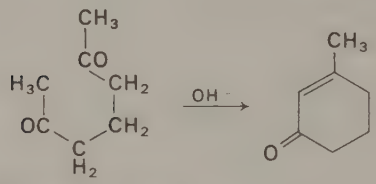


(43)

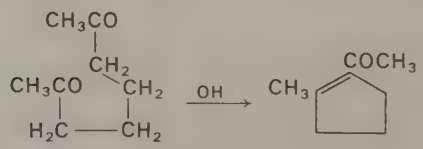
(1,5-diketones)



Heptane-2,6-dione

(44)

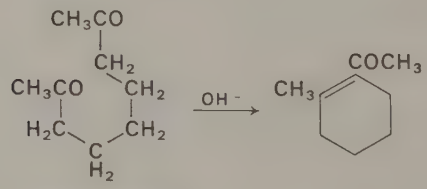
(1,6-diketones)



Octane-2,7-dione

(45)

(1,7-diketones)



Nonane-2,8-dione

(46)

An alternative mode of cyclization of $\overset{1}{C}H_3\overset{2}{C}O\overset{3}{C}H_2\overset{4}{C}H_2\overset{5}{C}H_2\overset{6}{C}O\overset{7}{C}H_3$ (44) is between the carbonyl group (C-2) and the α-methylene (C-5), to give a cyclobutene derivative. This is not observed, for the angle strain required to form a four-membered ring, coupled with the reversibility of the aldol condensation, favors the exclusive formation of the unstrained 6-membered ring.

Exercise 5

What is an alternative mode of ring closure, by aldol condensation, of octane-2,7-dione, and why is this not the principal course of the reaction?

Problems

1. By what simple experimental test or observation (both chemical and physical properties may be used) could you distinguish between the compounds in each of the following pairs? NOTE: This does not require a detailed demonstration of the complete structure; assume that there is in hand an unknown compound known to have one or the other structure:
   (*a*) $CH_3CH_2CH_2COCH_3$ and $CH_3CH_2COCH_2CH_3$
   (*b*) $CH_3CH_2CH{=}CHCOCH_3$ and $CH_3CH{=}CHCH_2COCH_3$
   (*c*) $HOCH_2CH_2CH_2CH_2OH$ and $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$
   (*d*) $BrCH_2CH_2COCH_2CH_2CH_3$ and $BrCH_2CH_2CH_2COCH_2CH_3$
   (*e*) $CH_3COCH_2CH_2COCH_3$ and $CH_3COCOCH_2CH_2CH_3$
   (*f*) cyclohexanone and cyclohexene oxide
   (*g*) $CH_3CH{=}CHCOCH_2CH_2NMe$ and $CH_3CH{=}CHCH_2CH_2CONMe_2$
   (*h*) $CH_3OCH_2CH_2CH_2OCH_3$ and $CH_3CH_2CH(OCH_3)_2$
   (*i*) $CH_3CH_2CH_2OCH_2Br$ and $CH_3CH_2OCH_2CH_2Br$
   (*j*) $Cl_3CCH_2CH_2CHO$ and $CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCCl_2CHO$

2. Using any necessary reagents in addition to the one given, show how you could synthesize
   (*a*) $CH_3N(CH_2CH_2COOH)_2$ from $CH_2{=}CHCOOCH_3$
   (*b*) $CH_3OCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)_2$ from $CH_2{=}CHCOCH_3$
   (*c*) 2-methylcyclohexanol from cyclohexene
   (*d*) 3-phenyl-2-cyclohexen-1-one from 3-hydroxy-2-cyclohexen-1-one (the enolic form of cyclohexane-1,2-dione)
   (*e*) isobutyraldehyde (2-methylpropanal) from CH_3OCH_2COOEt

22

Acidity of carbon-linked hydrogen. Aldol and related condensations

This chapter describes a second conspicuous property of carbonyl compounds: the unique character of the hydrogen atoms that are α to (adjacent to) the carbonyl group. These "active" hydrogen atoms have a demonstrable potential for ionization, or abstraction by bases. The resulting α-carbon anions are highly nucleophilic species and react readily with electrophilic centers. When the electrophilic center is a carbonyl carbon atom, carbon-carbon bond formation occurs. This is a general description of many reactions known as *aldol condensations*, and of related reactions of the aldol type.

Reactions of the aldol type take many forms, all of which, it will become clear, are variants of a single fundamental process. Further discussion of aldol-like reactions will be found in succeeding chapters; indeed, reactions of this class are among the most commonly encountered in organic chemistry. It is important for the student to perceive the basic mechanistic unity of this family of reactions, and to recognize that they all depend upon the formation of an α-carbon anion and its subsequent attack upon the electrophilic carbonyl group—whether this carbonyl group be that of an aldehyde, a ketone, or a carboxylic acid derivative—or upon the carbon atom of a Schiff base.

22-1 Structural effects upon acidity

The degree of ionization of hydrogen attached to an atom Y in the general reaction

$$Y{:}H + \underset{\text{(a base)}}{B{:}^-} \rightleftharpoons Y{:}^- + B{:}H \qquad (1)$$

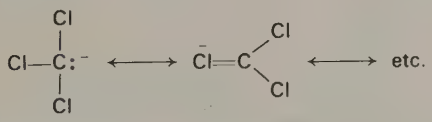
is a function of both the character of Y and the strength of the base. One of the principal factors determining the strength of an acid YH is the electron-attracting ability of the atom Y to which the proton is attached. Consider the last four elements of the first row of the periodic table: these form the hydrides CH_4, NH_3, H_2O, and HF. Of these, it is well known that HF is an acid in the usual sense of the term and that OH^- and NH_2^- are the conjugate bases of H_2O and NH_3, which can accordingly be considered acids. Since ammonia is a stronger base than water, it is a corollary that ammonia is the weaker acid of the two. These properties can be related to the nuclear charge on the central atom; this rises from 6 on carbon to 9 on fluorine.

Simple extension of these concepts would lead to the conclusion that $CH_3{:}^-$ is an exceptionally strong base and that CH_4 is an extremely weak acid. This is indeed the case. Methane and other paraffin hydrocarbons (alkanes) have no demonstrable acidic character; they are "acids" with pK_a values of about 40. In general, hydrogen attached to a saturated (sp^3) carbon atom that is not α to an "activating" group (to be described in what follows) has no demonstrable acidic character.

Purely inductive effects upon the C—H bond in sp^3 hybridization can be demonstrated, but they are not strong acidifying influences. Chloroform, bromoform, and fluoroform ($CHCl_3$, $CHBr_3$, CHF_3) are weakly acidic, and strong bases (for example, alkoxide ions) can ionize them:

$$CHX_3 + RO^- \longrightarrow {:}CX_3^- + ROH \qquad (2)$$

It is interesting to note, however, that although fluoroacetic acid (FCH_2COOH, pK_a = 2.6) is a stronger acid than chloroacetic acid (pK_a = 2.9), chloroform is more acidic than fluoroform. This indicates that the electron-withdrawing inductive effect of the halogen is not the sole reason for the acidity of the haloform. It is probable that electron delocalization in the $:CX_3^-$ ion plays a part when X can utilize 3*d* orbitals in the following way:

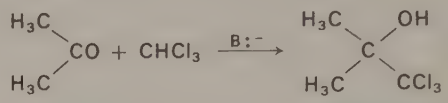


(3)

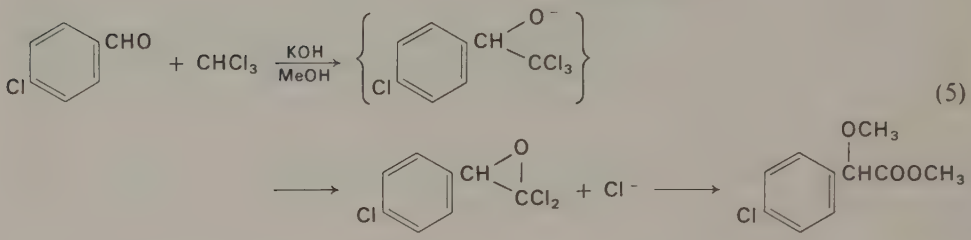
Fluorine, which cannot utilize 3*d* orbitals, cannot contribute in this way.

The formation of the $:CCl_3^-$ ion under the influence of a base can be demonstrated experimentally by the base-catalyzed addition of chloroform to carbonyl

groups. The overall mechanism of these reactions is the same as that of the addition of nucleophiles of other kinds, as discussed in Chapter 19.



"Chloretone" (4)



(5)

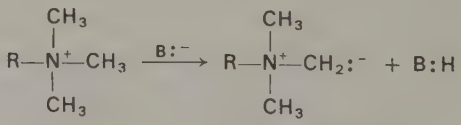
Exercise 1

Write a reasonable course for the conversion of *p*-chlorobenzaldehyde into the methoxy ester shown in equation (5).

"Chloretone" (and the corresponding "brometone") have hypnotic properties similar to those of chloral hydrate. Now obsolete in human therapy, they still find some use in veterinary medicine.

The formation of the reactive intermediate, dichlorocarbene (Section 33-7), also results from an initial formation of the $Cl_3C:^-$ ion.

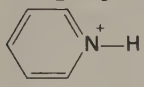
Purely inductive effects upon the acidity of H—C bonds play a relatively minor role in organic chemistry. Certain reactions of quaternary ammonium compounds are explainable by their ionization to the nitrogen ylid:



A nitrogen ylid (6)

Sulfonium ions $(R_2S—CH_3)^+$ behave similarly to form the sulfur ylids, $R_2\overset{+}{S}—\overset{-}{C}H_2$. These are described at appropriate places in other parts of this book (see Sections 20-4 and 20-5).

Table 22-1
Relationship of acidity to bond type

Nitrogen acids		*Carbon acids*		
Compound	pK_a	*Compound*	pK_a	*Bond type*
$RCH_2\overset{+}{N}H_3$	11	RCH_2CH_3	>40	sp^3
	5	$RCH{=}CH_2$	~35	sp^2
$RCH_2C{\equiv}\overset{+}{N}H$	−10	$RC{\equiv}CH$	~26	*sp*
—		$N{\equiv}CH$	9.4	*sp*

Olefins (alkenes) are also very weak acids (although many orders of magnitude stronger than alkanes) in ionization of the following kind. Their pK_a's lie in the range of extremely weak acids (>30).

$$CH_2{=}CH_2 + B{:}^- \rightleftharpoons CH_2{=}CH{:}^- + B{:}H \tag{7}$$

Acetylenes (alkynes) containing a terminal triple bond show demonstrable acidity, and can be converted into their anions under readily attainable experimental conditions (pK_a of acetylene = 26).

The differences in acidity of the protons in RCH_2CH_3, $RCH{=}CH_2$, and $RC{\equiv}CH$ (giving the ions $RCH_2CH_2{:}^-$, $RCH{=}CH{:}^-$, and $RC{\equiv}C{:}^-$) can be attributed to the differences in the character of the relevant C—H bond in sp^3-, sp^2-, and *sp*-hybridized carbon atoms. The greater degree of *s* character in the C—H bond in *sp*-hybridized acetylene constrains the unshared electron pair in the anion to remain closer to the carbon nucleus, with a consequent increase in stability of $RC{\equiv}C{:}^-$. A parallel may be drawn with similar hybridization in nitrogen acids, for which pK_a values are known with more accuracy. In Table 22-1 are shown some comparative data. Since $N{\equiv}C{-}H$ is a much stronger acid than $RC{\equiv}C{-}H$, it can be concluded that the added inductive effect of the nitrogen increases the acidity of $N{\equiv}C{-}H$ over that of the acetylene.

Acetylenes form metallic compounds of salt-like character by replacement of the acidic hydrogen:

$$RC{\equiv}CH + EtMgBr \longrightarrow RC{\equiv}CMgBr + C_2H_6 \tag{8}$$

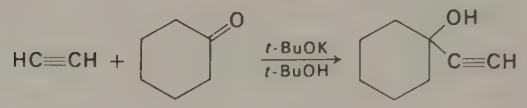
$$RC{\equiv}CH + Ag(NH_3)_2{}^+ \longrightarrow RC{\equiv}CAg + NH_3 + NH_4{}^+ \tag{9}$$

$$RC{\equiv}CH + NaNH_2 \longrightarrow RC{\equiv}C{:}^-Na^+ + NH_3 \tag{10}$$

$$RC{\equiv}CH + t\text{-}BuO^-K^+ \longrightarrow RC{\equiv}C{:}^-K^+ + t\text{-}BuOH \tag{11}$$

The ion $RC{\equiv}C:^-$ (or $HC{\equiv}C:^-$ from acetylene itself) is an effective nucleophile. One of its useful reactions is addition to an aldehyde or ketone to form a carbon-carbon bond; another is its reaction with primary alkyl halides to give substituted acetylenes:

$$HC{\equiv}CH + (CH_3)_2CO \xrightarrow[NH_3]{NaNH_2} \begin{matrix} H_3C & & OH \\ & C & \\ H_3C & & C{\equiv}CH \end{matrix} \qquad (12)$$



(13)

$$CH_3C{\equiv}CH \xrightarrow[NH_3]{Na} CH_3C{\equiv}C:^-Na^+ \xrightarrow{n\text{-}C_4H_9Br} CH_3C{\equiv}CCH_2CH_2CH_2CH_3 + NaBr \qquad (14)$$

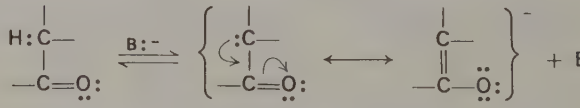
The addition of the acetylide anion to ketones can be compared to the base-catalyzed addition of HCN, from which it differs in degree but not in kind.

22-2 Resonance, or charge-delocalization, effects upon H—C acidity

By far the most important influence in stabilization of carbon anions is resonance, or charge delocalization.

It will be recalled that the stability of the ions $:CH_3^-$, $:\ddot{N}H_2^-$, $:\ddot{O}H^-$, and $:\ddot{F}:^-$ is chiefly due to the kernel charge on the nucleus, that of fluorine (9) being greatest, carbon (6) smallest. There are no other formal structures that can be written for these ions; the charge is localized. When, however, the charge is not constrained to exist upon a single atom, but can be distributed over several, localized electron density is reduced, stabilizing the ion.

Such charge dispersion is most commonly seen when a carbon atom is adjacent to a carbonyl group. In this case, the negative charge is delocalized over the C—C=O system, greatly increasing the acidity of the α hydrogen atom:



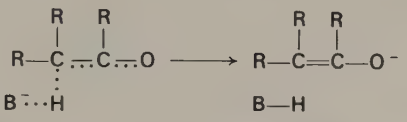
(15)

It is only the α hydrogen whose ionization (removal by a base) can give rise to the resonance-stabilized anion (often referred to as an *enolate ion*), because no comparable charge-delocalized structures can be written for an anion with the negative charge β or γ to the carbonyl group.

Exercise 2

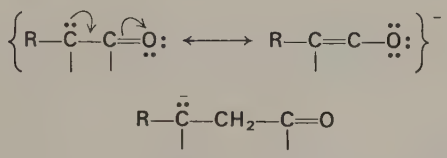
Certain base-catalyzed reactions of crotonaldehyde, $CH_3CH{=}CHCHO$, can be accounted for by an initial deprotonation to form an anion $(C_4H_5O)^-$. Which proton is removed, and why?

The transition state in the ionization reaction can be represented as



(16)

in which it can be seen that the developing charge delocalization during proton abstraction tends to stabilize the transition state (TS) for ionization, by lowering its energy compared with a TS in which no such delocalization is possible.



Resonance stabilization (charge delocalization)

vs.

(17)

No charge delocalization, thus no resonance stabilization

Aldehydes and ketones are very weak hydrogen acids. The pK_a of acetone is about 20, and thus the concentration of the anion $CH_3COCH_2{:}^-$ formed in the reaction

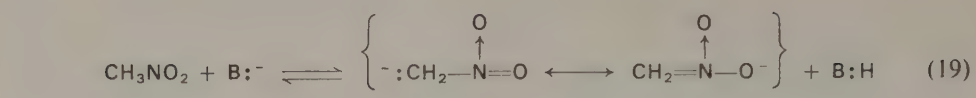
$$CH_3COCH_3 + OH^- \rightleftharpoons CH_3COCH_2{:}^- + H_2O \qquad (18)$$

in aqueous solution is very low. Nevertheless, the anion is formed under such conditions; if a subsequent reaction removes it, it is restored by maintenance of the equilibrium.

22-3 α activation by other groups

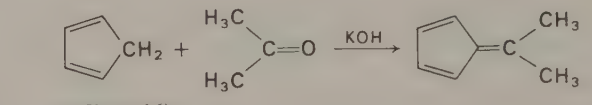
Other groups with a capacity similar to that of carbonyl groups for accommodating the delocalization of an electron pair would be expected to enhance α-hydrogen acidity. This is the case. The nitro group, $—NO_2$, is an activating group* more powerful than the carbonyl group; nitromethane, CH_3NO_2, has a pK_a of about 10.

* The term "active hydrogen" is used in the same sense as "acidic hydrogen," and refers here to those hydrogen atoms that can be removed by bases (hydroxide, alkoxide, amide ions, and, in some cases, organometallic reagents) under usual experimental conditions. Hydrogen atoms α to such groups as carbonyl and nitro are "activated," and the carbonyl and nitro groups are called "activating" groups. In this terminology a nitro group is more powerfully activating than a carbonyl group.

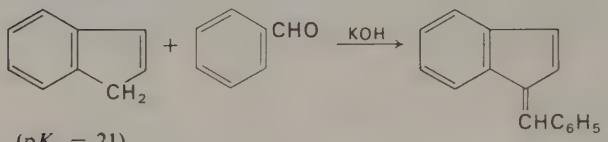


(19)

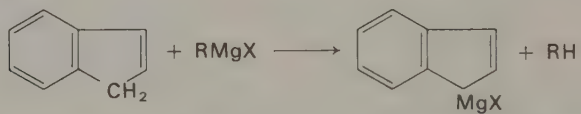
Less pronounced, but experimentally demonstrable, activation of hydrogen can be observed in certain hydrocarbons in which carbon-carbon unsaturation or aromatic rings make charge delocalization possible. The following examples illustrate this; the condensation reactions shown in these formulations will be dealt with in following sections.



(pK_a = 16) (20)



(pK_a = 21) (21)



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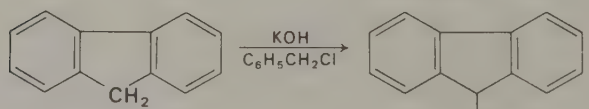
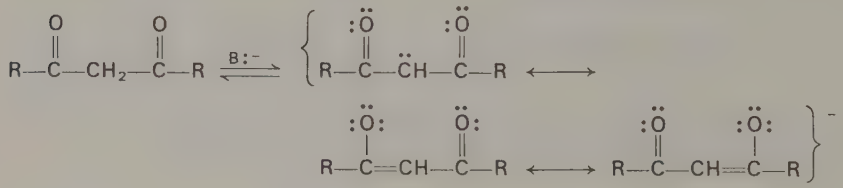


(pK_a = 26) (23)

When additional opportunity for delocalization of charge exists, the acidity of α hydrogen is increased. For example, 1,3-diketones form carbanions with more extensively delocalized structures:



(24)

A *triketone* of the type $(RCO)_3CH$ is, for the same reasons, even more acidic. The pK_a values in Table 22-2 illustrate these effects.

It will be noted that dinitromethane, $CH_2(NO_2)_2$, is an acid of about the same strength as acetic acid, while $CH(NO_2)_3$ is a "strong" acid.

Table 22-2
pK_a's of some compounds containing doubly- and triply-activated C—H bonds

Compound	pK_a
CH_3COCH_3	20
$(CH_3CO)_2CH_2$	9
$(CH_3CO)_3CH$	6
CH_3NO_2	10
$CH_2(NO_2)_2$	4
$CH(NO_2)_3$	1

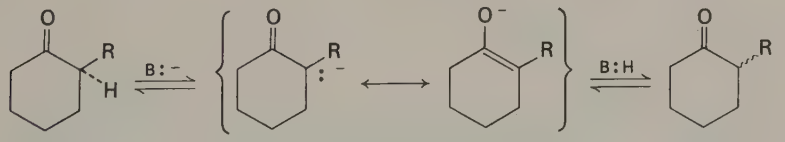
22-4 Additional evidence for the ionization of α hydrogen

Acetone in deuterium oxide (D_2O) containing NaOD undergoes hydrogen-deuterium exchange and is transformed in successive steps into CD_3COCD_3:

$$\begin{aligned} CH_3COCH_3 + DO^- &\rightleftharpoons CH_3COCH_2{:}^- + HOD \\ CH_3COCH_2{:}^- + D_2O &\rightleftharpoons CH_3COCH_2D + DO^-; \text{ etc.} \end{aligned} \qquad (25)$$

This exchange reaction is often of diagnostic value in determining the number of α (replaceable) hydrogen atoms in an unknown carbonyl compound. Exchange of this kind, followed by analysis of the recovered compound for its deuterium content, shows the number of α hydrogen atoms.

When the ketone (or aldehyde or ester) possesses an asymmetric α carbon atom, the formation of the enolate anion destroys this asymmetry, with the result that optically active carbonyl compounds of this type are racemized by bases:



Optically active — Symmetric — Racemic (±) (26)

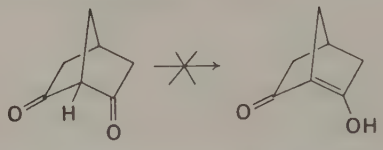
The symmetrical enolate anion can be reprotonated with equal probability to give either enantiomer.*

* If the molecule contains another, stable, center of asymmetry, the final result will be mutarotation instead of racemization.

Many 1,3-diketones exist in solution to a large extent as the enolic tautomers. Acetylacetone, for example, is an equilibrium mixture of the diketone and the enolic ketone that, depending to some extent upon the solvent and concentration, contains about 70% of the enol:

$$CH_3COCH_2COCH_3 \rightleftharpoons CH_3\overset{\overset{OH}{|}}{C}{=}CHCOCH_3 \qquad (27)$$

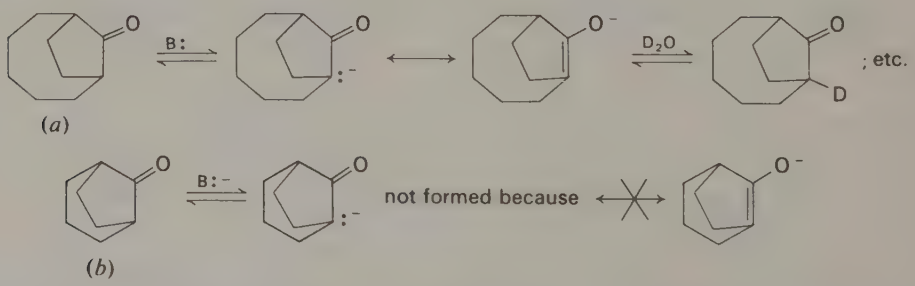
The equilibrium between the keto and enol forms is established by a deprotonation-protonation reaction that, when base catalyzed, can be regarded as proceeding *via* the enolate anion. Since the initial dissociation of the proton from the $—CH_2—$ group is energetically dependent upon the possibility of charge delocalization, it may be expected that if such delocalization is for some reason not possible, the diketone will not undergo the initial deprotonation and will thus show no enolic properties. This is indeed observed. The bicyclic diketone



(28)

shows no enolic properties, and lacks the acidity characteristic of other β-diketones. The enolic form shown would be a highly strained (distorted) molecule and (as its anion) incapable of contributing to the keto-enol equilibrium.

A related example is found in the two bicyclic ketones (*a*) and (*b*) shown below. Ketone (*a*) undergoes deuterium exchange at the two α carbon atoms, while (*b*) does not exchange. A model would show that (*b*) is incapable of enolizing, while (*a*), with a larger and more flexible ring, can accommodate the enol structure without prohibitive strain:



The non-exchangeability of the hydrogens in (*b*) is expressed in Bredt's rule, which states that a bicyclic compound cannot contain a double bond at a bridgehead. It is apparent that the rule does not apply when the ring system is large enough to accommodate the double bond, as in compound (*a*).

22-5 The α-carbon anion as a nucleophile

The α-carbanions (enolate ions) of carbonyl compounds, as the conjugate bases of very weak acids, are strong bases and effective nucleophiles.

A large class of mechanistically related reactions with countless applications in numerous areas of organic chemistry involves the attack of an α-carbanion upon a carbonyl group. The first stage of such reactions is illustrated by the following example. Consider the events that ensue when acetone is treated with a base. The anion formed in the equilibrium

$$CH_3COCH_3 + OH^- \rightleftharpoons CH_3COCH_2{:}^- + H_2O$$

can attack the undissociated ketone in a typical carbonyl addition reaction, which is completed by proton exchange with the solvent in the usual way:

$$CH_3COCH_3 + B{:}^- \rightleftharpoons CH_3COCH_2{:}^- + B{:}H$$

$$CH_3COCH_2{:}^- + \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C{=}O}}}} \rightleftharpoons CH_3COCH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}{-}O^- \underset{B:^-}{\overset{B:H}{\rightleftharpoons}} \underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\diagdown\!\!\diagup}}\!\!C(OH)\!-\!CH_2COCH_3$$

Diacetone alcohol

(29)

This reaction is an example of the *aldol condensation*, so called because its simplest prototype is the corresponding reaction with acetaldehyde:

$$CH_3CHO + OH^- \rightleftharpoons {}^-{:}CH_2CHO + H_2O$$

$$CH_3CHO + {}^-{:}CH_2CHO \rightleftharpoons CH_3CH(O^-)CH_2CHO \overset{H^+}{\rightleftharpoons} CH_3\underset{OH}{CH}CH_2CHO \qquad (30)$$

Aldol

The product of the self-condensation of acetaldehyde is called *aldol*, a name derived from the structural features of the compound: it is both an *alde*hyde and an alcoh*ol*. The term *aldol condensation* is used in a broad generic sense to describe a large and varied class of reactions, which are characterized by their mechanistic unity.

The equilibrium in the first stage of aldol condensations is often unfavorable to the products, but good yields can in most cases be obtained, for reasons that will appear in the discussion to follow. The equilibrium yield of *diacetone alcohol*, for instance, is only a few percent [that is, the equilibrium lies far to the left in equation (29)], but this disadvantage can be overcome by the use of a special technique. Since the condensation reaction is reversible in the presence of a base, removing the product from the presence of the basic catalyst will permit it to accumulate. This is done by

refluxing acetone and allowing the vapors to condense and flow over the catalyst (barium hydroxide) suspended in a porous container above the boiling flask. The equilibrium mixture of acetone and diacetone alcohol returns to the boiling flask where the acetone (but not the higher-boiling diacetone alcohol) is revaporized and again brought into contact with the catalyst.

Aldol condensations of the simpler aliphatic aldehydes and ketones have some industrial importance but are not of wide and general application. For one thing, practical uses are usually limited to the "self-condensation" of a simple aldehyde or ketone, as in the cases of acetone and acetaldehyde. When two different carbonyl compounds condense with one another, mixtures of products result unless there is an appreciable difference between the activity of the α hydrogen atoms or the reactivities of the two carbonyl groups. For instance, in propionaldehyde and *n*-butyraldehyde (propanal and butanal) the α-CH_2 groups differ very little in kind, and the aldehyde groups are essentially alike. Thus, if a mixture of these two aldehydes were subjected to the conditions of the aldol condensation a mixture of four products would be expected.

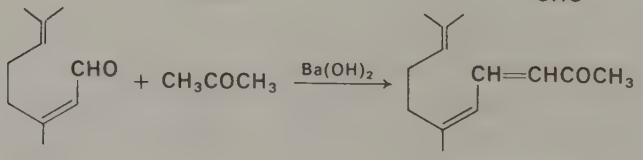
Exercise 3

Write equations showing the products that would be formed in the aldol condensation of an equimolar mixture of propanal and butanal.

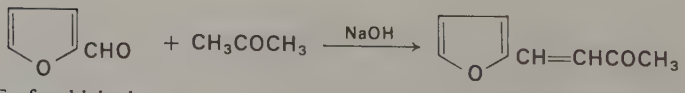
22-6 Dehydration of aldols

The β-hydroxy aldehydes and ketones that are the first products of aldol condensations can often be isolated, but in most cases the reaction proceeds a step further, by loss of the elements of water, to yield the α,β-unsaturated aldehyde or ketone:

$$2CH_3CH_2CHO \xrightarrow{OH^-} CH_3CH(CHO)-CH(OH)-CH_2CH_3 \xrightarrow{-H_2O} CH_3C(CHO)=CHCH_2CH_3 \qquad (31)$$



Citral — Pseudoionone (32)



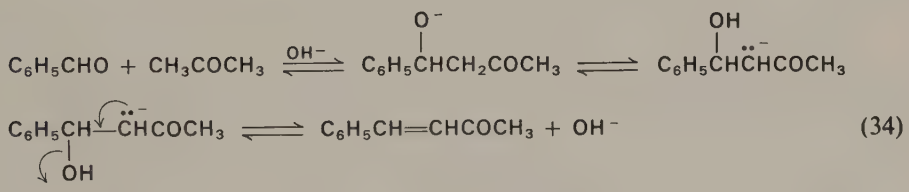
Furfuraldehyde — Furfuralacetone (33)

Exercise 4

In the condensation of furfuraldehyde with acetone, if the aldehyde is in excess the product is not furfuralacetone but a compound $C_{13}H_{10}O_3$. What is its structure and how is it formed?

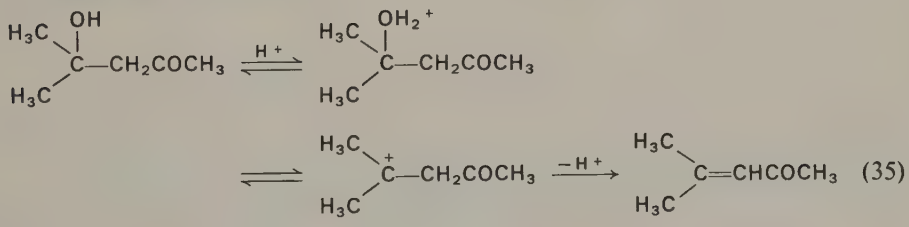
The dehydration of a β-hydroxy aldehyde or ketone may be brought about by the action of acid or base. When the α,β-unsaturated aldehyde or ketone is the direct product of the base-catalyzed aldol condensation it is apparent that the dehydration has occurred under basic conditions. When the aldol (the β-hydroxy carbonyl compound) is isolable, it can usually be easily dehydrated in a separate operation by heating with a trace of an acid catalyst:

Base-catalyzed dehydration



(34)

Acid-catalyzed dehydration



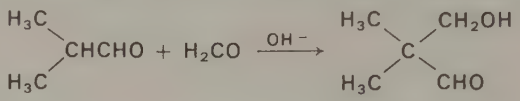
(35)

22-7 Aldol condensations with aldehydes lacking α hydrogen atoms

Formaldehyde. If one of the two reacting carbonyl compounds in an aldol condensation reaction lacks an α hydrogen atom it can act only as the acceptor of the carbanion provided by the other. Two aldehydes often used in this way are benzaldehyde and formaldehyde, neither of which has α hydrogen and both of which take part in carbonyl addition reactions. The use of formaldehyde in aldol condensation is attended by a second type of reaction that depends upon the fact that formaldehyde is an

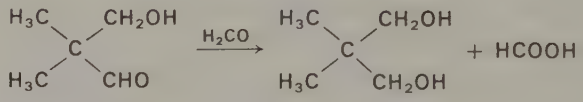
effective reducing agent. Overall, a reaction of the following kind occurs, the final product of which is the result of the reduction of —CHO to —CH_2OH:

(*a*) Formation of initial aldol condensation product



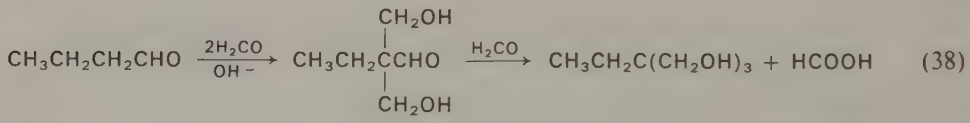
(36)

(*b*) Reduction of —CHO by formaldehyde



(37)

When more than one α hydrogen atom is present, successive additions of formaldehyde occur. Final reduction of the formyl group (—CHO) leads to the formation of a diol, a triol, or, in the case of acetaldehyde, the tetrol:



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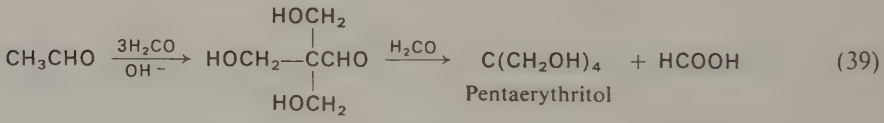
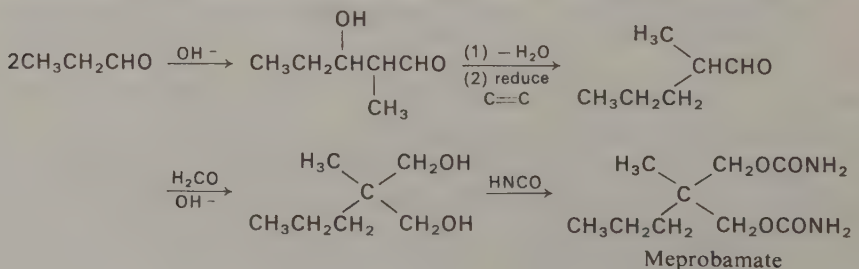


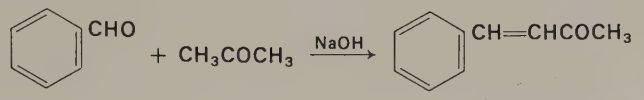
(39)

In industrial practice these reactions are applied to the production of important materials. *Pentaerythritol* can be converted into the nitric acid ester, pentaerythritol tetranitrate, valuable both as an explosive and as a drug used to dilate coronary arteries and relieve the symptoms of *angina pectoris*. Another widely used compound produced by a reaction of this kind is *meprobamate*, a sedative and tranquilizing drug. As the following equations show, meprobamate is the product of two different aldol condensations; it is the carbamic acid ester (RO—$CONH_2$) of the final diol:



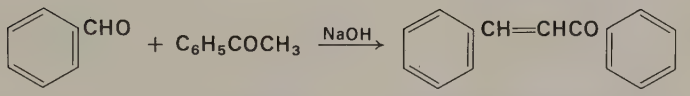
(40)

Aromatic aldehydes. Benzaldehyde, a typical aromatic aldehyde, condenses with compounds having a $—CH_3$ or $—CH_2—$ group α to a carbonyl group to give *benzal* derivatives. The intermediate aldol is not isolated, for it is readily converted into the α,β-unsaturated product, the stability of which is enhanced by the conjugation in the system $Ar—\overset{|}{C}=\overset{|}{C}—C=O$.



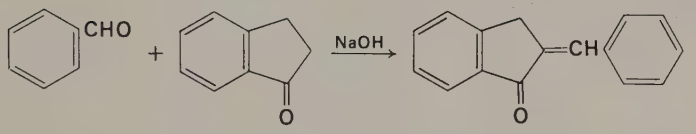
(41)

Benzalacetone



(42)

Acetophenone Benzalacetophenone



(43)

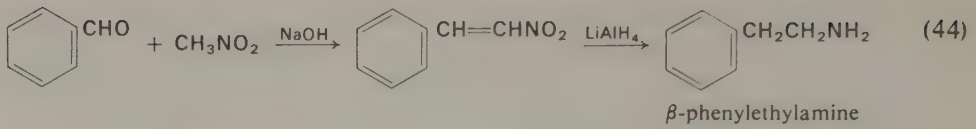
1-indanone 2-benzal-1-indanone

This reaction is valuable, aside from its application to synthesis, as a diagnostic test for the $—CH_2CO—$ grouping. It can be used, for example, to distinguish between 2,2-dimethylcyclohexanone and 2,6-dimethylcyclohexanone, or between 2-methyl-1-indanone and 3-methyl-1-indanone.

Exercise 5

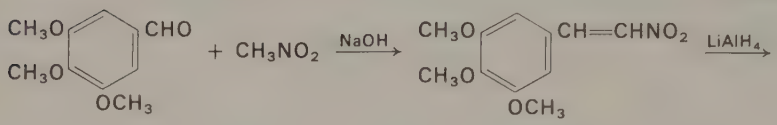
Account for the fact that di-isopropyl ketone (2,4-dimethyl-3-pentanone) does not give a stable aldol condensation product with benzaldehyde.

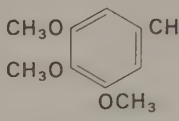
Primary nitroalkanes, the α $CH_2—$ grouping of which is activated by the nitro group, can add to carbonyl groups in aldol-like addition reactions. The intermediate α-hydroxy nitro compounds are not isolated but lose the elements of water to yield α,β-unsaturated nitro compounds. This reaction provides a convenient route to certain β-arylethylamines, for reduction of the system $—CH=CHNO_2$ to $—CH_2CH_2NH_2$ can be readily accomplished by the use of lithium aluminum hydride. The procedure affords a simple and convenient synthesis of the important psychoactive drug *mescaline*:



(44)

β-phenylethylamine



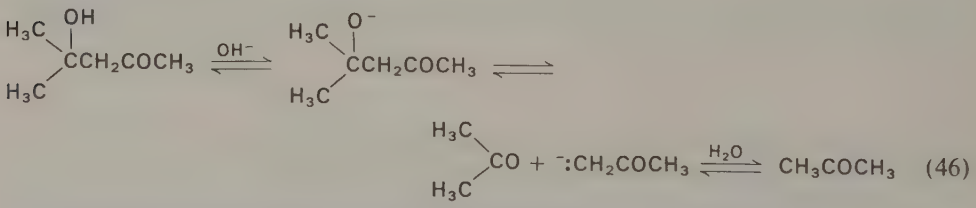


(45)

Mescaline

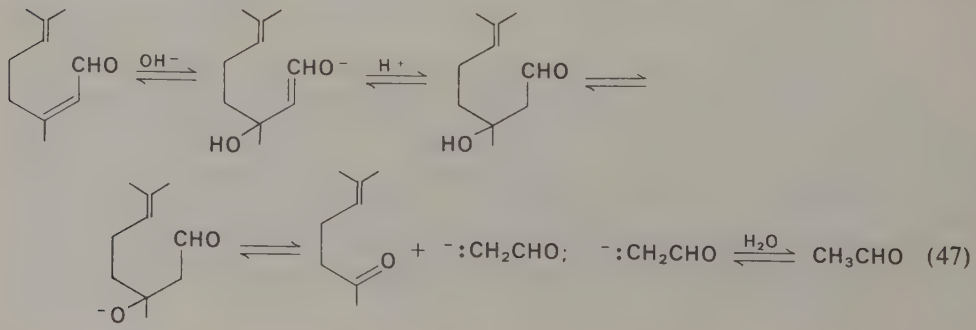
22-8 The reversibility of the aldol condensation. Alkaline cleavage of β-hydroxy ketones and α,β-unsaturated carbonyl compounds

The aldol condensation reaction is reversible and proceeds to an equilibrium, as the equations written to describe its mechanism have indicated. It may be concluded, therefore, that the products of aldol condensations will undergo reversion to their precursors when subjected to the action of alkali. Diacetone alcohol, for example, will revert in alkaline solution to the equilibrium mixture of diacetone alcohol and acetone (about 95% of the latter):



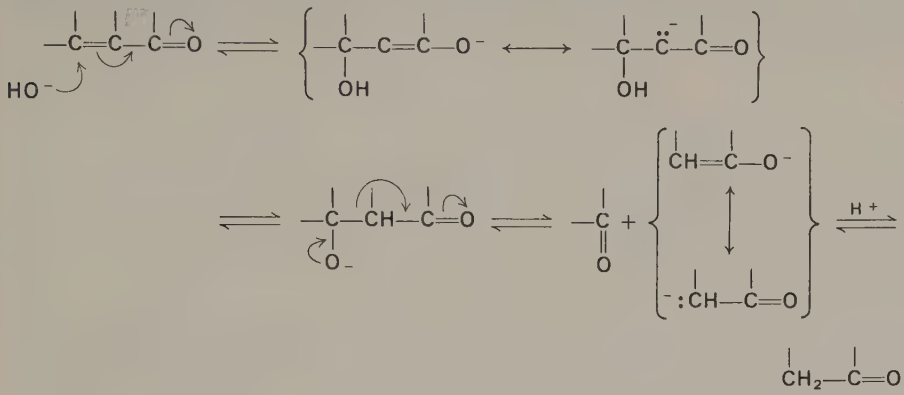
(46)

The α,β-unsaturated carbonyl compounds formed by dehydration of aldols are also subject to alkaline cleavage. Citral, an α,β-unsaturated aldehyde, is decomposed by alkali (aqueous potassium carbonate) in the following way:



(47)

The mechanism of cleavage is shown in detail in the following:

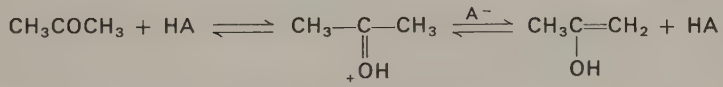


(48)

22-9 Acid-catalyzed aldol condensation

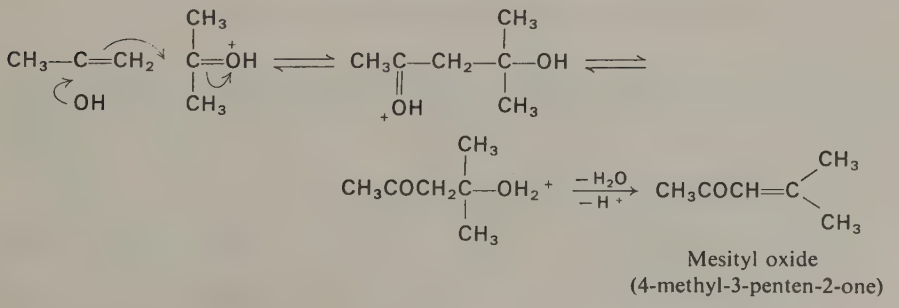
The condensation reaction between an active methylene group and a carbonyl group can also be brought about by acid catalysis. Although under these conditions the nucleophilic carbon anion is not formed, protonation of the carbonyl group increases its electrophilic character, rendering it susceptible to attack by the enolic form of the active methylene compound. The details of the process can be illustrated by the reaction of acetone to give mesityl oxide (a common name for 4-methyl-3-pentene-2-one):

(*a*) Enolization



(49)

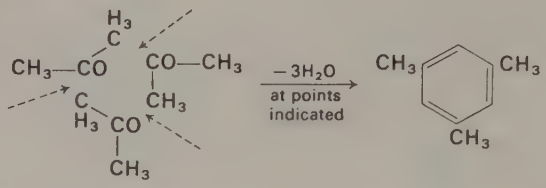
(*b*) Addition of enol to protonated carbonyl group



Mesityl oxide
(4-methyl-3-penten-2-one)

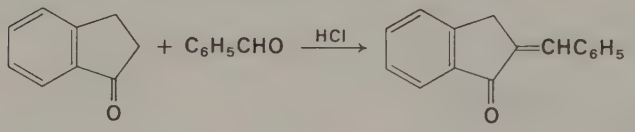
(50)

Under the influence of an excess of strong acid (for example, concentrated H_2SO_4), further condensations can occur. Acetone is converted under these conditions into the aromatic hydrocarbon mesitylene:

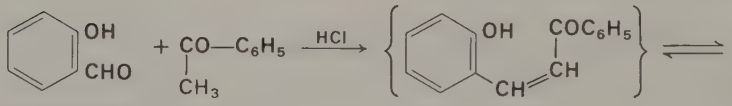


(51)

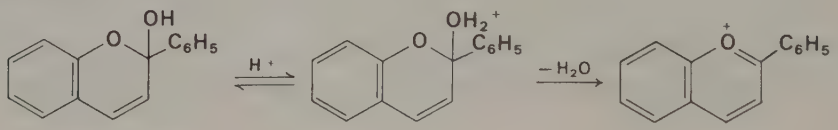
Acid-catalysis is often useful when reactants or products are unstable to alkali, or when alkali causes undesirable side reactions. The following two reactions are satisfactorily performed under acid conditions:



(52)



Salicylaldehyde



Cyclic hemiketal

(53)

The acid-catalyzed reactions shown in (53) subsequent to the initial aldol condensation will be recognized as belonging to the class of reactions described earlier (Section 12-9) in connection with hemiacetal formation.

22-10 The haloform reaction. Halogenation of ketones

The reaction of bromine under alkaline conditions with carbonyl compounds containing α hydrogen atoms results in the formation of α-bromo ketones, aldehydes, and so on:

$$RCOCH_3 + OH^- \rightleftharpoons RCOCH_2{:}^- + H_2O$$

$$RCOCH_2{:}^- \curvearrowright Br{-}Br \longrightarrow RCOCH_2Br + Br^- \qquad (54)$$

Nucleophilic attack of $RCOCH_2:^-$ upon the bromine molecule leads to the formation of the α-bromo ketone. If R is CH_3, further bromination occurs on the $—COCH_2Br$ group (why?), leading finally to CH_3COCBr_3.

Exercise 6

In bromination of a ketone RCH_2COCH_3 with bromine and alkali, the first product is RCH_2COCH_2Br. Would a second bromination yield $RCHBrCOCH_2Br$ or $RCH_2COCHBr_2$? Explain.

This bromination (or, with the respective halogens, chlorination or iodination) is the basis of a valuable diagnostic and synthetic reaction called the *haloform reaction.* When a methyl ketone $RCOCH_3$ is used, the tribrominated ketone is cleaved by attack of OH^- in the following way:

$$RCOCH_3 \xrightarrow[NaOH]{Br_2} RCOCBr_3 \underset{}{\overset{OH^-}{\rightleftharpoons}} R—C(O^-)(OH)(CBr_3)$$

$$RC(O^-)(OH)(CBr_3) \longrightarrow \left\{ R—C(=O)(OH) + {}^-:CBr_3 \right\} \longrightarrow RCOO^- + HCBr_3 \qquad (55)$$

This reaction depends upon the formation of the $:CBr_3^-$ anion, and its irreversible nature upon the final formation of the $RCOO^-$ anion, which is not susceptible to attack by nucleophiles. It should be noted that the cleavage reaction has a close kinship with ester saponification.

Exercise 7

Compare ester saponification with the alkaline cleavage of the tribromomethyl ketone shown in (55).

The haloform reaction is useful in structure diagnosis for demonstrating the presence of the $—COCH_3$ grouping. When iodine is used, the product is iodoform (CHI_3), a crystalline solid that is easily recognized and can be readily isolated and identified.

The haloform reaction is also a valuable method for synthesizing carboxylic acids whose corresponding methyl ketone is available or easily prepared; in general:

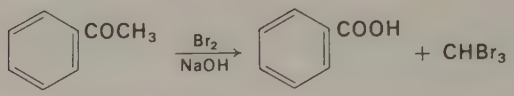
$$RCOCH_3 + NaOX(X_2 + NaOH) \longrightarrow RCOONa + CHX_3 \qquad (56)$$

For example:

$$CH_3COCH_3 \longrightarrow (CH_3)_2C{=}CHCOCH_3 \xrightarrow[NaOH]{Cl_2} (CH_3)_2C{=}CHCOOH + CHCl_3 \quad (57)$$

$$(CH_3)_3CCOCH_3 \xrightarrow[NaOH]{Br_2} (CH_3)_3CCOOH + CHBr_3 \quad (58)$$

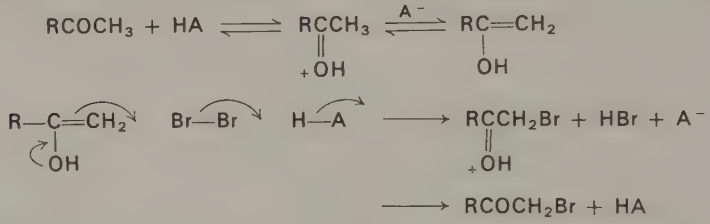
Pinacolone



(59)

Acetophenone

Acid-catalyzed halogenation can also be accomplished. In this case it is the enolic form of the ketone that is the nucleophile (compare the acid-catalyzed aldol condensation):

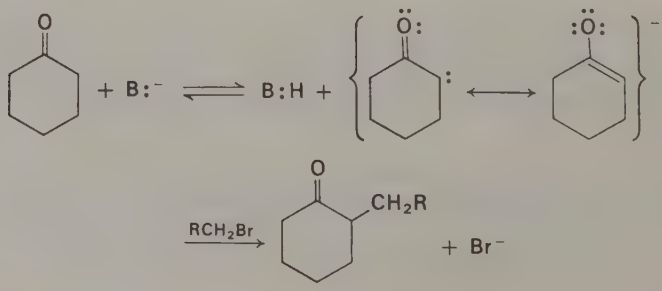


(60)

In acid-catalyzed halogenation, the introduction of a second halogen atom is not directed exclusively to the $—COCH_2X$ group as it is in base-catalyzed halogenation. Acetone, for example, is dichlorinated to a mixture of 1,1-dichloro- and 1,3-dichloro-2-propanone. Cyclohexanone gives a mixture of the 2,2- and 2,6-dichloro compounds.

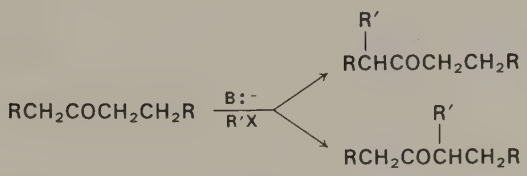
22-11 Alkylation of mono-carbonyl compounds

The enolate anion (carbanion) derived by removal of a proton from the α carbon atom of a ketone is the conjugate base of a very weak acid; consequently it is a strong base. It is also an effective nucleophile, and can attack an alkyl halide in a typical nucleophilic displacement reaction. Using cyclohexanone as a typical example:



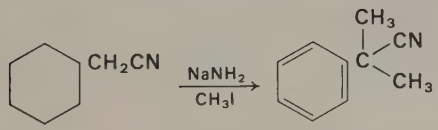
(61)

Although this overall process represents a valid synthetic procedure, it is seldom practical. In the presence of the strong base $B:^-$, which may be sodamide or a sodium alkoxide, the alkylated product may also be deprotonated, and di- or poly-alkylation will occur. Furthermore, many ketones and aldehydes can and will undergo base-catalyzed aldol condensation under the conditions of this reaction. Another practical disadvantage is that the alkylation is often not selective, and an unsymmetrical ketone can be alkylated at either α position:



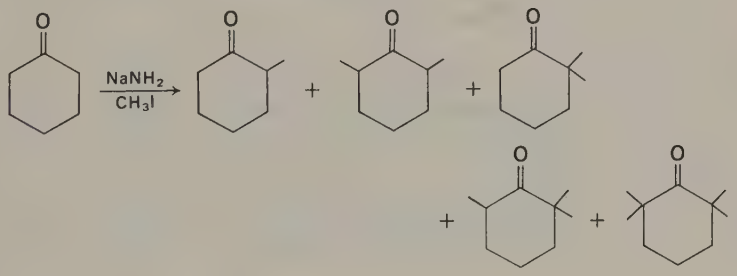
(62)

When poly-alkylation is the desired end, or when the poly-alkylated products can conveniently be separated, the reaction is useful:



(63)

$$(CH_3)_2CHCOCH(CH_3)_2 \xrightarrow[CH_3I]{NaNH_2} (CH_3)_3CCOC(CH_3)_3 \qquad (64)$$



(65)

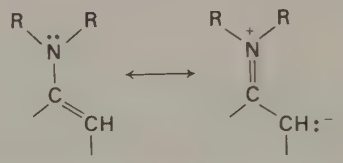
22-12 Alkylation of β-dicarbonyl compounds

The controlled mono-alkylation of β-diketones and β-keto esters is a useful and widely employed synthetic procedure. Its success depends upon the greatly enhanced acidity of the —CH_2— group flanked by two carbonyl groups, making possible its deprotonation under relatively mild basic conditions. The synthetic applications of this procedure are described in Section 24-10 and should be referred to at this time.

22-13 Alkylation and acylation of enamines

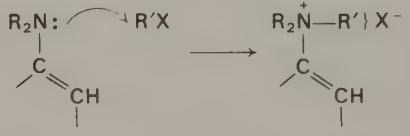
A practicable procedure for the mono-alkylation and -acylation of ketones and aldehydes is an indirect method that involves the preparation of an *enamine* (Section 19-9).

Enamines are nucleophiles whose nucleophilic character can be expressed at both carbon and nitrogen:

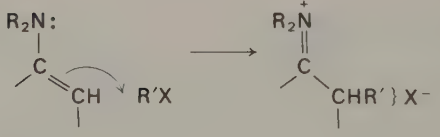


(66)

Although alkylation can occur at either nitrogen or carbon, it is carbon-alkylation that usually predominates:

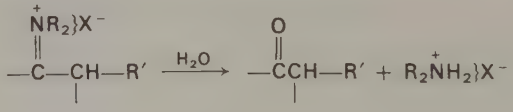


(*N*-alkylation) (67)



(*C*-alkylation) (68)

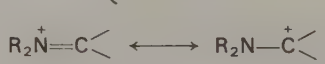
The alkylated enamine, an imonium salt, is readily hydrolyzed to the ketone:



(69)

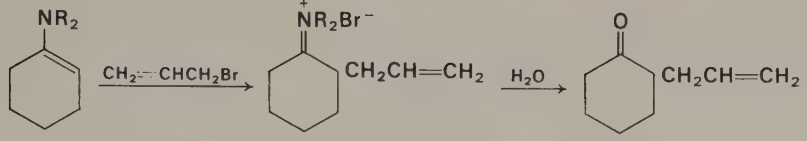
Exercise 8

Formulate the stepwise course of the hydrolysis of a carbon-alkylated enamine. Recall that the grouping $R_2\overset{+}{N}{=}C\diagup\diagdown$ is a resonance hybrid:

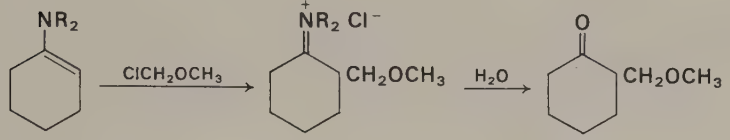


The alkylation of enamines, which are only moderately nucleophilic, is most

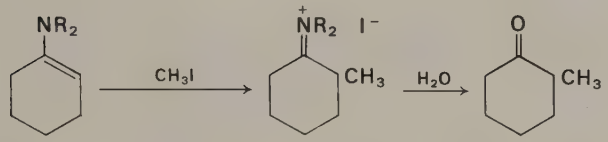
successful with reactive halides. Methyl, allyl, benzyl, and α-alkoxyl halides react most readily:



(70)

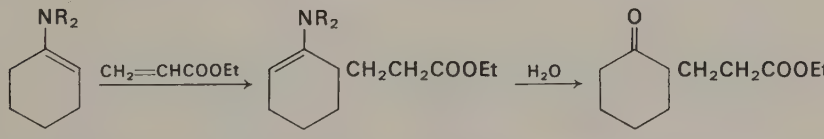


(71)



(72)

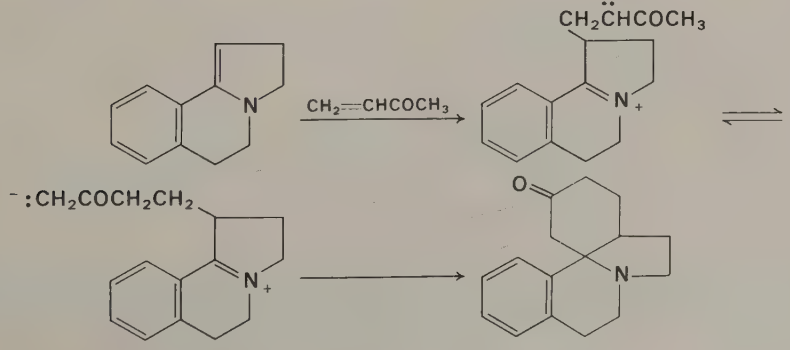
α,β-Unsaturated carbonyl compounds also act as alkylating agents in a reaction equivalent to the Michael condensation (Chapter 25):



(73)

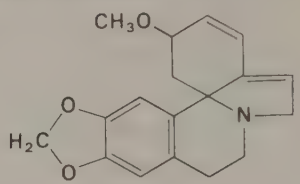
The advantage of alkylating by way of the enamine is that poly-alkylation seldom occurs and the mono-alkylated ketone is generated in good yield.

The scope of enamine chemistry is too wide to be dealt with fully in this text. One example of the use of a bicyclic enamine to produce a unique polycyclic system will show the versatility of the reaction. The ring system that is formed is found in alkaloids that occur naturally in the seeds of *Erythrina* (coral tree):



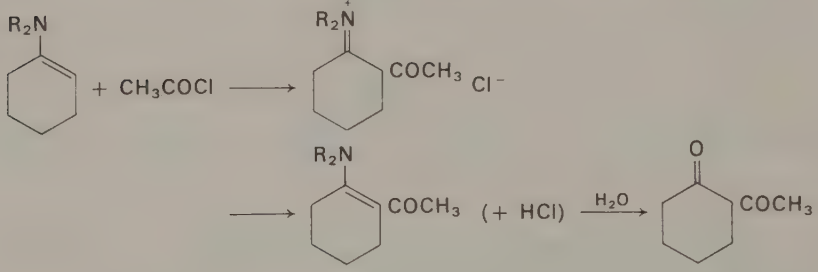
(74)

One of the natural alkaloids has the structure



Erythraline

Enamines react readily with acyl halides to produce β-diketones:*



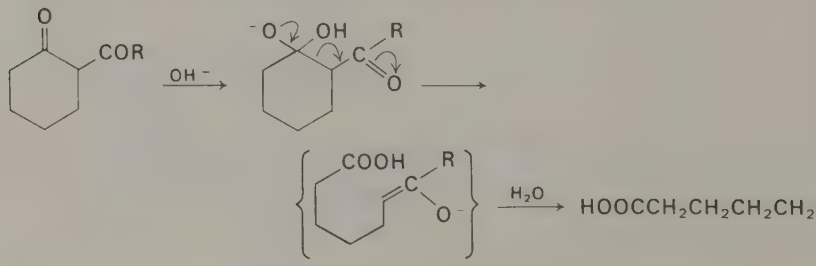
(75)

Exercise 9

Treatment of the enamine 1-diethylaminocyclohexene with an *excess* of acetyl chloride, followed by treatment with water, gives a compound A, $C_{10}H_{14}O_3$. Careful hydrolysis of A with H_2O/OH^- gives B, $C_8H_{12}O_2$. Compound B is the product obtained when the enamine is allowed to react with only *one mole* of acetyl chloride. What are A and B, and how is B formed? HINT: Consider the system

$$R_2N{-}C{=}C{-}C{=}O \longleftrightarrow R_2\overset{+}{N}{=}C{-}C{=}C{-}O^-$$

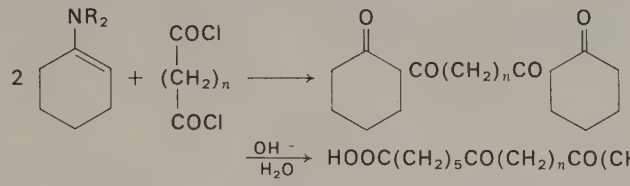
There are numerous special uses for 2-acylcyclohexanones. Since they are α-substituted 1,3-diketones, they are cleaved by alkali to yield keto acids:



(76)

* The HCl formed should be neutralized by the addition of a tertiary amine (for example, triethylamine); otherwise it will protonate and thus deactivate some of the starting enamine, reducing the yield.

Acylation of two moles of enamine with acid chlorides of dicarboxylic acids, followed by alkaline cleavage, proceeds as follows:

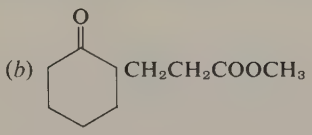


(77)

Exercise 10

Show how the following compounds could be prepared, using any required enamine as one reagent:

(*a*) $CH_3CHCH_2CH{=}CH_2$ with $COCH_2CH_3$ on the second carbon

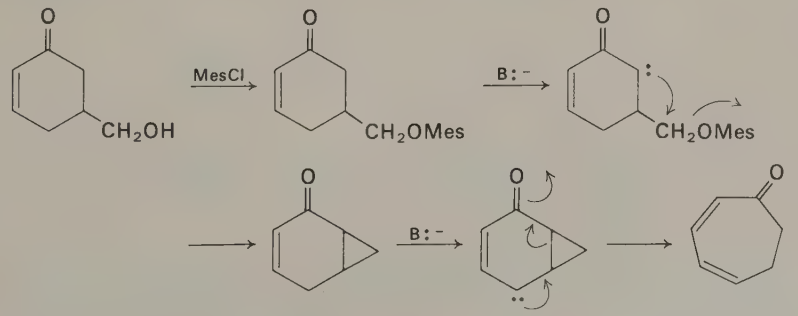
(*b*) 

(*c*) $CH_3CH_2COCHCOCH_3$ with CH_3 on the middle carbon

(*d*) $CH_3CH_2COCH_2CH_2CH_2CH_2COOH$

22-14 Intramolecular displacement by α-carbon anions

When the α-carbon anion is suitably placed with respect to a displaceable halogen substituent, *intramolecular* attack can take place, leading in some cases to simple ring closure, in others to ring closure followed by further reaction. The following examples should be examined carefully and interpreted in light of the discussion in this and previous chapters (some of the intermediate proton exchanges are not made explicit in these equations):*



(78)

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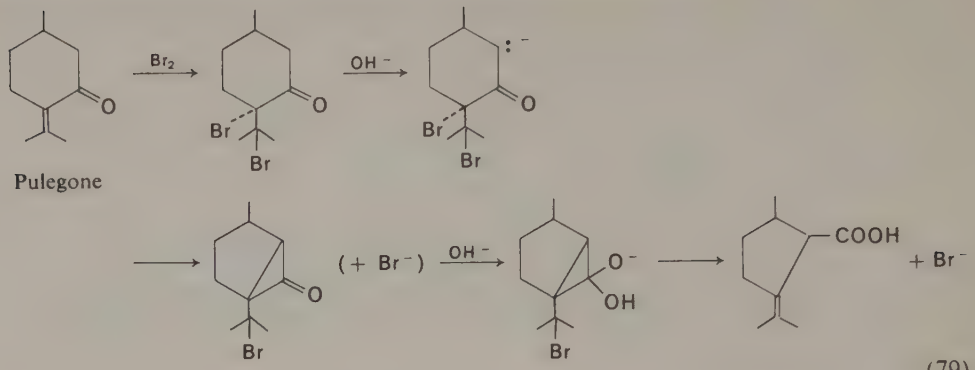
* MesCl is an abbreviation for methanesulfonyl chloride, CH_3SO_2Cl; and Mes is the CH_3SO_2— group.

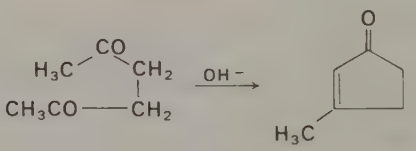


(79)

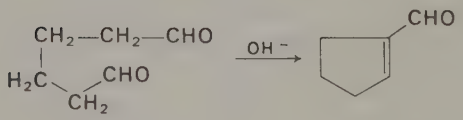
Further discussion of cyclization reactions of this kind will be found in Chapter 27.

22-15 Cyclization by aldol condensations

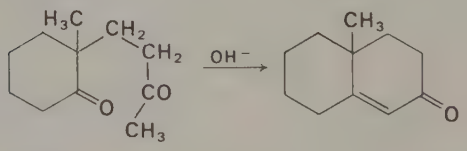
When the two reacting centers—the active methylene group and the carbonyl group—are in the same molecule, aldol condensation will lead to ring closure, provided that the ring to be formed is five- or six-membered:



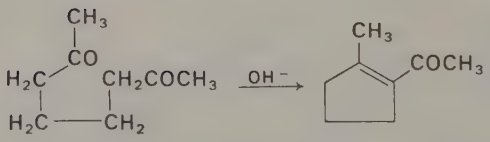
(80)



(81)



(82)



(83)

It will be noticed that in the last example there is an alternative course for intramolecular ring closure.

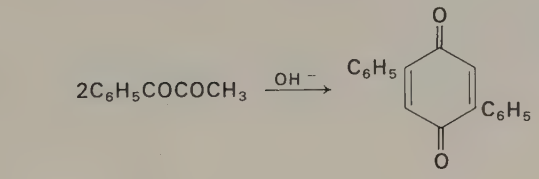
$$\overset{1}{CH_3}\overset{2}{CO}\overset{3}{CH_2}\overset{4}{CH_2}\overset{5}{CH_2}\overset{6}{CH_2}\overset{7}{CO}\overset{8}{CH_3}$$

Condensation between either 1 and 7 or 2 and 8 would lead to a seven-membered ring. Although a seven-membered ring is quite capable of existing and is essentially strainless, the probability of its formation is much less than that of the five-membered ring. Ring closure to the latter has a high degree of probability because the "ends" (—CH_2— and —CO—) are disposed in closer proximity. In the case of

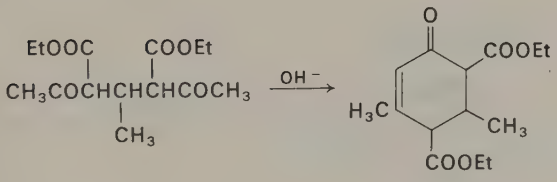
$$\overset{1}{CH_3}\overset{2}{CO}\overset{3}{CH_2}\overset{4}{CH_2}\overset{5}{CO}\overset{6}{CH_3}$$

in which ring closure takes place between 1 and 5, the alternative condensation between 3 and 5 would yield a three-membered ring. Although the probability of such a reaction is high because of the proximity of the reacting centers, the three-membered ring would be highly strained. Since the aldol condensation is reversible, a strained ring can not exist when condensation to the strainless cyclopentenone can supervene.

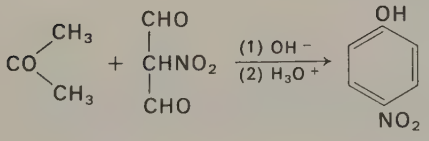
Aldol cyclization takes many forms; a few additional typical examples are these:



(84)



(85)



(86)

Exercise 11

Formulate the reactions shown in examples (84)–(86), writing all the steps leading to the final products.

Exercise 12

What product would be obtained by the cyclic aldol condensation of (*a*) heptane-2,6-dione; (*b*) nonane-2,8-dione?

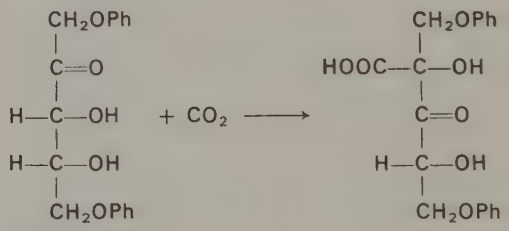
22-16 Reactions of the aldol type in biological systems

Bond formation by condensation reactions of the aldol class, and reactions that involve bond-breaking by the reversal of aldol condensations, are of great importance in many areas of the chemistry of cellular metabolism. Indeed, in the most fundamental processes of all—the conversion of carbon dioxide into the carbon compounds of which living organisms are made—the chemistry of the carbonyl group is of prime importance.

The processes to be described here take place in living cells and are mediated by the presence of catalytic enzymes, most of which are specific for the reactions they control. Nevertheless, these reactions are comprehensible in rational mechanistic terms: they follow courses that are consistent with the character of the functional groups involved, and take place by way of "normal" mechanisms. The enzyme in whose presence a biological reaction occurs affects the rate of the reaction, the stereochemistry of the product, and often the structural site (when more than one of similar type is present) at which the reaction occurs. In many cases the role of the enzyme can be interpreted as that of an acid-base catalyst in which the catalytic functional groups are advantageously disposed for acting *stereospecifically* and *regiospecifically*.

22-17 Carbon dioxide fixation

A key reaction that incorporates carbon dioxide into the carbon compounds of photosynthesizing organisms is the condensation of the five-carbon sugar ribulose (as the 1,5-diphosphate ester) and carbon dioxide:*



D-ribulose-1,5-diphosphate

(87)

This is clearly a nucleophilic attack upon CO_2 by C-2 of the ketose; yet it is apparent

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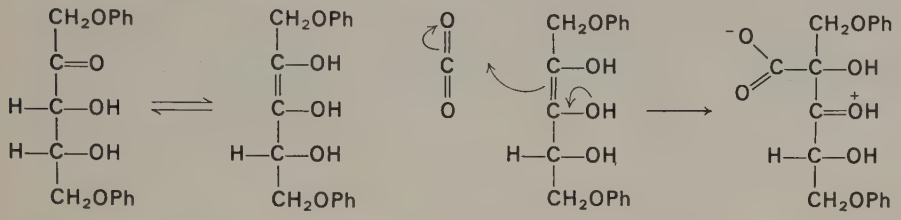
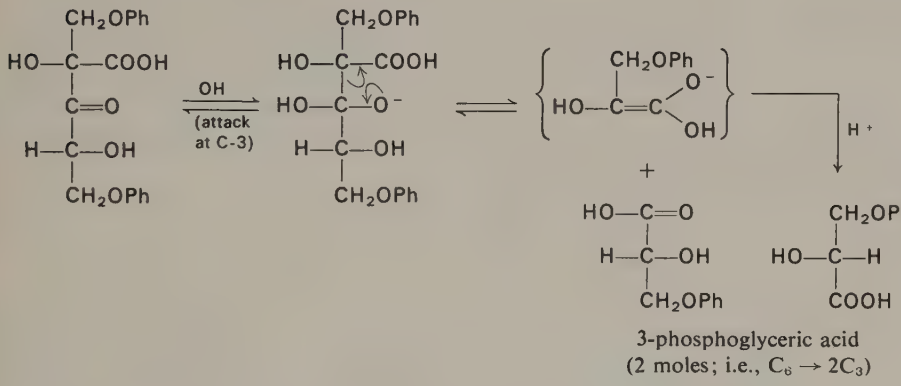
* The symbol "Ph" is used for the phosphate grouping; thus RO—P(=O)(OH)—OH (the phosphate ester of ROH) is written R—OPh.

that C-2 in ribulose is not nucleophilic: it is the carbon atom of a carbonyl group. The enol form of the ketose does, however, have the necessary nucleophilic center at C-2, so that the overall reaction may be pictured as follows; simple proton exchange in the final stage leads to the desired product:



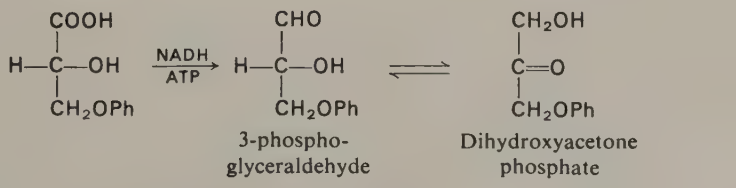
(88)

Base-catalyzed cleavage of the hydroxy acid converts it into two molecules of a three-carbon acid, 3-phosphoglyceric acid:*



(89)

The final step in carbon dioxide incorporation at this early stage of the total process is the enzymatic reduction of 3-phosphoglyceric acid into 3-phosphoglyceraldehyde, and isomerization of the latter, by way of an intermediate enolization, into dihydroxyacetone phosphate:

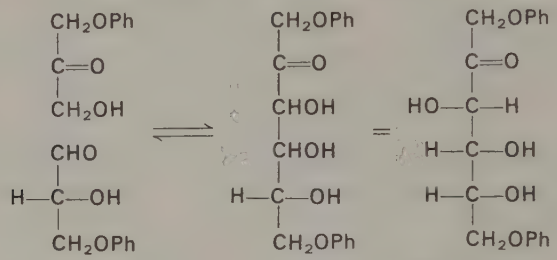


(90)

* The use of OH^- and H^+ as the agents in these formulations is a convenience. They correspond to proton-donating and -accepting groups in the catalytic enzyme.

22-18 Aldolase. Aldol condensation of trioses

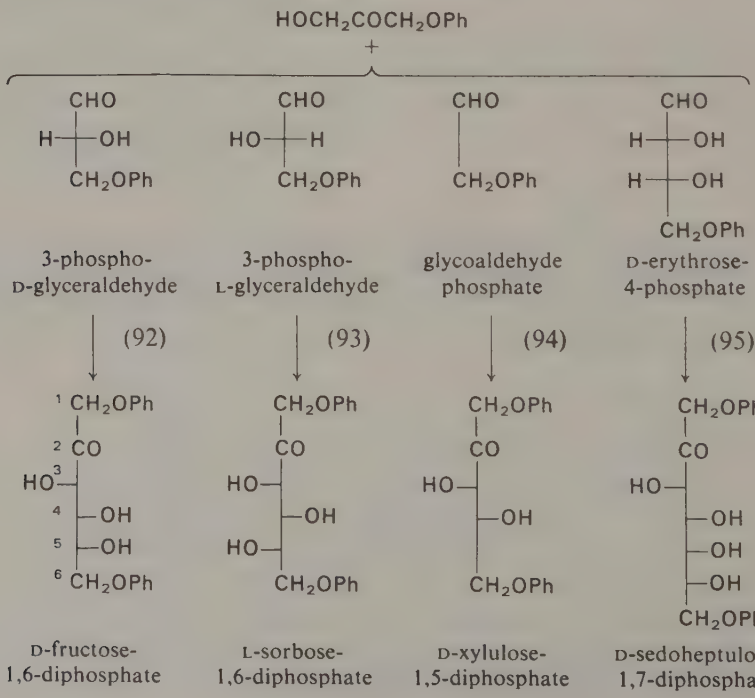
It is apparent upon inspection of the structures of glyceraldehyde and dihydroxyacetone that they possess the typical functional requirements for aldolization; one contains the —CHO group, the other a methylene group adjacent to a carbonyl carbon atom. Aldol condensations of this kind—and their reverse—are fundamental processes of cellular metabolism and are catalyzed by a well-characterized enzyme, *aldolase*. The simplest expression for the reaction is the following:



Fructose-1,6-diphosphate

(91)

Aldolase has the capacity for catalyzing a number of aldol condensations of this kind, in which dihydroxyacetone phosphate condenses with a variety of compounds, all of which contain the terminal —CHO grouping:

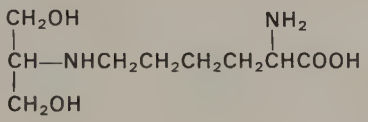


3-phospho-D-glyceraldehyde | 3-phospho-L-glyceraldehyde | glycoaldehyde phosphate | D-erythrose-4-phosphate

D-fructose-1,6-diphosphate | L-sorbose-1,6-diphosphate | D-xylulose-1,5-diphosphate | D-sedoheptulose-1,7-diphosphate

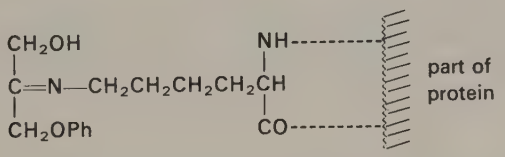
It will be noted that the products possess a uniform stereochemistry at the point at which the $-COCH_2OH + -CHO \rightarrow -COCHOH-CHOH-$ addition has occurred (that is, at C-3 and C-4).

Evidence has been found that these aldolase reactions include an added step that is not shown in the above expressions. This evidence is the observation that when the reaction mixture of enzyme and substrate (dihydroxyacetone phosphate) is reduced with sodium borohydride, and the resulting mixture hydrolyzed to separate the enzyme polypeptide into its constituent amino acids, there can be isolated from the mixture a compound of the following structure:



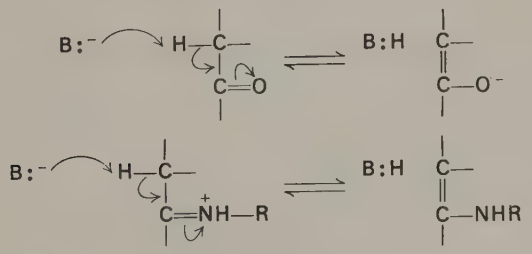
(96)

This indicates that at the point at which the enzyme and substrate combine to form the reactive complex the carbonyl group of dihydroxyacetone phosphate forms a Schiff base with the terminal amino group of a lysine residue:



(97)

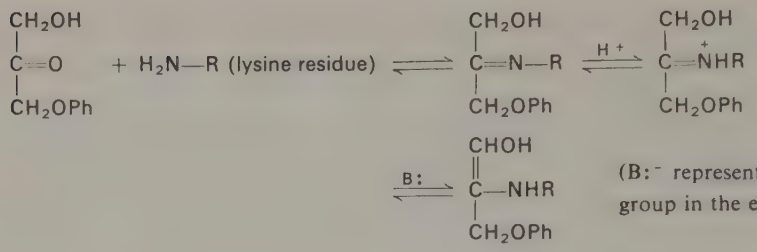
If one compares the carbonyl group with the protonated Schiff base, it is apparent that both can act in the same way to activate an α hydrogen atom:



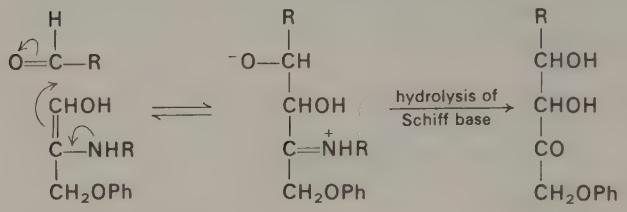
(98)

The C=O and $C{=}NH^+$ groupings are also similar in their susceptibility to nucleophilic attack on carbon.

The detailed picture of aldolase catalysis can thus be represented by the following partial expressions:



(99)



(100)

It should be recognized that the ionic intermediates shown may not exist as discrete compounds, but that the proton-transfer reactions may occur simultaneously, as a concerted process.

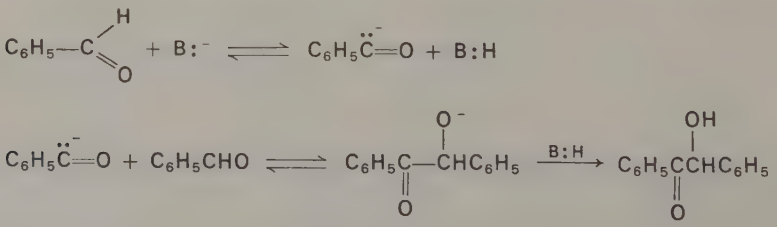
It can be seen from this that the enzyme not only plays a specific role in the catalysis of the condensation but, because of the formation of an intermediate substrate-enzyme compound, *specifies the site on the asymmetric protein molecule* at which the reaction occurs, thus controlling the stereochemistry of the process.

22-19 The benzoin condensation. Activation of formyl hydrogen

When benzaldehyde is treated with an alcoholic solution of KCN, a "dimer" of benzaldehyde, benzoin, is formed. The reaction is called the *benzoin condensation*:

$$2C_6H_5CHO(+\ KCN) \longrightarrow C_6H_5COCHOHC_6H_5\ (+\ KCN)$$

The simplest (but incorrect) explanation for this might appear to be the following:

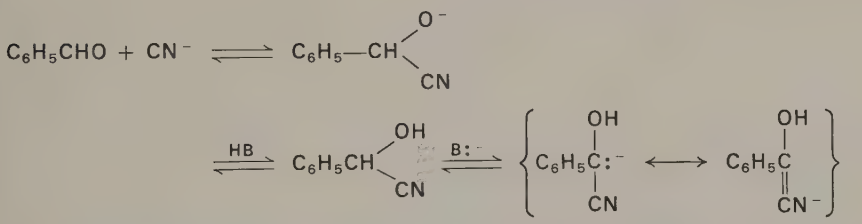


(101)

This mechanism can be discarded on several grounds. For one thing, the hydrogen

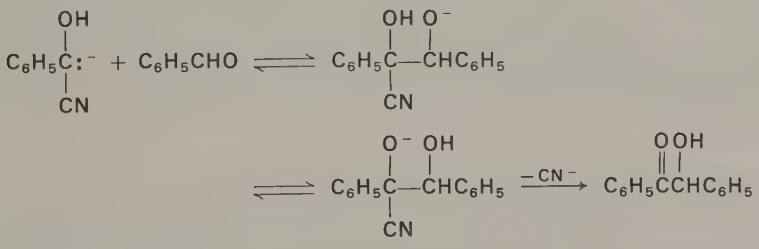
atom of the —CH=O group is not an α hydrogen; it is attached *directly* to the carbonyl carbon atom. The ion $(R\ddot{C}{=}O)^-$ lacks the capability for electron delocalization found in the α-carbanion $(-\ddot{C}-C{=}O)^-$ and has no important stabilizing resonance. For another, the benzoin condensation is not a simple base-catalyzed reaction, as the above mechanism would suggest, but is *specifically catalyzed* by an alkali cyanide.* Finally, it is known that cyanide ion attacks the carbonyl carbon atom as a first step in cyanohydrin formation.

An examination of benzaldehyde cyanohydrin discloses a significant feature: the hydrogen attached to the carbon atom is α to the cyano group, and thus has the capability of ionizing to form an α-carbanion. In brief, the cyanohydrin possesses an active α hydrogen atom. The following equilibria can be postulated [where H:B and $B:^-$ represent the proton-donating (for example, ROH) and proton-accepting (for example, CN^-) species that would be present in alcoholic KCN]:



(102)

The α-carbanion in this equilibrium can now act in the expected manner as a nucleophilic addend to the carbonyl group of the aldehyde. It will be recognized that the product of this addition is the cyanohydrin of benzoin, and that the equilibrium benzoin ⇌ cyanohydrin is far to the side of free benzoin:



(103)

It is apparent from this that the *overall* process of benzoin formation can after all be represented, although crudely, by the simplistic mechanism that was first put forward.

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* It will be seen in Section 22-24 that a biological catalyst (an enzyme prosthetic group), thiamin, can also catalyze the benzoin condensation *in vitro*.

The formyl hydrogen atom is indeed "activated," but only after the initial combination with cyanide, which acts as an "operator" that enters and leaves the reaction sequence but does not appear in the overall expression.

22-20 Biological synthesis of acetoin

A product sometimes formed in the biological degradation (metabolism) of carbohydrates is acetoin, $CH_3COCHOHCH_3$. It can be seen that this compound could be formed from acetaldehyde just as benzoin is formed from benzaldehyde. That the dimerization of acetaldehyde in a biological system is catalyzed by cyanide ion itself is, however, scarcely to be believed, because of the highly cytotoxic properties of cyanide and its absence from normal biological systems.

Biological systems do contain, as a prosthetic group, a compound that can perform the same catalytic function as cyanide in the benzoin condensation. This is *thiamin pyrophosphate*. Its role as a biological catalyst will be described in Section 22-24.

22-21 Enzymes as biological catalysts

The transformations of organic molecules in biological systems proceed by rational mechanisms that can be interpreted and understood in the same terms as those used for describing organic reactions of all kinds. The enzyme catalyzes the reaction, it does not cause it. It brings about an enormous increase in the rate of the reaction, and often directs its stereochemical course. When a reacting molecule (the *substrate*) is so constituted that two or more pathways, leading to different products, can be envisaged, the enzymatic reaction often directs it to only one of the several products that might be regarded as possible on purely structural or energetic grounds.

What peculiarities do enzymes possess that enable them to act with such efficiency and precision?

1. Enzymes are proteins. Many (but not all) of them contain as part of their structure low-molecular-weight compounds called co-enzymes or *prosthetic groups*. As polypeptides consisting of long sequences of L-amino acids, enzymes are asymmetric molecules. The asymmetry is due not only to the chirality of the amino acids but also to the fact that the long peptide chains are coiled, with parts of the chains connected by bridging elements. Consequently, in the enzyme or upon the enzyme surface, portions of the amino acid components are uniquely oriented to provide a region upon which a substrate molecule can fit in only one (preferred) attitude.

2. The surface of an enzyme is composed of amino acid side chains, arranged in accordance with the order in which the amino acids are linked in the peptide chain and the manner in which the peptide chain is coiled. The result of this is that various regions of the enzyme surface possess different physical and chemical properties. Some are lipophilic, others hydrophilic; some are charged, others neutral; some are nucleophilic, and others are electrophilic.

3. The local environment of an enzyme at the site at which reaction with a substrate occurs may be quite different from the protic (aqueous or alcoholic) media in which most reactions usually take place. For example, a proton-donating group or a nucleophilic group may be essentially non-solvated, and thus be enormously more reactive toward a substrate than if it were in a solvating milieu.

4. Because of the dissymmetry of the enzyme or protein, an asymmetric substrate may find it possible to fit its functional groups to their complementary functions in the enzyme in only one way, so that the surrounding structures at the *active site* may permit one chiral substrate to approach the site but impede approach of its enantiomer, or fail to provide suitably oriented points for its attachment.

5. Because the reaction occurs in an enzyme-substrate complex in which the substrate functionality and the complementary enzyme functionality are in position to react, only a minimal decrease in entropy is required to bring the reactive centers into proximity. This is in contrast to many reactions in solution, where the disorder of randomly distributed reactants must be converted into the order of the transition state before reaction can occur. This requirement for "ordering" the reacting molecules in a non-enzymatic reaction often entails a decrease in the entropy of the system, a factor that diminishes the reaction rate.

6. The capacity of an enzyme for arranging its substrate in accordance with the structure of the catalytic site not only can direct the rate and stereochemistry of the reaction, but can also effect a selection of one reaction course over another that is equally likely. There are known, for instance, naturally occurring compounds of quite different structures that can be assumed to arise from the same precursor. It is reasonable to presume that the reactions in which they are formed occur at quite different enzyme sites. Enzymes can thus act with *regiospecificity* as well as stereospecificity.

22-22 Prosthetic groups as biocatalysts

In other sections of this book are discussions of a number of reactions that occur in biological systems:

(*a*) Stereospecific reduction by the $NAD^+ \rightleftharpoons NADH$ enzymes (Section 11-14).

(*b*) Methyl transfer by "active" methionine (Section 8-3).
(*c*) The chemistry of esterase action (Sections 23-14–16).
(*d*) The role of pyridoxine in transamination (Section 19-10).
(*e*) Nucleophilic displacement reactions involving phosphate esters as "leaving groups" (Section 8-4).
(*f*) Oxidation reactions involving the FAD $\rightleftharpoons$ $FADH_2$ system (Section 36-18), and the transfer of oxygen by oxygenases.
(*g*) The carboxylation of coenzyme A to produce malonyl coenzyme A, with the participation of biotin as the prosthetic group (Section 24-7).

In some of these enzymatic reactions (*a*, *b*, *d*, and *f*) the active catalytic agent is a prosthetic group whose structure is known and the nature of whose action is either known with reasonable certainty or has been reasonably conjectured. In the others, the two reactants are under the stereochemical and entropic control of an enzyme but without the participation of a known enzyme-bound prosthetic group.*

22-23 Vitamins and prosthetic groups

Vitamins are organic compounds that are essential, in small amounts, for the maintenance of normal body functions. Lack or deficiency of vitamins causes various disease syndromes: vitamin C (ascorbic acid), scurvy; nicotinamide or niacin, nervous disorders; vitamin B_2 (riboflavin), cutaneous lesions; vitamin B_1 (thiamin), beri-beri; vitamin B_6 (pyridoxine), pellagra; and others. Most of these conditions are readily reversed upon administration of the vitamin.

Although the existence of vitamins was first deduced from the clinical observation of disease syndromes resulting from dietary deficiencies, later studies resulted in the isolation of vitamins from their natural sources, the establishment of their structures, their synthesis in the laboratory, and the discovery of the modes of action of most of them. Although there remain some vitamins whose deficiency syndromes are not clearly defined, and some whose mode of action is not known in detail, most of the principal vitamins are now recognized as enzyme prosthetic groups. This is especially true of the vitamins of the B group, which include pantothenic acid (a constituent of coenzyme A), nicotinic acid, riboflavin, thiamin, biotin, folic acid, pyridoxine, and cobalamine. The catalytic roles of some of these have been described; others will be described in chapters to follow.

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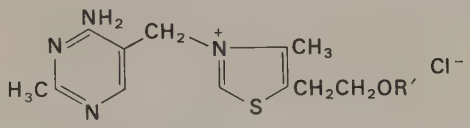
* This statement is guarded because in the future it may be discovered that prosthetic groups or elements (for example, metal ions) are involved in these enzymes.

22-24 Thiamin

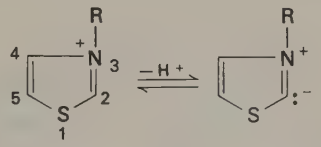
One of the chemically most interesting of enzyme prosthetic groups is *thiamin*:



Thiamin (chloride)*

Although thiamin pyrophosphate was originally called co-carboxylase because of its role in the decarboxylation of α-keto acids (see below), this term is now seldom used. Moreover, the role of thiamin in enzymatic processes is much more various than this simple function. All of its chemical properties may, however, be attributed to a common mode of action.

The principal catalytic site of action of thiamin is the thiazole ring. Thiazolium salts of this general structure are unusual in that they readily lose the carbon-linked proton at C-2 to form the resonance-stabilized zwitterion (an ylid) shown in the following expression (the substituents are omitted for brevity):†

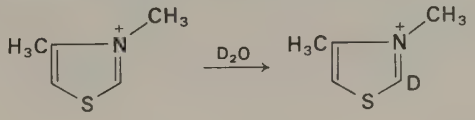


(104)

The delocalization of the negative charge may be attributed to the participation of the *d* orbitals of sulfur.

Three experimental observations support the view that the 2 position is indeed capable of supporting an unshared electron pair:

(1) Thiazolium salts—for example, 3,4-dimethylthiazolium bromide—undergo ready base-catalyzed exchange with deuterium in D_2O:



(105)

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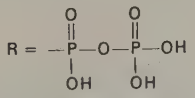
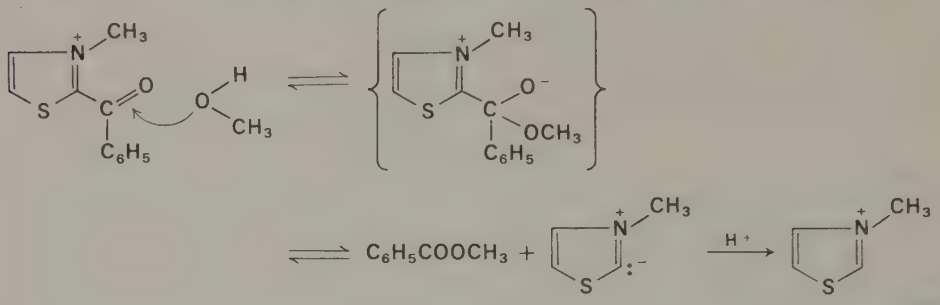
* Thiamin, the vitamin (B_2) administered therapeutically or as the dietary supplement, is the compound shown, with R = H. The form in which it is found as the enzyme prosthetic group is the pyrophosphate ester, with



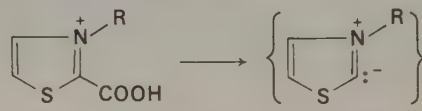
† It can be assumed that under the actual conditions of an enzymatic reaction, not only the substituents, but the pyrophosphate grouping as well are important in binding together the prosthetic group and the specific protein to form the complete enzyme.

(2) 2-Acylthiazolium salts are active acylating agents, which indicates that the expulsion of the thiazolium zwitterion is an energetically feasible process:



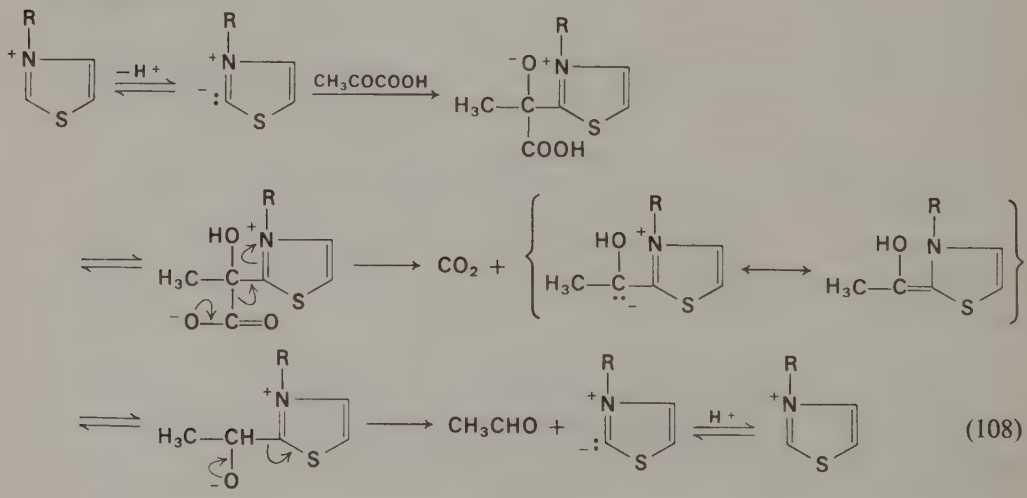
(106)

(3) Thiazolium-2-carboxylic acids are readily decarboxylated:



(107)

The catalytic action of thiamin can be attributed to the uniquely nucleophilic zwitterion produced by removal of the C-2 proton. Its decarboxylation of pyruvic acid (α-ketopropionic acid) is formulated as follows; only the thiazole ring is shown in the equations:

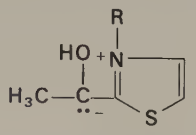


(108)

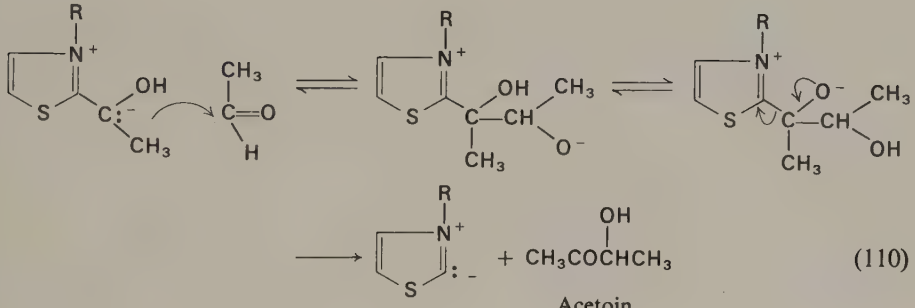
It will be observed that the thiazole participates as a catalyst in the reaction but does not appear in the stoichiometric expression

(109)

Various alternative courses may be taken, starting from the intermediate



This may condense with a molecule of acetaldehyde with the eventual formation of acetoin:



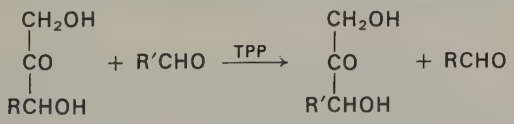
Acetoin

(110)

The thiazolium ylid (zwitterion) bears a striking resemblance, in its behavior, to the cyanide ion. The cyanide-catalyzed condensation of two molecules of benzaldehyde to yield benzoin (Section 22-19) is a reaction that parallels the thiamin-catalyzed formation of acetoin from acetaldehyde. It is not surprising to find that thiamin can also catalyze the benzoin condensation of benzaldehyde *in vitro*.

Exercise 13

Thiamin-containing enzymes catalyze a "transfer" reaction that can be briefly summarized as follows (TPP represents thiamin pyrophosphate):



Formulate the course of this reaction, showing how thiamin (which you may represent simply by the thiazolium ring) participates.

22-25 Summary remarks

The reactions of carbonyl compounds described in Chapter 19 and this chapter are some of the most commonly encountered reactions in organic chemistry; many

examples of addition to carbonyl groups and reactions at α carbon atoms will be met with in the chapters to come. The fundamental character of these reactions has been discussed in terms of relatively simple examples, but it will be recognized in the more complex examples yet to be described.

Reactions of the "aldol family" include a number of kinds that have not yet been mentioned. It should always be borne in mind that these related reactions, which are known by such names as the Claisen, Knoevenagel, Perkin, Thorpe, Michael, Dieckmann, and Stobbe reactions, proceed by mechanistic courses in which the principles of the simple aldol condensation can be discerned.

The subject of the next chapter is the behavior of a group of substances that, while not ordinarily referred to as carbonyl compounds, are indeed members of that class. These are the carboxylic acid derivatives—esters, amides, anhydrides, halides, whose structure is represented by R—C(=O)—X in which the C—X bond is not C—H (as in aldehydes) or C—C (as in ketones), but is C—O, C—N, or C—halogen.

Problems

1. Write the acid-base equilibrium showing the conversion of each of the following compounds into its monoanion by the strong base sodium ethoxide: (*a*) acetone, (*b*) 3,3-dimethyl-2-butanone, (*c*) 2,2-dimethyl-3-pentanone, (*d*) diethyl ketone, (*e*) 2,4-pentanedione, (*f*) propionaldehyde, (*g*) isobutyraldehyde, (*h*) cyclopentanone, (*i*) 2,6-dimethyl-3,5-heptanedione.

2. Write all of the equilibria involved in the base-catalyzed aldol condensation of propionaldehyde to form 2-methyl-3-hydroxypentanal.

3. Show the steps in the base-catalyzed cleavage ("reverse aldol") of (*a*) diacetone alcohol and (*b*) 3-hydroxybutanal.

4. Show the reactants required for the preparation of the following compounds by the aldol condensation: (*a*) 3-hydroxyhexanal, (*b*) 4-hydroxy-2-butanone, (*c*) pentaerythritol, (*d*) 2-(hydroxymethyl)-cyclohexanone.

5. Explain in detail why propionaldehyde is transformed by the action of a strong base into anion (*a*) and *not* into anion (*b*).

   (*a*) $(CH_3\ddot{C}HCHO)^-$ (*b*) $(\ddot{C}H_2CH_2CHO)^-$

6. Write structures for the contributing forms that represent the structures of the following:

   (*a*) $(:CH_2CHO)^-$ (*b*) $(CH_3CO\ddot{C}HCOCH_3)^-$ (*c*) $(CH_2{=}CH\ddot{C}HCHO)^-$

   (*d*) $(CH_2{=}CH\ddot{C}HCH{=}CH_2)^-$ (*e*) $CH_2{=}CHCH{=}\overset{+}{O}H$

7. Write the structure of the predominant product that would be formed by the base-catalyzed aldol condensation of each of the following pairs: (*a*) acetone, acetone; (*b*) acetone, acetaldehyde; (*c*) cyclohexanone, acetaldehyde; (*d*) isobutyraldehyde, formaldehyde; (*e*) propionaldehyde, 2,4-pentanedione; (*f*) nitromethane, acetaldehyde.

8. The aldol condensation of vinylacetaldehyde, $CH_2{=}CHCH_2CHO$, with acetaldehyde in the presence of alkali as a catalyst yields the product $CH_3CH{=}CH{-}CH{=}CHCHO$. Explain this result and formulate the sequence of steps that leads to it.

9. The reaction of 3,3-dimethyl-2,4-pentanedione with alcoholic sodium ethoxide gives ethyl acetate and methyl isotropyl ketone. Formulate this reaction, recalling the principles of nucleophilic attack upon carbonyl groups, and point out the relationship of the cleavage of the diketone to the "reversal" of the aldol condensation.

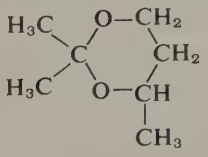
10. A useful method for demonstrating the presence of the grouping $-CH_2-\overset{|}{C}{=}O$ in an organic compound consists in treating the compound with benzaldehyde, C_6H_5CHO, and a trace of alkali (such as sodium ethoxide). The aldol condensation at the active methylene group gives rise to a "benzal" derivative, of the partial structure $-C{=}CHC_6H_5$ (with $-C{=}O$ on the C). Show the formation of the benzal derivatives of the following: (*a*) acetone, (*b*) cyclopentanone, (*c*) diethylketone, (*d*) pinacolone.

11. How could a chemical test distinguish between (*a*) acetone and diethyl ketone, (*b*) methyl isopropyl ketone and isobutyraldehyde, (*c*) diisopropyl ketone and di-*n*-propyl ketone, (*d*) di-*n*-butyl ether and 2-butanone, and (*e*) 2-pentanone and 3-pentanone?

12. Explain why acetylacetone $CH_3COCH_2COCH_3$ is a stronger acid than acetonylacetone, $CH_3COCH_2CH_2COCH_3$. Write the structures of the monoanions formed by the reactions of these two ketones with a base such as sodium ethoxide.

13. What product would you predict to be formed by the intramolecular aldol condensation of 2,8-nonanedione?

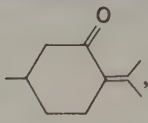
14. Using acetone as the starting material, devise practical syntheses for the following. Show steps and reagents.
(*a*) $(CH_3)_2CHCH_2COOH$ (*b*) $CH_3CHOHCH_2CH_2OH$
(*c*)



15. A compound (A), C_6H_8O, gave cyclohexanone upon catalytic reduction. It had no high-intensity ultraviolet absorption above 200 mμ, but had a weak

(ϵ about 100) maximum at about 290 mμ. When A was treated with alcoholic alkali it was converted into an isomeric ketone (B). Compound B also gave cyclohexanone upon catalytic hydrogenation, and had λ_{max} = 255 mμ with ϵ more than 10,000. Write possible structures for A and B, and suggest what further experiments might be performed to establish the structure of A.

16. A compound (A), $C_7H_{12}O_3$, showed no high intensity ultraviolet absorption above 200 mμ. When A was treated with alcoholic KOH there were formed two products: one was acetic acid; the other (B) was a compound C_5H_8O with an ultraviolet absorption maximum at 225 mμ (ϵ about 10,000). Both A and B gave iodoform when treated with iodine in alkaline solution. Write a reasonable structure for A.

17. Pulegone,  , shows an absorption maximum of 252 mμ (log ϵ about 3.7). When a solution of pulegone in alcoholic KOH is allowed to stand, the intensity of the ultraviolet maximum at 252 mμ falls off with time and eventually disappears. Why?

23

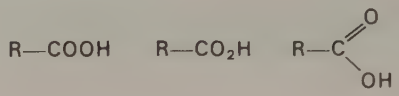
Carboxylic acids and acid derivatives

Little has so far been said about the large class of compounds containing the —COOH group, the *carboxylic acids*, which are described in this chapter. Associated with the carboxylic acids are the so-called *acid derivatives*: esters, amides, halides, and anhydrides. These are called acid derivatives because all of them can be hydrolyzed to regenerate the carboxylic acid. In acid derivatives one of the bonds to the carbonyl group is to oxygen, nitrogen, sulfur, or halogen. They are thus distinguished from ketones, in which the carbonyl group is bonded only to carbon, and from aldehydes, in which the carbonyl group is bonded to carbon and hydrogen.

Carboxylic acids and their derivatives have many important roles in organic chemistry. They include compounds valuable for industrial uses, compounds of cellular metabolism, and reagents of wide application to organic synthesis. Although they are described in this chapter as a discrete class, they will be encountered in all areas of organic chemistry. The methods of their synthesis and their typical modes of reaction are described here with the principal emphasis upon mechanistic rationale.

23-1 The carboxylic acids

The carboxylic acids, RCOOH, constitute a large and important class of organic compounds, widespread in nature in free or combined form, having many applications to the synthesis and transformation of organic molecules. The *carboxyl group* may be represented in the following ways:



Carboxylic acids, their anions ($RCOO^-$), and certain of their derivatives (for example, RCOOR′) behave chemically in ways that are summarized below. They may act as

(*a*) *acids*, by ionization in water, neutralization with bases:

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+ \quad (1)$$

$$RCOOH + OH^- \rightleftharpoons RCOO^- + H_2O \quad (2)$$

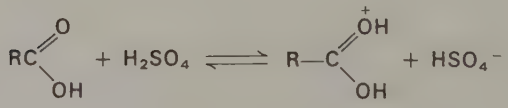
$$RCOOH + NH_3 \rightleftharpoons RCOO^- + NH_4^+ \quad (3)$$

$$RCOOH + CH_3NH_2 \rightleftharpoons RCOO^- + CH_3\overset{+}{N}H_3 \quad (4)$$

(*b*) (*very weak*) *bases.* Carboxylic acids can be protonated by strong mineral acids (H_2SO_4, $HClO_4$):

$$RCOOH + H_2SO_4 \rightleftharpoons RCOOH_2^+ + HSO_4^-$$

that is,



(5)

(*c*) *nucleophiles*, as the carboxylate anions:

$$RCOO^- + R'Br \longrightarrow RCOOR' + Br^- \quad (6)$$

(*d*) *a source of carbon* (*enolate*) *anions*, by loss of α hydrogen (chiefly from esters) to a base:

$$RCH_2COOR' + :B^- \rightleftharpoons (R\ddot{C}HCOOR')^- + H:B \quad (7)$$

Such carbon anions are strongly nucleophilic and can engage in reactions that involve their attack upon an electrophilic center.

(*e*) *electrophiles*, in which the center of nucleophilic attack is the carbonyl carbon atom of the acid derivative.

The nature of the R— groups in these summary expressions can vary over an almost limitless range of structural types. The simplest carboxylic acid is formic acid, HCOOH. Some other representatives, including some of biological importance, are the following:

HCOOH	Formic acid	HOOCCOOH	Oxalic acid
CH_3COOH	Acetic acid	$CH_3COCOOH$	Pyruvic acid
F_3CCOOH	Trifluoroacetic acid	$HOOCCH_2CH_2COCOOH$	α-ketoglutaric acid
H_2NCH_2COOH	Glycine	C_6H_5COOH	Benzoic acid

23-2 Acid strength

Most carboxylic acids in which the carboxyl group is attached to an aliphatic or aromatic group are acids of moderate strength, with pK_a values about 3–5. With electron-withdrawing groups attached to —COOH, the strength of the acids increases, often approaching the level of "strong" acids. Some selected values are given in Table 23-1.

Table 23-1
Strengths (pK_a values) of some carboxylic acids

Acid	*Name (acid)*	pK_a
HCOOH	formic	3.7
CH_3COOH	acetic	4.8
$CH_3COCOOH$	pyruvic	2.7
$ClCH_2COOH$	chloroacetic	2.9
$Cl_2CHCOOH$	dichloroacetic	1.3
Cl_3CCOOH	trichloroacetic	0.7
F_3CCOOH	trifluoroacetic	0.2
$HOOC \cdot COOH$	oxalic	1.3
$HOOCCH_2COOH$	malonic	2.9
$HOOCCH_2CH_2COOH$	succinic	4.2
C_6H_5COOH	benzoic	4.2
$p\text{-}NO_2 \cdot C_6H_4COOH$	*p*-nitrobenzoic	3.4

Exercise 1

Notice that trichloroacetic acid is a much stronger acid than chloroacetic acid, and the latter is stronger than acetic acid. Account for the increase in acid strength in the series: acetic, succinic, malonic, oxalic.

The pK_a values in Table 23-1 show that acid strength increases substantially when electron-withdrawing groups are attached to the α carbon atom, as in chloroacetic acid, trifluoroacetic acid, pyruvic acid. The effect of these substituents is to diminish electron density on the α carbon atom and, by induction (thus the *inductive effect* ascribed to such atoms or groups), on the carboxyl carbon atom.

$$\overset{\longleftarrow\!\!+}{\mathrm{Cl{-}CH_2COOH}}$$

The inductive effect diminishes as additional single bonds are interposed between the electron-attracting center and the carboxyl group. This is illustrated by the pK_a's of the three (α-, β-, and γ-) chlorobutyric acids (Table 23-2). This effect of chlorine upon acid strength is known as its *negative inductive effect* ($-$I). Since the carbonyl group is polarized $\rangle C{=}O \leftrightarrow \rangle \overset{+}{C}{-}O^-$, it too would be expected, when it is present in an α substituent, to be electron-attracting and have a negative inductive effect. The pK_a of acetoacetic acid (CH_3COCH_2COOH) is 3.5, which is in accord with this expectation. The strongly electron-attracting, positively charged $(CH_3)_3\overset{+}{N}-$ group has a marked acid-strengthening effect: the pK_a of $(CH_3)_3\overset{+}{N}CH_2COOH$ is 1.9. The effects of nuclear substituents on the strengths of benzoic acid derivatives are comparable.

Table 23-2
pK_a values for α-, β-, and γ-chlorobutyric (2-, 3-, and 4-chlorobutanoic) acids

Acid	pK_a
$CH_3CH_2CH_2COOH$	4.8
$ClCH_2CH_2CH_2COOH$	4.5
$CH_3CH(Cl)CH_2COOH$	4.1
$CH_3CH_2CH(Cl)COOH$	2.9

Positive inductive effects (+I) are exerted by alkyl groups. Propionic acid (pK_a = 4.9) is slightly weaker than acetic acid. Trimethylacetic acid, with three (+I) α methyl groups, is still weaker (pK_a = 5.1).

23-3 Naming of carboxylic acids

The systematic suffix for carboxylic acid is *-oic acid.* The stem name is derived from the name of the alkane having the same number of carbon atoms, and numbering begins with —COOH = 1.

Acid	*Common name*	*Systematic name*
HCOOH	formic	methanoic (acid)
CH_3COOH	acetic	ethanoic
$(CH_3)_2CHCOOH$	isobutyric	2-methylpropanoic
$(CH_3)_2CHCH_2COOH$	isovaleric	3-methylbutanoic
$CH_3CH{=}CHCOOH$	crotonic	2-butenoic
$BrCH_2CH{=}CHCH_2COOH$	—	5-bromo-3-pentenoic
$HOOCCH_2CH_2CH_2COOH$	glutaric	pentanedioic

The simpler acids are usually referred to by common, or trivial, names, but systematic names are always acceptable. Another general practice is to use *substitution* names based upon a common name:

Acid	*Substitution name*	*Systematic name*
$(CH_3)_3CCOOH$	trimethylacetic (acid)	2,2-dimethylpropanoic (acid)
$C_6H_5CH_2CH_2COOH$	β-phenylpropionic	3-phenylpropanoic
CH_3OCH_2COOH	methoxyacetic	methoxyacetic
$BrCH_2COOH$	bromoacetic	2-bromoethanoic
$HOOCCH(CH_3)CH_2COOH$	methylsuccinic	2-methylbutanedioic

It is to be noticed that where Greek letters are used to designate the position of a substituent, the α carbon atom is the one adjacent to the carboxyl group, and a systematic base name is not used:

$CH_3CHBrCH_2CH_2COOH$ γ-bromovaleric (acid) (*not* γ-bromopentanoic)

$ClCH_2CH(Cl)COOH$ α,β-dichloropropionic (*not* α,β-dichloropropanoic)

23-4 Preparation of carboxylic acids

Oxidation. The carboxyl group represents the highest oxidized state of carbon in organic combination. Carboxylic acids are the end products of the formal oxidation series

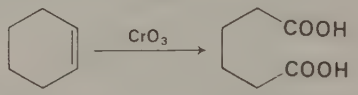
$$RCH_3 \longrightarrow RCH_2OH \longrightarrow RCHO \longrightarrow RCOOH \qquad (8)$$

and in many cases they can be prepared by reactions corresponding to the steps in this series.

When R is an aromatic nucleus (for example, as in toluene, RCH_3) this sequence of steps can be realized by successive separate operations, or *in toto* by oxidation under vigorous conditions. In the latter case the separate intermediates need not be isolated, as the acid itself is the final product.

When R is a saturated or unsaturated aliphatic group the first step, $RCH_3 \rightarrow RCH_2OH$, is seldom realizable in laboratory practice; but oxidation of alcohols to aldehydes, and aldehydes to acids, can be accomplished by a proper selection of reagents and reaction conditions. The most generally applied step in the above sequence is the terminal reaction, $RCHO \rightarrow RCOOH$. This is so for two reasons: (1) since aldehydes are more easily oxidized than alcohols, it is often difficult to interrupt the sequence $RCH_2OH \rightarrow RCHO \rightarrow RCOOH$ at the aldehyde stage; and (2) aldehydes can be prepared in other ways than by oxidation of alcohols, then oxidized further to the carboxylic acids in a separate operation. Further, aldehydes can be oxidized to carboxylic acids with reagents of limited oxidizing power, thus avoiding unwanted oxidative attack at other centers in a molecule.

Some synthetic oxidation procedures leading to carboxylic acids are the following:



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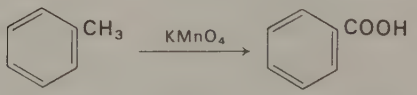

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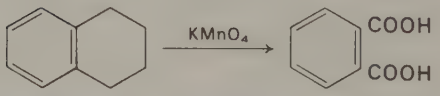


(11)

$$ClCH_2CH_2CH_2OH \xrightarrow{HNO_3} ClCH_2CH_2COOH \qquad (12)$$

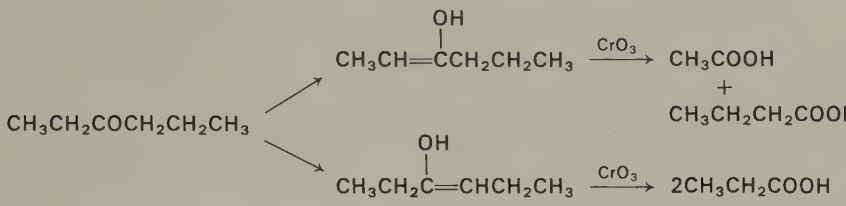
$$CH_3CH_2CH_2CHO \xrightarrow{KMnO_4} CH_3CH_2CH_2COOH \qquad (13)$$

$$CH_3(CH_2)_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH{=}CH(CH_2)_7COOH \xrightarrow{KMnO_4} HOOC(CH_2)_7COOH + CH_3(CH_2)_5COOH \qquad (14)$$

$$CH_3(CH_2)_5COCH_3 \xrightarrow{NaOH/Br_2} CH_3(CH_2)_5COOH + CHBr_3 \qquad (15)$$

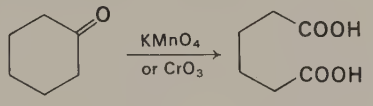
Ketones are much less susceptible to oxidation than aldehydes, and their oxidation usually involves rupture of the carbon chain. Since it is probable that the oxidation of ketones proceeds through the enol, as shown in the following equations, an unsymmetrical ketone gives rise to a mixture of oxidation products. For this reason, the reaction is not usually of preparative value:

$$\begin{array}{l} \\ \\ \\ \\ \end{array}$$

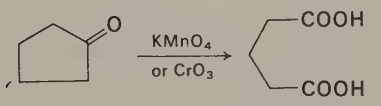


(16)

When enolization can occur only in one way, or when the ketone is symmetrical, oxidation can be a useful preparative procedure:



Adipic acid (17)

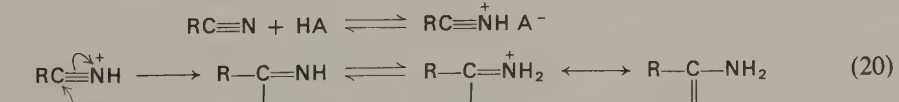


Glutaric acid (18)

Oxidation of an olefin of the type RCH=CHR′ by means of potassium permanganate or chromic acid cleaves the molecule at the double bond, yielding two carboxylic acids:

$$\mathrm{RCH{=}CHR' \xrightarrow{KMnO_4} RCOOH + R'COOH} \qquad (19)$$

Hydrolysis of nitriles. Nitriles are a class of *acid derivatives*; that is, they are converted into carboxylic acids by hydrolysis with acids or alkalis. This reaction has a close kinship with the carbonyl addition reaction, as the following reaction mechanism shows:



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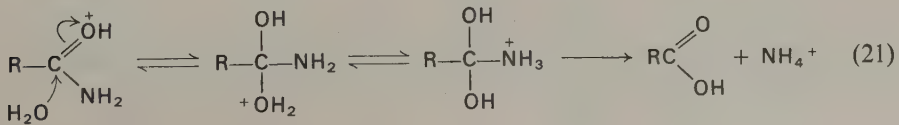


(21)

Because the reaction involves nucleophilic attack upon the carbon atom of the (protonated) —C≡N group, it is subject to steric inhibition by substituents on the α carbon atom.

Alkaline hydrolysis (aqueous NaOH) of nitriles is also practicable. In this case, the reaction is initiated by nucleophilic attack of OH^- upon the nitrile carbon atom.

Exercise 2

Formulate the course of the hydrolysis of a nitrile RCN with aqueous alkali.

A valuable variant of the acid-catalyzed hydrolysis of a nitrile is *alcoholysis*. Heating a nitrile in an alcoholic solution containing a strong acid (for example, H_2SO_4) results in its conversion into an ester. Ethanolysis of *n*-butyronitrile* can be formulated as follows:

$$CH_3CH_2CH_2CN + EtOH \xrightarrow{H_2SO_4} CH_3CH_2CH_2COOEt + (NH_4)_2SO_4 \qquad (22)$$

Exercise 3

Formulate the steps in the course of the ethanolysis of *n*-propyl cyanide.

The practical importance of the synthesis of carboxylic acids from nitriles lies in the ease of preparation of the latter. They can be obtained

(1) from aldehydes and ketones by the cyanohydrin reaction; or
(2) by the nucleophilic displacement reaction of (potassium) cyanide with alkyl halides, sulfonic acid esters, and some quaternary ammonium salts:†

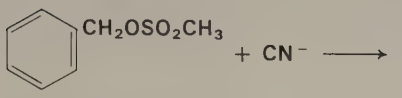
$$CH_3COCH_2CH_3 + HCN \longrightarrow \begin{matrix} H_3C & & OH \\ & \diagdown\ \diagup & \\ & C & \\ & \diagup\ \diagdown & \\ H_3CH_2C & & CN \end{matrix} \qquad (23)$$

---

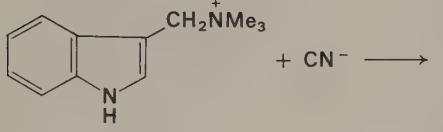
* Nitriles can be named as alkyl cyanides, or by names derived from the corresponding acid. Thus, CH_3CH_2CN is ethyl cyanide or propionitrile. When named as a substituent, —CN is *cyano*; thus CH_3CH_2CN is also cyanoethane.

† Equations of this kind are ordinarily written showing only the ionic participants. It is understood, however, that the corresponding cations (for example, Na^+ and K^+) or anions (for example, Cl^-) are part of the actual reagent.

$$CH_3CH_2CH_2CH_2Br + CN^- \longrightarrow CH_3CH_2CH_2CH_2CN + Br^- \quad (24)$$



(25)



(26)

$$BrCH_2CH_2Br + 2CN^- \longrightarrow \begin{matrix} CH_2CN \\ | \\ CH_2CN \end{matrix} \quad (27)$$

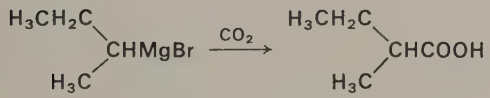
In general:

$$BrCH_2(CH_2)_nCH_2Br + CN^- \longrightarrow (CH_2)_n\begin{matrix} CH_2CN \\ \diagdown \\ \diagup \\ CH_2CN \end{matrix} \quad (28)$$

It will be seen from the examples given that dinitriles can be formed from terminal dibromo compounds; hydrolysis (or alcoholysis) of these leads to the formation of dicarboxylic acids (or esters); these are discussed in Section 23-30.

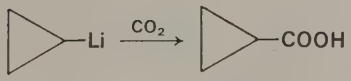
Carbonation of organometallic compounds. The reaction of Grignard reagents and certain organolithium compounds with carbon dioxide is a special case of the addition of RMgX to the carbonyl group. The addition product is the halomagnesium (or lithium) salt of the carboxylic acid, which, as was mentioned in Chapter 20, does not react further with the Grignard reagent. The reaction is very versatile; the reaction of CO_2 with RMgX is quite general, and Grignard reagents of a wide variety of structural types are readily accessible. Some specific examples are the following:

$$CH_3MgI \xrightarrow{CO_2} \left\{ \begin{matrix} OMgI \\ | \\ CH_3C{=}O \end{matrix} \right\} \xrightarrow[H^+]{H_2O} CH_3COOH + Mg^{++} \text{ salts} \quad (29)$$

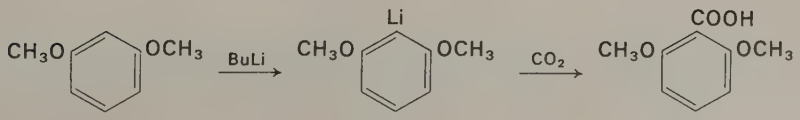


(30)

$$(CH_3)_3CMgCl \xrightarrow{CO_2} (CH_3)_3CCOOH \quad (31)$$



(32)



(33)

Miscellaneous methods. Acids and acid derivatives can be prepared in many ways other than those described above. These procedures are more appropriately discussed in the context of material to be considered in later sections. Briefly, these methods include:

(*a*) Oxidation of ketones with peroxyacids to give esters or lactones (Bayer-Villiger reaction).
(*b*) Alkylation and acylation of β-keto esters, malonic esters, and enamines.
(*c*) Carboxylation of phenols (Kolbe reaction).
(*d*) The haloform reaction.
(*e*) The Beckmann rearrangement of oximes.
(*f*) The Perkin and allied condensation reactions.

Hydrolysis (saponification of esters, amides, and other acid derivatives). As a practical preparative procedure, the hydrolysis of *carboxylic acid derivatives* to the acids is limited by the fact that such derivatives are most often prepared from the acids themselves.

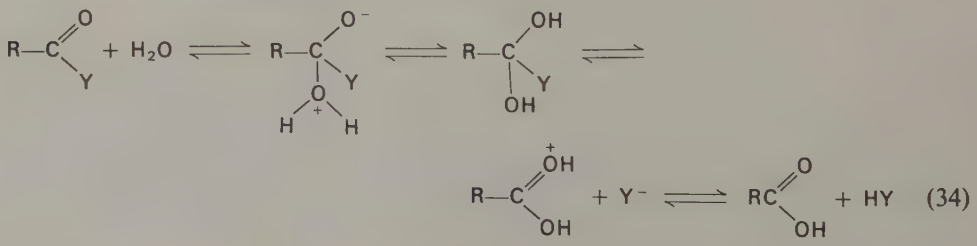
Two large classes of acid derivatives are, however, frequently encountered as such in natural sources, and their hydrolysis leads to acids of great technical, biological, and theoretical importance. These are (*a*) natural fats, oils, and waxes and (*b*) natural polypeptides and proteins.

23-5 Carboxylic acid derivatives

Derivatives of carboxylic acids are compounds that can be transformed into acids by hydrolysis. The commonest are

(*a*) acid halides RCOX (X = halogen)
(*b*) acid anhydrides RCO—O—COR
(*c*) esters RCOOR′
(*d*) amides $RCONH_2$, RCONHR′, $RCONR'_2$

A general expression for the hydrolysis of acid derivatives is the following; it can be seen that attack of the nucleophile, which is water in this formal expression, upon the carbonyl carbon atom corresponds to the first step in the carbonyl addition reactions described in Chapter 19.



(34)

Thus overall:

$$R{-}C(=O){-}Y + H_2O \longrightarrow RCOOH + HY \qquad (35)$$

where Y = —Cl, —OCOR, —OR′, —NH_2, —NHR, or —NR_2.

In practice, most hydrolyses of this sort are performed with the use of alkali or mineral acid; thus, the final reaction mixture in alkaline hydrolysis contains the carboxylate anion. Alkaline hydrolysis of esters is known as saponification.

23-6 Fats and oils. Saponification

Natural fats and oils, members of the class of compounds known as *lipids*, are esters of glycerol in which the acid portions are derived from long-chain carboxylic acids, commonly called "fatty" acids. The natural fatty acids are typified by the saturated 16-carbon-atom compound *palmitic* acid. *Stearic* acid is the 18-carbon-atom homolog; acids with less than sixteen and more than eighteen carbon atoms are known, but are less widely distributed. Olefinic (unsaturated) fatty acids are also known. The commonest are oleic and linoleic acids.

Fats (solids) and oils (liquids) are esters of fatty acids with the trihydroxy compound glycerol (propane-1,2,3-triol). Natural fats and oils vary widely in composition, and the three hydroxyl groups of glycerol may be esterified with more than one kind of fatty acid. Those in which the three acyl groups are all alike bear common names: the tristearoyl ester is *tristearin*, the trioleyl ester is *triolein*, and so on. Glycerol triacetate is *triacetin*.

When heated with aqueous alkali, fats and oils undergo hydrolysis to yield one molecule of glycerol and three molecules of fatty acid (as the sodium salt). Such sodium salts are called *soaps*, from which the term *saponification* is derived. It is general practice to describe the alkaline hydrolysis of an ester as saponification even when the product is not a soap.

Table 23-3
Some common naturally occurring (as esters) fatty acids

Name	*Formula*	*Melting point* (°C)
palmitic acid	$CH_3(CH_2)_{14}COOH$	63
stearic acid	$CH_3(CH_2)_{16}COOH$	70
oleic acid	$CH_3(CH_2)_7CH{\overset{c}{=}}CH(CH_2)_7COOH$	13
linoleic acid	$CH_3(CH_2)_4CH{\overset{c}{=}}CHCH_2CH{\overset{c}{=}}CH(CH_2)_7COOH$	−5

NOTE: The letter c or t over a double bond indicates configuration (*cis* or *trans*).

23-7 Detergents

Soaps are detergents, but not all detergents are soaps. Indeed, in present-day usage the term detergent is commonly used only for cleansing agents that are not soaps. Soaps and detergents have an essential quality in common: they consist of a large hydrophobic (lipophilic) portion attached to a hydrophilic (lipophobic) group. In a soap, the hydrophobic portion of the molecule is the long hydrocarbon ("fatty") chain; the hydrophilic part is the anionic carboxylate group. Both detergents and soaps act in the same way: the fatty portions of the molecules form aggregates with fat-soluble materials (dirts and greases) in such a way as to enclose the "dirt" in an envelope having peripheral water-solubilizing $—COO^-Na^+$ groups. This permits the dirt to be dispersed in the washing medium and allows it to be rinsed away.

Many common detergents consist of a fatty portion, like those in soaps; however, the lipid portion is attached to a hydrophilic "head" that is not always $—COO^-Na^+$, but is often an ionized sulfate group. For example, the mono-ester of sulfuric acid with a C_{12} alcohol, lauryl alcohol, is the soap-like detergent sodium lauryl sulfate, $CH_3(CH_2)_{10}CH_2OSO_2O^-Na^+$. Other useful ionic detergents are similarly constituted, but with various other combinations of lipophilic and hydrophilic groups. *Non-ionic* detergents, like soaps, have a lipophilic portion; however, it is attached to a hydrophilic portion that is not ionic, but possesses water-solubilizing properties by its high content of hydroxyl groups. In Table 23-4 are shown the formulas of a number of common detergent compounds. The lipophilic and hydrophilic portions are indicated.

A practical disadvantage of the use of ordinary soaps is that when they are used in "hard" water containing calcium, iron, or magnesium salts, the insoluble fatty-acid salts of these metals separate as a scum or curd, which deposits on the material being cleansed. The heavy-metal salts of the sulfated fatty alcohols are soluble in water and such detergents are useful even in hard water. The non-ionic and cationic detergents do not, of course, form metal salts.

Certain of the sulfate-ester detergents in use during the early years of their commercial development suffered from the serious fault that they were resistant to

Table 23-4
Some common detergents

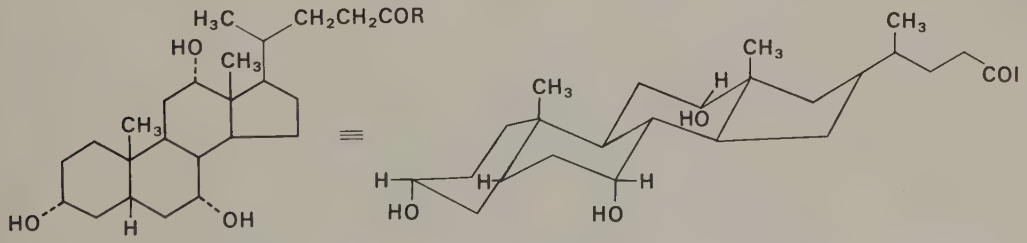
Type	*Lipophilic part—hydrophilic part*
anionic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7—COO^-Na^+$
anionic	$CH_3(CH_2)_{10}CH_2—OSO_2O^-Na^+$
anionic	$CH_3(CH_2)_7CH{=}CH(CH_2)_7—CONHCH_2CH_2SO_2O^-Na^+$
non-ionic	$CH_3(CH_2)_{16}—COOCH_2C(CH_2OH)_3$
non-ionic	$CH_3(CH_2)_{16}—OCH_2CHOHCH_2OCH_2CHOHCH_2OH$
cationic	$CH_3(CH_2)_{16}—CONHCH_2CH_2\overset{+}{N}(CH_3)_3(SO_4^{=})_{1/2}$

attack by microorganisms and so persisted unchanged when carried with sewage into rivers and lakes; bodies of water became contaminated with domestic and industrial detergents. Increasing pollution of this kind made it necessary to compel detergent manufacturers to produce only biodegradable materials. Those that are not degraded by natural biochemical processes are characterized by the presence in their molecules of branches in the alkyl chains beyond which biological degradation processes cannot proceed. Such straight-chain detergents as ordinary soaps and those containing stearyl, palmityl, lauryl, and other such residues can be metabolized by microorganisms and broken down to small molecular fragments. Present laws require that domestic and industrial detergents and the structurally allied "wetting agents" be biodegradable.

23-8 Biological detergents (emulsifying agents)

The digestion of fats ingested as food involves their initial hydrolysis by enzymatic "saponification" or *lipolysis*. The major site of lipolysis is the upper portion of the small intestine, and a principal agent in the digestion of fat is the *bile*. The bile, secreted by the gall bladder, meets the descending food at the duodenum, where hydrolysis of the fats begins. The principal constituents of the bile are *natural detergents*, or emulsifying agents, the function of which is to disperse the water-insoluble fats in a fine emulsion; in this state they are susceptible to the action of the intestinal lipases, or fat-hydrolyzing enzymes.

The constituents of the bile having this emulsifying action are compounds with the typical characteristics of the detergents described above. Taurocholic and glycocholic acids, the principal bile acids, have the structures shown below. It should be noted that they possess a large lipid portion (the steroid part) and a hydrophilic portion (the carboxyl or sulfonic acid part). Their anions are close counterparts of the ion detergents, and their salts are very effective emulsifying agents.



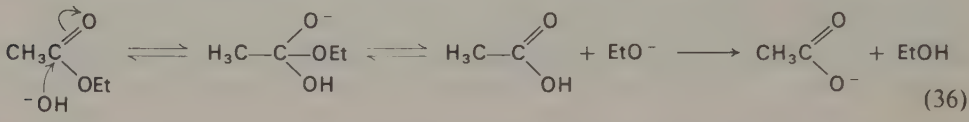
R = —$NHCH_2CH_2SO_3H$ taurocholic acid
R = —$NHCH_2COOH$ glycocholic acid

It is further to be noted that the shape of the bile acid molecule is such that the hydrophilic —OH groups (at 3α, 7α, 12α) all lie on the same side of the molecule.

23-9 The saponification reaction

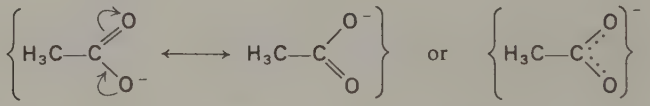
Saponification of an ester, like other reactions initiated by nucleophilic attack upon the carbonyl carbon atom, is influenced by the structure and number of the α substituents and, to a lesser degree, by the structure of the —OR group of the ester.

Attack of the nucleophilic OH^- ion upon the ester and the subsequent events are represented by the following reactions (using ethyl acetate as the example):



(36)

The first step of this reaction is reversible, and so is the second. The overall reaction, however, in the presence of an excess of alkali proceeds to completion, yielding the acid anion (the sodium salt if NaOH is used) and the alcohol corresponding to —OR of the ester. The reason for the irreversibility of the overall process is that the acid anion formed in the final step is essentially immune to nucleophilic attack, since the anionic oxygen atom reduces the electron-deficiency upon the carbonyl carbon atom:



(37)

An energy diagram for the saponification reaction is shown in Figure 23-1.

It will be recalled that substitution on the carbon atom α to the carbonyl group influences both rate and equilibrium in carbonyl addition reactions. In ester saponification the *equilibrium* position in the first stage of the reaction (attack of OH^-) is not critical because of the essential completion of the last step. The *rate* of the reaction, however, is markedly reduced by the presence of bulky alkyl substituents in the α

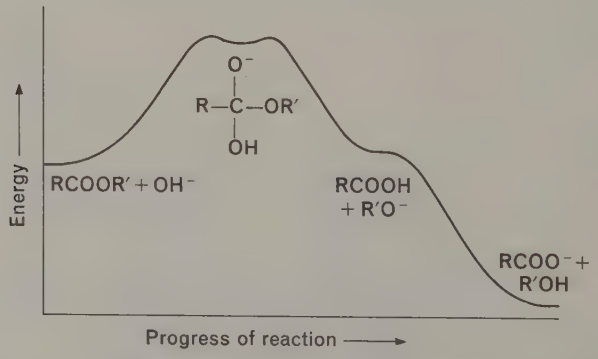


Figure 23-1
Energy profile for ester saponification.

Table 23-5
Relative rates of alkaline saponification of methyl esters of a series of substituted acetic acids:

$$RCOOCH_3 + NaOH \rightarrow RCOO^-Na^+ + CH_3OH$$

R	*Relative rate*
CH_3	1
Et	0.47
*n*Pr	0 27
*n*Bu	0.26
*i*Pr	0.10
*t*Bu	0.01
H	223

position. Table 23-5 presents some data on the influence of structure on the rate of alkaline saponification. The decrease in rate with increasing α substitution parallels the effect of such substitution in addition reactions to aldehydes and ketones.

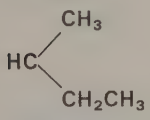
It is also found that electronic effects can overcome steric retardation, and α-chloro-substituted esters show *increased rates* of saponification as a result of the inductive electron withdrawal by chlorine, which decreases electron density on the carbonyl carbon atom, thus promoting nucleophilic attack. Some data are given in Table 23-6.

It will be recalled that acid-catalyzed esterification of carboxylic acids is subject to the same kind of steric influences (Section 12-12). In that case, too, it is the *rate*, not the equilibrium, that is affected, for an unfavorable overall equilibrium can be overcome in practice by using a large excess of the esterifying alcohol. The figures in Table 23-7 show this relationship between rate and structure.

Table 23-6
Relative rates of saponification of methyl esters $RCOOCH_3$, showing the effect of α-Cl substitution

R	*Relative rate*
H	223
CH_3	1
$ClCH_2$	761
Cl_2CH	16,000

Table 23-7
Rate and equilibrium in esterification of carboxylic acids:
$(CH_3)_2CHCH_2OH + RCOOH \rightleftharpoons$ ester

R	*Rate* (*% esterified in 1 hour*)	*Equilibrium* (*final % esterified*)
H	62	64
CH_3	44	67
$(CH_3)_2CH$	29	69
	21	74
$(CH_3)_3C$	8	73
$((CH_3)_2CH)_3C$	3	74
C_6H_5	9	73
$2,6\text{-}(CH_3)_2C_6H_3$	0	—

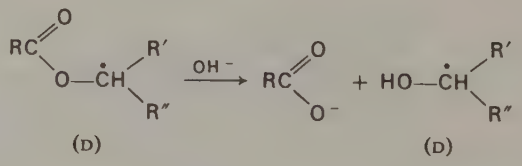
23-10 Evidence for the mechanism of ester saponification

Acid-catalyzed esterification and acid-catalyzed hydrolysis of esters are, in effect, reverse reactions. When an alcohol containing ^{18}O reacts with an acid to form an ester, the ester contains the isotopic label, showing that the nucleophilic oxygen

$$R'COOH + R^{18}OH \longrightarrow R'CO^{18}OR + H_2O \tag{38}$$

of the alcohol has become attached to the carbonyl oxygen atom. Further, alkaline saponification of an ester $R'CO^{18}OR$ gives the isotopic alcohol $R^{18}OH$.

Additional evidence is found in the observation that when the ester of an optically active alcohol is saponified, the configuration of the alkyl group is not changed; that is, there is neither inversion or racemization:

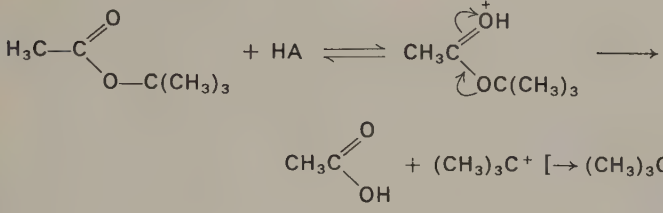


(D) (D) (39)

This experiment shows that in saponification of an ester RCOOR′, it is the carbon-alkoxyl bond that is broken (namely, RCO—OR′), while the R′—O bond remains intact.

Certain esters, however, hydrolyze under acidic conditions with breaking of the *O*-alkyl bond. These esters are distinguished by a complex alkyl group that (1) impedes

attack on the carbonyl carbon atom and (2) is capable of ready conversion into a stable carbonium ion. *t*-Butyl acetate has these properties, and its acid-catalyzed hydrolysis proceeds as follows:



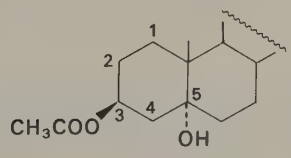
$$+ (CH_3)_3C^+ \; [\rightarrow (CH_3)_3COH + (CH_3)_2{=}CH_2] \qquad (40)$$

Exercise 4

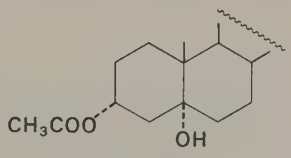
Methyl 2,4,6-trimethylbenzoate is hydrolyzed extremely slowly with alkali, but when it is heated with sodium methoxide in methanol it yields the sodium salt of 2,4,6-trimethylbenzoic acid. What other product is formed? Devise an experiment, using appropriate isotopic labeling, by which you could demonstrate the course of the reaction.

23-11 Electrophilic assistance in ester hydrolysis

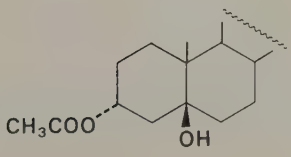
The rates of saponification of certain esters are markedly influenced by structural features that are somewhat distant from the ester grouping. The study of systems of this kind has shown that some functions showing this accelerating effect upon hydrolysis do so by participating in the reaction as catalytic agents. An example is the following, where the rate of saponification of an acetate depends upon the stereochemical disposition of a hydroxyl group at some distance from the ester grouping:



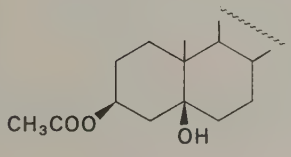
I



II



III

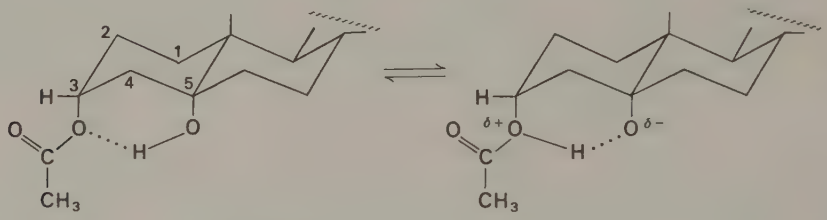


IV

	% *hydrolysis**	C=O *stretch* (cm^{-1})
I	18	1731†
II	70	1744‡
III	13	1734†
IV	78	1745‡

* Conditions: 60 mg compound, 4 ml MeOH, 7 mg $KHCO_3$, 0.5 ml H_2O, 20°C, 65 hours.
† No hydrogen bonding.
‡ Hydrogen bonding to —O—$COCH_3$.
Compounds are cholestanol and coprostanol derivatives; only the A and B rings are shown.

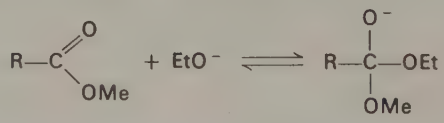
The marked difference in the degree of hydrolysis (under identical experimental conditions) can be attributed to the hydroxyl group at the 5-position, which in configurations II and IV can hydrogen-bond to the ester oxygen atom:



(41)

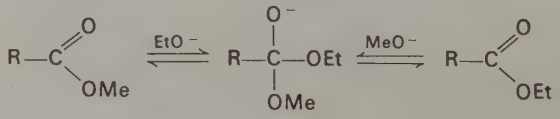
23-12 Ester interchange

When an ester is treated with a sodium alkoxide instead of sodium hydroxide, the attack of the nucleophilic RO^- upon the ester carbonyl group exactly parallels the attack of OH^- in the saponification reaction:



(42)

The nucleophilic character of alkoxide anions derived from different aliphatic alcohols does not vary greatly; methoxide, ethoxide, and other alkoxides would be expected to be comparable, although not identical, in this respect. It follows then that the reaction shown above would lead to the very similar equilibria



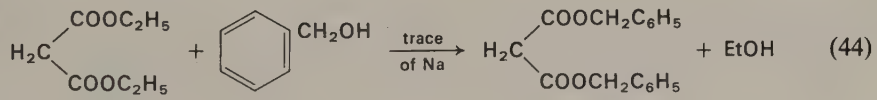
(43)

that the equilibrium constant for the overall reaction

$$RCOOMe + EtO^- \rightleftharpoons RCOOEt + MeO^-$$

would be close to unity; and that if, as in this example, ethanol were present in large excess, the final mixture would consist largely of the ethyl ester.

This reaction, known as *base-catalyzed ester interchange*, is a useful method for converting one ester into another; it often avoids the more time-consuming procedure of saponifying an ester to the acid and then re-esterifying to form the desired new ester. It is especially convenient when the desired ester is of an alcohol that does not lend itself easily to conventional acid-catalyzed esterification. An example is the preparation of benzyl esters, which are valuable intermediates in certain synthetic procedures because of the ease with which the benzyl groups can later be removed by catalytic hydrogenolysis:



Diethyl malonate Benzyl alcohol Dibenzyl malonate (44)

Exercise 5

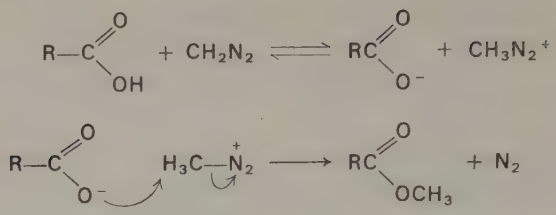
(*a*) Why would base-catalyzed ester interchange be useful in converting $(CH_3O)_2CHCH_2COOCH_3$ into $(CH_3O)_2CHCH_2COOEt$? (*b*) Suppose it were attempted to esterify $(CH_3O)_2CHCH_2COOH$ by treatment with ethanol, with HCl as catalyst. Would the product be $(CH_3O)_2CHCH_2COOEt$? If not, what would the product be?

23-13 Esterification with diazomethane

A convenient reagent for the preparation of methyl esters is diazomethane, CH_2N_2, the electronic structure of which is

$$^-:CH_2—\overset{+}{N}\equiv N: \longleftrightarrow CH_2=\overset{+}{N}=\ddot{N}:^-$$

In the presence of a proton donor, such as a carboxylic acid, diazomethane is protonated, which converts it into a methylating agent. Attack of the nucleophilic carboxylate anion upon the protonated diazomethane gives the methyl ester and nitrogen:



(45)

The ease and convenience of this reaction, usually carried out in ether solution at ordinary temperature, and of which the by-product is only nitrogen, lend it to the esterification of carboxylic acids of all kinds, with excellent yields of pure methyl esters.

23-14 Biological hydrolysis of esters

Hydrolysis of esters is a biological reaction of wide significance and great physiological importance. The most common example is the enzymatically catalyzed hydrolytic conversion of fats into their constituent fatty acids (and glycerol) prior to the oxidative degradation of the fatty acids for metabolic purposes.* Other well-known processes of this kind are:

(*a*) The hydrolysis of acetylcholine ($(CH_3)_3\overset{+}{N}CH_2CH_2OCOCH_3$), a ubiquitous agent in nerve activity, into choline ($(CH_3)_3\overset{+}{N}CH_2CH_2OH$) and acetic acid, neither of which possesses the physiological activity of the ester.

(*b*) The hydrolysis of ester groupings in certain drugs and toxic agents to convert them into the corresponding physiologically inactive alcohols. One example is the hydrolysis of the toxic alkaloid atropine, an ester of an amino alcohol, into the less toxic tropine (an amino alcohol) and tropic acid (the esterifying acid). Another is the hydrolysis of the muscle-paralyzing (curare-like) drug succinylcholine, $(CH_3)_3\overset{+}{N}CH_2CH_2OCOCH_2CH_2COOCH_2CH_2\overset{+}{N}(CH_3)$, into the non-curare-like choline and succinic acid, with the result that the muscle-relaxing action of the drug is limited and disappears in a short time after administration.

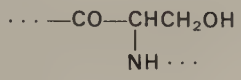
23-15 The chemical nature of esterase action

Esterases (ester-hydrolyzing enzymes) are proteins, and as such are very large molecules of complex structure. Although the complete structures of some of them have been established, chiefly by X-ray crystallography, the features of their structure

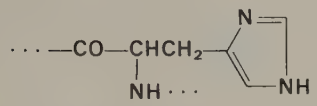
* The enzymatic hydrolysis of proteins into their constituent amino acids is a closely allied process, and many enzymes have both ester-hydrolyzing (esterase) and peptide-hydrolyzing (peptidase) properties.

essential to their esteratic activity can be discussed in terms of what is referred to as the "active site," that location on the macromolecule at which the catalytic effect of the enzyme is exerted and at which the ester is converted into its constituent parts.

Much experimental evidence points to the conclusion that the active sites of esterases contain two particular amino acid residues, serine and histidine:

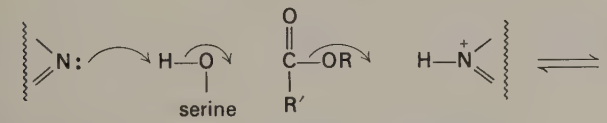


Serine (as part of a polypeptide)

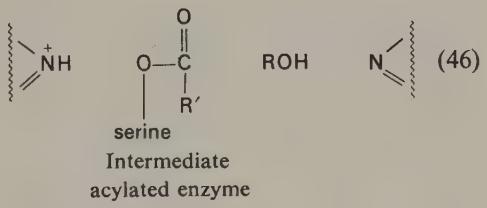


Histidine (as part of a polypeptide)

Serine and histidine act as an acid-base catalyst pair, providing for nucleophilic attack upon the ester carbonyl group and for proton-assisted loss of the —OR group of the ester (as HOR). A summary expression for this action is the following:



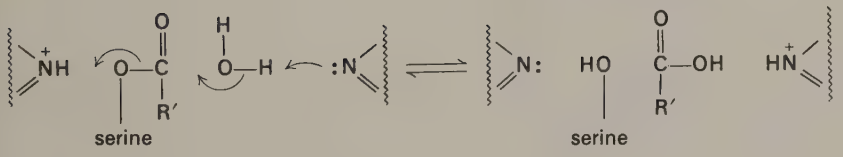
Histidine | Ester | Histidine (protonated)



(46)

serine

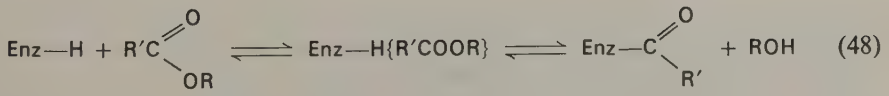
Intermediate acylated enzyme



(47)

serine | serine

or in brief:



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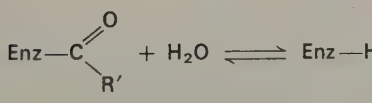
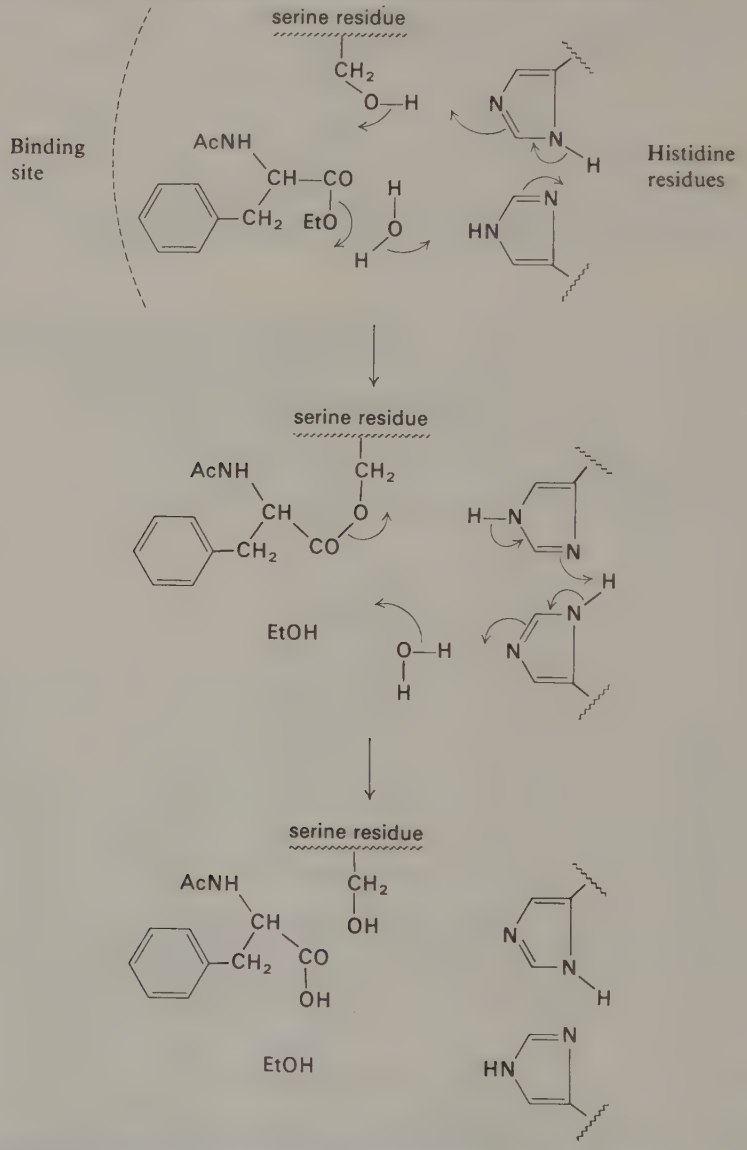


(49)

A more detailed picture of this process, showing a probable orientation of substrate (ester) and enzyme at the active site, is the following, in which the substrate is the synthetic model compound *N*-acetylphenylalanine ethyl ester:



Note that the final system is structurally identical with the first, except that the initial ester + water has been replaced by acid + alcohol. The "base" in this scheme is histidine (the imidazole ring), which can accept a proton during the nucleophilic attack of the serine hydroxyl group, thus enhancing the nucleophilicity of the latter.

Evidence to support this model comes from experiments in which reagents are employed that place substituents on the serine hydroxyl group or the imidazole —NH

group. When these functional sites are "covered" by such substitution, esterase activity is destroyed (see the following section).

23-16 Acetylcholine and acetylcholinesterase

Acetylcholine mediates the transmission of nervous impulses in animals and insects. Its function is controlled by the presence of the enzyme *acetylcholinesterase*, which catalyzes the hydrolysis of acetylcholine into its component parts, choline and acetic acid. The action of acetylcholine is therefore intermittent and evanescent because of the rapidity of its destruction by the esterase; but in the presence of inhibitors of the enzyme its action is prolonged, and serious derangement of nervous activity results.

$$\text{nerve stimulus} \longrightarrow \text{acetylcholine release} \longrightarrow \text{response} \qquad (50)$$

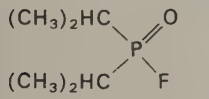
$$CH_3COOCH_2CH_2\overset{+}{N}Me_3$$

$$\downarrow$$

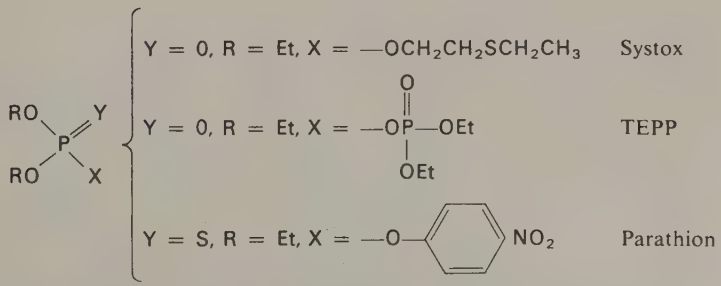
$$HOCH_2CH_2\overset{+}{N}Me_3 + CH_3COOH$$

Choline Acetic acid

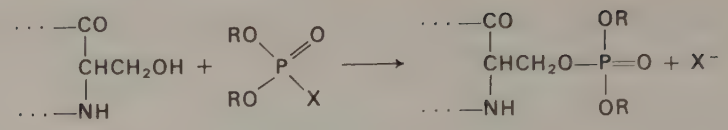
Prolongation of the lifetime of acetylcholine by inhibition of its destruction can produce effects that range from therapeutically beneficial to toxic or fatal. Many inhibitors of acetylcholinesterase are known. Among them are clinically useful drugs (for example, Prostigmin) and many highly toxic agents. The latter include the compounds known by the vernacular term "nerve gases," many of which are powerful and effective insecticides. A typical compound of this class is diisopropylphosphofluoridate (DFP). Many analogs of this compound are known; most of them have the general structure shown below, where X is a group readily displaced as an anion by nucleophilic attack upon phosphorus:



DFP



The fundamental mechanism of action of all of these insecticides appears to be the same: the formation of a phosphate ester at the hydroxyl group of the serine residue of the esterase.



Serine in the esterase polypeptide

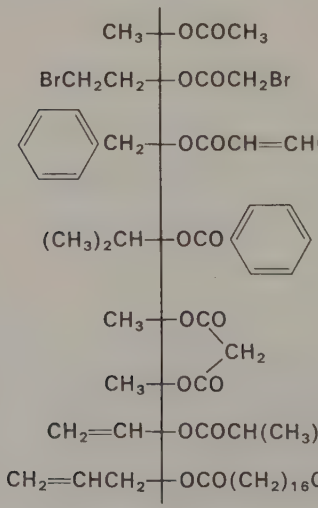
(51)

This conversion of serine into a phosphate ester effectively nullifies its ability to participate in ester hydrolysis as described in the preceding section. The inhibition is effectively irreversible; that is, the hydrolysis of the serine phosphate is so slow that the effects of the acetylcholine, which would otherwise be rapidly destroyed, are prolonged. Carefully regulated dosage of certain of these phosphorus-containing compounds can achieve valuable therapeutic results in those clinical conditions in which insufficient acetylcholine is available for normal physiological needs. A typical syndrome of this kind is myasthenia gravis.

Compounds such as DFP, Parathion, Systox, and many more of related structure are powerful insecticides; they act to destroy acetylcholinesterase, with consequent derangement of the acetylcholine-dependent nervous system of the insect. Needless to say, most of them are extremely toxic to higher organisms as well. They are readily absorbed through the skin and mucous membranes, and many human deaths have resulted from their careless or indiscriminate use.

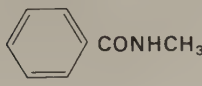
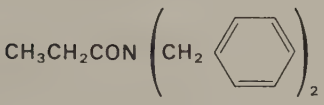
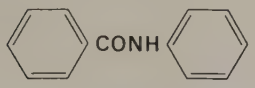
23-17 Nomenclature of acid derivatives

Esters are named by naming separately the group derived from the alcohol (or phenol) and the acyl portion, using the ending *-oate*, as in the following examples:



Methyl	acetate
2-bromoethyl	bromoacetate
Benzyl	2-butenoate
Isopropyl	benzoate
Dimethyl	malonate
Vinyl	isobutyrate
Allyl	stearate

Amides are named by using the stem name of the acid (*acet*ic, *benz*oic, *stear*ic), adding the suffix *-amide*. In substituted amides the capital letter *N* precedes the name of the substituent on nitrogen. Occasionally, trivial names are used or the compound is named as an acylated amine:

CH_3CONH_2	Acetamide
$CH_3CH_2CH_2CONH_2$	*n*-butyramide
	*N*-methylbenzamide
	*N*,*N*-dibenzylpropionamide
$CH_3(CH_2)_{16}CONH_2$	Stearamide
	Benzanilide
$CH_3CONHCH_2CH_2NHCOCH_3$	*N*,*N*′-diacetylethylenediamine (or 1,2-diacetamidoethane)

Acid anhydrides are named simply by using the name of the acid followed by the word *anhydride*; the abbreviated formula $(RCO)_2O$ is commonly used:

$CH_3CO—O—COCH_3$	Acetic anhydride
$((CH_3)_2CHCO)_2O$	Isobutyric anhydride
$(C_6H_5CO)_2O$	Benzoic anhydride

Acid halides are named by replacing the ending *-ic* (as in acet*ic*) by *-yl* (acet*yl*), followed by the name of the halide:

CH_3COBr	Acetyl bromide
$CH_3CH{=}CHCH_2CH_2COCl$	4-hexenoyl chloride

Occasionally the letter "o" is interposed to avoid ambiguity arising from a similarity to the name applied to the corresponding alcohol:

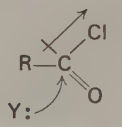
$C_6H_5CH{=}CHCOCl$	Cinnamoyl chloride
$C_6H_5CH{=}CHCH_2Cl$	Cinnamyl chloride
$CH_3(CH_2)_{16}COCl$	Stearoyl chloride
$CH_3(CH_2)_{16}CH_2OH$	Stearyl alcohol

It will be recalled that the systematic suffix for carboxylic acids is *-oic* acid; thus, the ending *-oyl* for the acyl group is used when systematic nomenclature is employed.

Acetyl chloride, derived from the (non-systematic) *acetic* acid, is also *ethanoyl* chloride (from *ethanoic* acid), but it is never called *acetoyl* chloride.

23-18 *O*-Acylation by acid derivatives. Ester formation

The acid derivatives most reactive toward nucleophilic reagents are the acid halides and anhydrides. The presence of the halogen (for example, Cl) atom on the carbonyl group greatly decreases electron density on the carbonyl carbon atom, increasing the rate of nucleophilic attack:

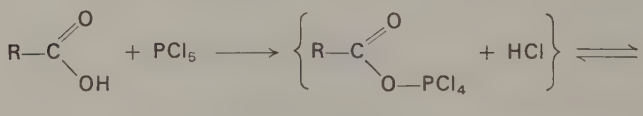


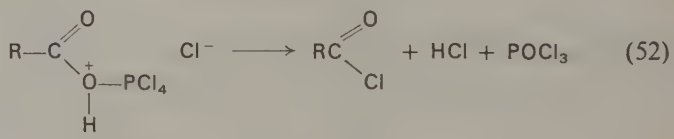
Nucleophile

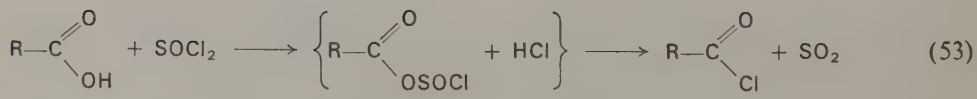
Inductive effect of Cl reduces electron density on carbonyl carbon atom, causing enhanced attraction of electron-deficient carbonyl carbon atom for nucleophile

The lower-molecular-weight acid halides—for example, acetyl chloride—react instantly with water, alcohols, and amines to give the corresponding carboxylic acids, esters, and amides. The ready displacement of the chloride ion from the intermediate addition product is effectively irreversible, because the weakly nucleophilic chloride ion cannot compete with the more effective nucleophiles that are displacing it. Acid chlorides of higher molecular weight and more complex constitution also react readily in the same way, but less vigorously.

Acid chlorides* are usually prepared by one of two procedures: (*a*) reaction of a carboxylic acid with a phosphorus chloride, PCl_5 or PCl_3; or (*b*) reaction of an acid with thionyl chloride, $SOCl_2$:







* For practical reasons, most acid halides used are the chlorides; they are sufficiently reactive, less costly than the bromides, and more stable than the iodides.

Depending upon the conditions, more than one mole of acid will react with PCl_3; in the limit,

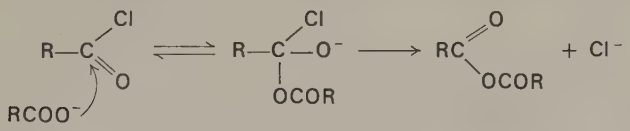
$$3RCOOH + PCl_3 \longrightarrow 3RCOCl + H_3PO_3 \qquad (54)$$

A method of preparing certain acid chlorides that is of restricted usefulness, but of great convenience and simplicity, depends upon the fact that an acid and an acid halide react to establish the equilibrium

$$RCOOH + R'COCl \rightleftharpoons RCOCl + R'COOH \qquad (55)$$

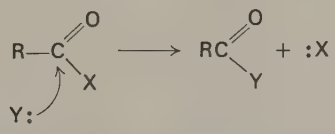
If the acid chloride R′COCl used as the reagent is present in excess, and if the acid chloride RCOCl whose synthesis is desired has a lower boiling point, it is possible to distill RCOCl from the mixture. The "reagent" acid chloride usually employed is the plentiful and inexpensive benzoyl chloride.

Acid anhydrides are also highly reactive in reactions for which acid halides are used, but less so than the halides. The formation of an acid anhydride illustrates again the general reaction of acid halides. The nucleophile is in this case the carboxylic acid anion, the overall attack being that shown in the equation below. Acetic anhydride, for example, is prepared by the reaction of sodium acetate with acetyl chloride:



(56)

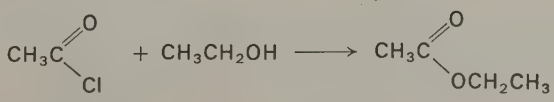
It can be seen from what has been said that in the overall reaction



(57)

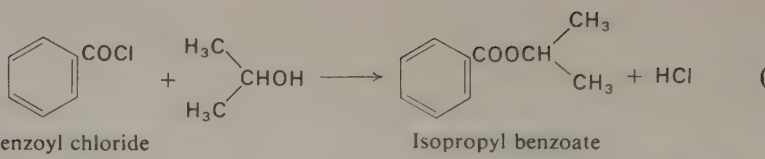
an electron-attracting atom or group X facilitates attack of the nucleophile Y:, and a poorly nucleophilic agent X:, such as Cl^- or $RCOO^-$, is readily displaced by the more nucleophilic H_2O, ROH, or RNH_2.

The following examples illustrate some of the applications of acid chlorides to the preparation of esters (*O*-acylation). The preparation of amides by *N*-acylation is described in the following section.

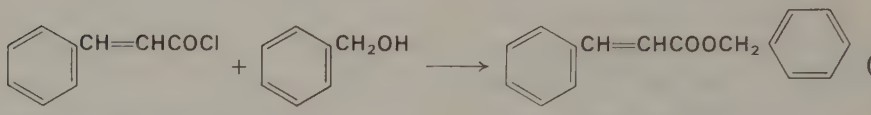


(58)

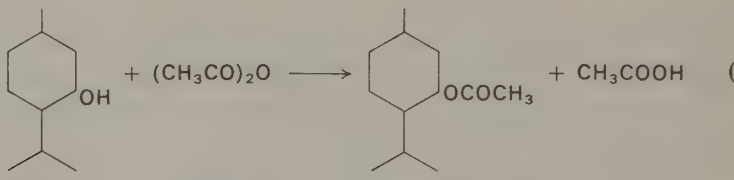
Acetyl chloride



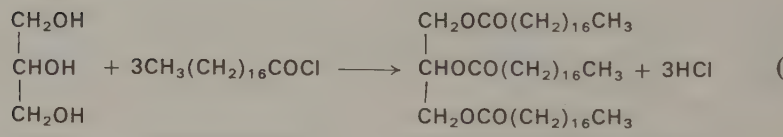
Benzoyl chloride — Isopropyl benzoate



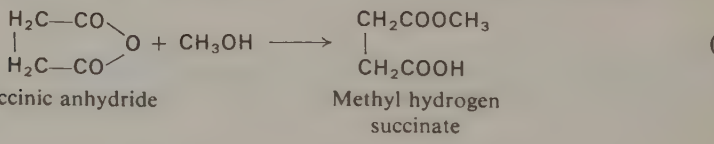
Cinnamoyl chloride — Benzyl cinnamate



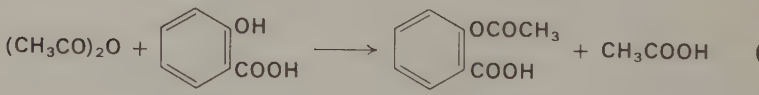
Menthol — Acetic anhydride — Menthyl acetate



Glycerol — Stearyl chloride — Glyceryl tristearate (tristearin)



Succinic anhydride — Methyl hydrogen succinate

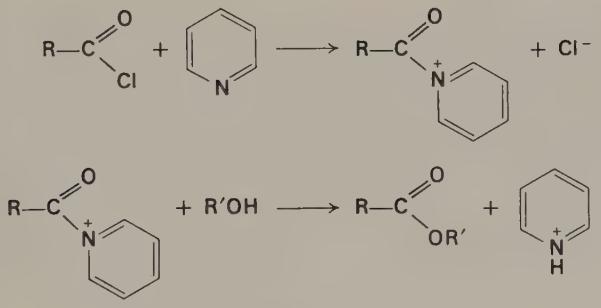


Salicylic acid — Acetylsalicylic acid (aspirin)

Exercise 6

The reaction between *t*-butyl alcohol and acetyl chloride does not give *t*-butyl acetate. Instead, *t*-butyl chloride and acetic acid are formed. If, however, an excess of a tertiary amine (for example, Et_3N) is added, the ester is formed. Explain. What is the role of the amine, and what is its fate?

Aromatic acid chlorides (for example, benzoyl chloride) and most acid anhydrides are considerably less reactive than the chlorides of low-molecular-weight acids such as acetic and propionic acids. Acetyl chloride reacts almost explosively with water at room temperature; benzoyl chloride can be left in contact with water without appreciable immediate reaction, and it hydrolyzes slowly; and acetic anhydride will dissolve in cold water before complete hydrolysis occurs. Because of the relatively slow reactivity of aromatic chlorides and most acid anhydrides, the esterification of alcohols with them is usually carried out with a basic catalyst. Pyridine, a tertiary amine, is often used. The basic catalyst may act in either of two ways: to remove the proton in the first stage of the reaction; or to engage in a double-displacement of the following kind:



(65)

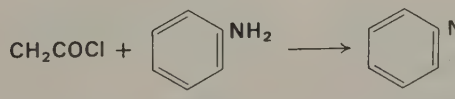
In the *Schotten-Bauman* reaction, benzoyl chloride reacts with an alcohol in the presence of sodium hydroxide. In this case it is probable that the alkoxide ion, present in the equilibrium

$$ROH + OH^- \rightleftharpoons RO^- + H_2O \qquad (66)$$

is the actual nucleophile.

23-19 *N*-Acylation by acid derivatives. Amide formation

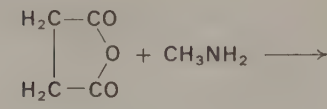
Ammonia and amines react rapidly with acid halides and acid anhydrides to yield amides:



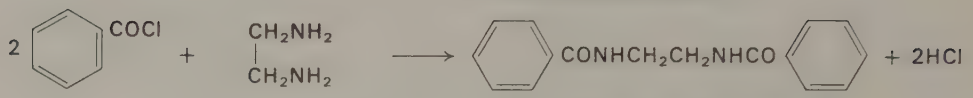
Aniline Acetanilide (67)

$$(CH_3CO)_2O + (CH_3CH_2)_2NH \longrightarrow (CH_3CH_2)_2NCOCH_3 + CH_3COOH \qquad (68)$$

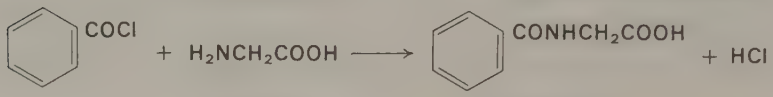
N,*N*-diethylacetamide



N-methylsuccinamic acid (69)



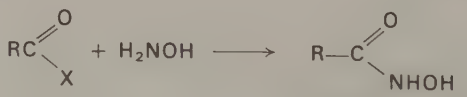
Ethylenediamine 1,2-dibenzoylaminoethane (70)



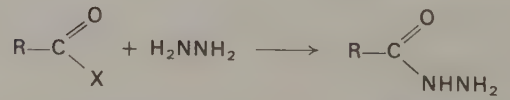
Glycine Hippuric acid (71)

It can be seen that the reaction of an amine with an acid chloride yields HCl as a product, along with the amide. The amine reacts with the HCl to form the salt (the protonated amine), which is non-nucleophilic. Thus, two moles of amine are required to consume one mole of acid chloride and yield one mole of amide. Complete acylation of the amine can be accomplished if a molar proportion of a tertiary amine such as pyridine or triethylamine (neither of which can be acylated to an amide) is added to neutralize the HCl. In practice, however, amides are commonly prepared with the use of acid anhydrides, for the organic acid formed (for example, acetic acid from acetic anhydride) is not a sufficiently strong acid to "tie up" the amine by protonation, so that it can be completely acylated.

Some of the most valuable applications of the *N*-acylation of amines and their derivatives make use of the reactions of acid derivatives with hydroxylamine ($HONH_2$), hydrazine (NH_2NH_2), and substituted hydrazines ($RNHNH_2$). Hydroxylamine reacts with acid anhydrides and, more importantly, with esters to form *N*-hydroxyamides, or *hydroxamic acids*. Hydrazine is acylated in a comparable reaction to yield *N*-acylated hydrazines, or *hydrazides*. In general:

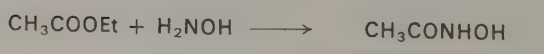


A hydroxamic acid (72)

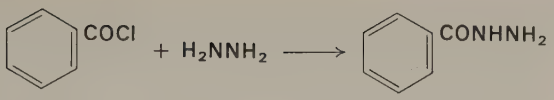


(X = halogen, acyl, OR) An acyl hydrazine, or a hydrazide (73)

For example:



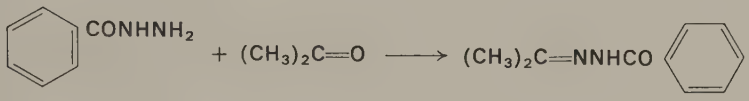
Acethydroxamic acid (74)



(75)

Benzhydrazide

The terminal amino group of acylhydrazines is basic and nucleophilic. It can react with the carbonyl group of aldehydes and ketones to yield derivatives that are useful in characterizing and identifying carbonyl compounds:



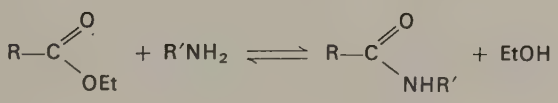
(76)

Acetone benzhydrazone

The largest and most important class of amides are those formed by acylation of the amino group of an α-amino carboxylic acid with the carboxyl group of another. Because they are derived from bifunctional precursors, such amides can form long chains bound together by amide (called "peptide") linkages. These "polypeptides" will be discussed in Chapter 37.

23-20 Reaction of amines with esters

The equilibrium



(77)

leads to *amide-ester interchange*, which can be used to convert esters into amides. The reaction is slow, for the ester carbonyl group is not strongly electrophilic. The attack of an amine upon the ester corresponds in kind to the saponification reaction. The latter proceeds to completion because of the final formation of the carboxylic acid anion. Amide-ester interchange, while slow, can be advantageously employed by carrying out the reaction at an elevated temperature (or allowing a long time) and brought to practical completion by using a large excess of the amine or by removing the alcohol by distillation.

When hydroxylamine is used, with formation of the *N*-hydroxyamide (a *hydroxamic acid*), the reaction serves as an excellent diagnostic test for esters, for hydroxamic acids form deeply colored (red to purple) complexes with ferric salts. The test is performed by heating a sample of the unknown compound with hydroxylamine, making the solution slightly acid with dilute aqueous acid, and adding a few drops of

ferric chloride solution. A deep red or purple color shows that the unknown compound is an ester.*

Exercise 7

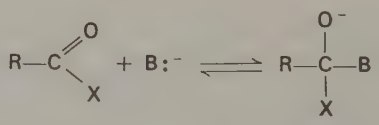
Account for the fact that the reaction of H_2NOH with an ester leads to RCONHOH and not $RCOONH_2$.

23-21 Relative reactivity of acid derivatives

The high degree of reactivity of acid halides and anhydrides toward nucleophilic reagents has been attributed (Section 23-18) to the inductive withdrawal of electron density from the carbonyl carbon atom by the halogen atom or the acyl group, the former being the more effective. The reactivity of acid derivatives in reactions involving initial nucleophilic attack on the carbonyl group is greatest in acyl halides, lowest in the carboxylate anion. Acid anhydrides, esters, and amides are intermediate in reactivity:

$$RCOCl > RCOOCOR > RCOOR' > RCONH_2 > RCOO^-$$

The rates of these reactions can be correlated with the activation energy of the initial process:†



(1) (2) (78)

Since the activation energy is a measure of the difference between the ground-state energy of the reactants (1) and the energy of the transition state, and the transition

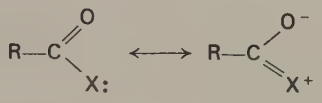
---

* Acid halides and anhydrides will, of course, give the same result, but their identity can ordinarily be revealed by other tests, for example, their rapid reaction with an amine, or a test for the presence of halogen.

† The attacking nucleophile is represented here as the anionic species $B:^-$ (as OH^-, OMe^-, etc.), but it may of course be a neutral molecule (as H_2O, NH_3, etc.).

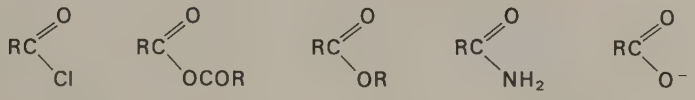
state may be represented by the tetrahedral species (2), in which charge delocalization is of minor importance, it is evident that the activation energy for the initial addition *will be greater the lower the ground-state energy of the reactants.*

The structures of acid derivatives RCOX are those of resonance-stabilized compounds



(79)

The greater the electron-donating power of —X:, the greater the degree of resonance stabilization represented by this ground-state structure. It is convenient to relate the electron-donating ability of —X: to the basicity (or nucleophilicity) of HX (or of $X:^-$, since we are comparing a series of different groups X). It is now apparent that in the series



the contribution to charge delocalization in the ground state is greatest in $RCOO^-$ and least in RCOCl. This follows from the relative nucleophilicity of HO^-, NH_3, ROH, RCOOH, and HCl.

The consequence of this is that the activation energy of the initial addition reaction is greater for an amide than for an ester, greater for an ester than for an acid anhydride, and least for an acyl chloride. This is illustrated by the simplified energy diagram in Figure 23-2, on the following page.

The reactivity of acid derivatives can be described in another way. The reactivity of a series of carbonyl compounds with a given nucleophile can be described in terms of the electrophilic character of the carbonyl carbon atoms. In an acid chloride, the halogen atom exerts a strong inductive withdrawal of electrons in the C—Cl bond, giving the electron-deficient carbonyl carbon atom a highly electrophilic character. In an ester or an amide, the relatively small inductive effect of —OR or $—NH_2$ is overcome by the ability of oxygen or nitrogen to donate their unshared electrons to the carbon atom.* It will be recognized that the inductive effect of the chlorine atom is an expression of its low degree of nucleophilicity; thus, the two descriptions of the reactivity of acid derivatives relate to the same fundamental nature of the groups —X in RCOX, and the final conclusions concerning relative reactivities are the same.

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* For example, CH_3OCH_2COOH is a somewhat stronger acid than acetic acid.

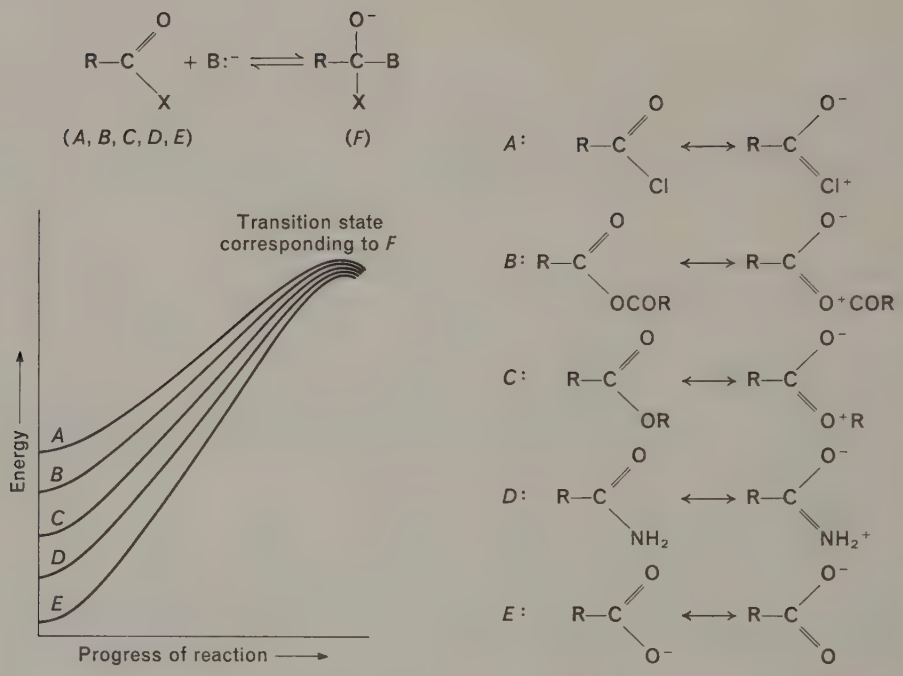
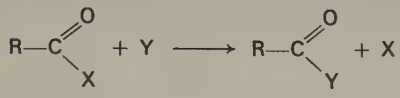


Figure 23-2
Energy profiles for nucleophilic attack upon carboxylic acid derivatives. Although the energies of the various transition states *F* are not identical, they differ by much less than the energies of the corresponding ground states.

This discussion can be summarized by the following résumé of relative reactivity:



(80)

(fastest)	X = Cl	Y = RNH_2, ROH, $RCOO^-$
	X = OCOR	Y = RNH_2, ROH
	X = OR	Y = RNH_2, RO^- (HO^-)
(slowest)	X = NH_2	Y = RO^-(HO^-)
	X = O^-	not reactive in this way

It will be noted that there is a rational order to this series: the RCOX (RCOCl) that reacts with the poorest nucleophile ($RCOO^-$) possesses the most weakly nucleophilic X (Cl); the RCOX ($RCONH_2$) that reacts with only the most strongly nucleophilic reagents (RO^- and HO^-) possesses the most nucleophilic X (NH_2).

Exercise 8

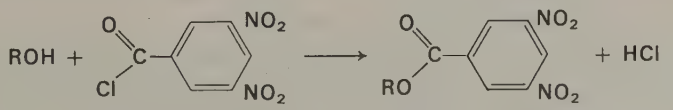
Base-catalyzed hydrolysis of an amide can be represented as follows:

$$RCONR_2 + OH^- \longrightarrow RCOO^- + R_2NH$$

Which would be more rapidly hydrolyzed, $CH_3CON(CH_3)_2$ or $(CH_3CO)_2NCH_3$? Why?

23-22 Acid halides as reagents for characterizing and identifying alcohols and phenols

Acyl derivatives are frequently used to *characterize and identify* alcohols and phenols. Although the low-molecular-weight acid halides and anhydrides are not usually crystalline compounds themselves, acid halides that yield crystalline esters are available. An acid chloride often used to characterize hydroxyl compounds is 3,5-dinitrobenzoyl chloride. The esters of 3,5-dinitrobenzoic acid, even with simple alcohols, are usually crystalline compounds:



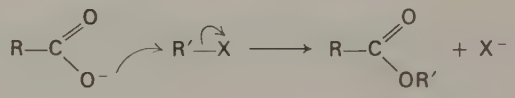
(81)

R in alcohol and ester: Me Et *n*Pr *i*Pr *n*Bu *i*Bu
Ester melting point (°C): 107 93 74 122 64 65

More complex compounds, such as hydroxyl-containing steroids, which are themselves crystalline solids, may be identified by their acetates or benzoates.

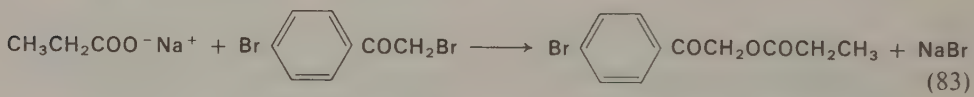
23-23 The carboxylate anion as a nucleophile. Ester formation by nucleophilic displacement

The carboxylate anion, $RCOO^-$, is a weak base and a moderately effective nucleophile. Esters can be prepared according to the general reaction



(82)

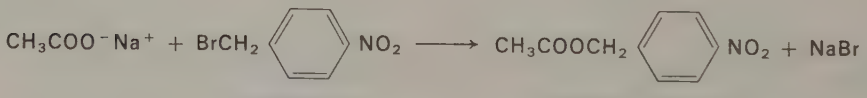
The principal use of this reaction is to identify *acids* by converting them into crystalline esters with characteristic melting points. The halides used (R′X in the above expression) are chosen with these properties in mind. The two most commonly employed are *p*-bromophenacyl bromide and *p*-nitrobenzyl chloride or bromide, although numerous related reagents can also be used. Two examples of ester formation with these compounds are the following:



p-bromophenacyl bromide

p-bromophenacyl propionate m.p. 59°

(83)



p-nitrobenzyl bromide

p-nitrobenzyl acetate m.p. 78°

(84)

23-24 Naturally occurring esters

Nature abounds in esters of many kinds—from simple, volatile compounds to involatile oils and solids of high molecular weight. Esters derived from the simple aliphatic acids and alcohols are responsible for the characteristic odors of many fruits and flowers; a few of these are listed in Table 23-8.

Certain solid esters, involatile and odorless, are important for their physical character. *Carnauba wax*, a hard waxy coating on the leaves of the palm tree *Copernicia cerifera*, is a mixture of esters of long-chain acids and alcohols, including myricyl cerotate, $CH_3(CH_2)_{24}COOCH_2(CH_2)_{28}CH_3$. *Beeswax* is also a mixture consisting

Table 23-8
Some naturally occurring esters

Name	*Structure*	*Characteristic odor* *
n-amyl acetate	$CH_3COOCH_2(CH_2)_3CH_3$	banana
n-octyl acetate	$CH_3COOCH_2(CH_2)_6CH_3$	orange
methyl *n*-butyrate	$CH_3CH_2CH_2COOCH_3$	apple
n-butyl *n*-butyrate	$CH_3CH_2CH_2COOCH_2CH_2CH_2CH_3$	pineapple
benzyl acetate	$CH_3COOCH_2C_6H_5$	jasmine
methyl salicylate		wintergreen

* The odors of fruits, flowers, and wines owe their distinctive characters to mixtures of several, often many, esters, as well as to small amounts of volatile alcohols, aldehydes, and ketones.

largely of esters of the general composition $CH_3(CH_2)_xCOOCH_2(CH_2)_yCH_3$, where x and y lie principally in the range from 22 to 34. Waxes are important constituents of insect and plant cuticles, forming a barrier impervious to water and foreign substances. Carnauba wax, beeswax, spermaceti, and other waxes of the same kind are important articles of commerce; they find wide use as coating materials, in candles, in modeling, and in engraving.

While the importance of fats and oils as foodstuffs is well recognized, natural oils play other significant roles in human economy. *Castor oil* is found in the seed of the castor bean (*Ricinus communis*), and constitutes a significant part of the agricultural production of many countries of the world. Like most natural fats and oils, castor oil is a mixture of triglycerides (glycerol esters of fatty acids), among them *ricinoleic acid.* An important industrial chemical, ricinoleic acid is the raw material for the production of sebacic acid, an ingredient in the manufacture of synthetic fibers and resins.

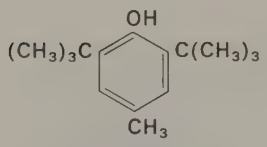
$$\underset{\text{Ricinoleic acid}}{CH_3(CH_2)_5\overset{\overset{OH}{|}}{C}HCH_2CH{=}CH(CH_2)_7COOH} \xrightarrow[\text{heat}]{NaOH} \underset{\text{2-octanol}}{CH_3\overset{\overset{OH}{|}}{C}H(CH_2)_5CH_3} + \underset{\text{Sodium sebacate}}{NaOOC(CH_2)_8COONa} \qquad (85)$$

Exercise 9

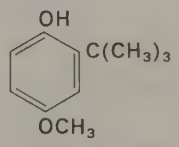
Devise a reasonable course for the conversion of ricinoleic acid into 2-octanol and sodium sebacate by the action of alkali, shown in (85).

Linseed oil and other "drying" oils absorb oxygen when exposed to air, forming tough, elastic films, probably by polymerization with cross-linking of the carbon chains by oxygen. They form the basis of paints and varnishes.

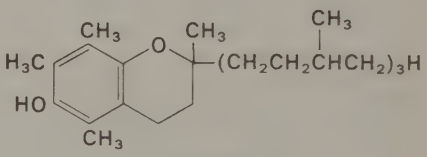
Edible oils (*cottonseed*, *corn*, *soybean*, *safflower*, and *peanut oils*, and *butter fats*) are used for cooking, as well as for ingestion as salad oils, butter, and butter substitutes. Because liquid fats contain a relatively large proportion of unsaturated fatty acid glycerides they are apt to oxidize upon long exposure to air. The oxidative breakdown of the hydrocarbon chain leads to the formation of volatile acids, ketones, and aldehydes that impart an undesirable rancid flavor to the oils. This deterioration is combatted by the addition to cooking and salad oils of antioxidants, compounds that inhibit oxidative breakdown. Synthetic antioxidants are in most cases alkylated phenols such as BHT and BHA. A natural antioxidant present in vegetable oils is α-tocopherol:



2,6-di-*t*-butyl-
4-methylphenol (BHT)



2-*t*-butyl-
4-methoxyphenol
(BHA)



α-tocopherol

Exercise 10

How are the names BHT and BHA derived? What is the origin of the name tocopherol?

Hydrogenation of unsaturated oils saturates them and prevents rancidity. Since saturated fats have higher melting points than those containing unsaturated fatty acids, hydrogenation of edible oils produces fats (for example, Crisco and Spry) that are solid at room temperature.

23-25 Applications to synthesis

1. Prepare 3,4-dibromobutanoic acid.
   (*a*) The final step in this synthesis is

$$CH_2{=}CHCH_2COOH + Br_2 \longrightarrow BrCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2COOH$$

(*b*) Vinylacetic acid can be prepared by the carbonation of an allyl Grignard reagent:

$$CH_2{=}CHCH_2MgCl + CO_2 \longrightarrow CH_2{=}CHCH_2COOH$$

2. Prepare pentanoic acid, using any reagents of two carbon atoms or less.

(*a*) The final steps could be:

$$CH_3CH_2CH_2CH_2Br + KCN \longrightarrow CH_3CH_2CH_2CH_2CN \xrightarrow[H_2O]{H^+} CH_3CH_2CH_2CH_2COOH$$

(*b*) 1-Bromobutane can be prepared *via* the reaction of ethylmagnesium bromide with ethylene oxide:

$$CH_3CH_2MgBr + H_2C\overset{O}{\diagup\diagdown}CH_2 \longrightarrow n\text{BuOH} \xrightarrow{HBr} n\text{BuBr}$$

3. Prepare 3-methylbutanoic acid (isovaleric acid), starting with acetone.

$$CH_3COCH_3 \xrightarrow{Ba(OH)_2} \text{diacetone alcohol} \xrightarrow[(-H_2O)]{H^+} (CH_3)_2C{=}CHCOCH_3$$

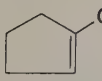
$$(CH_3)_2C{=}CHCOCH_3 + NaOCl \longrightarrow (CH_3)_2C{=}CHCOOH + CHCl_3$$

$$(CH_3)_2C{=}CHCOOH \xrightarrow{H_2/Pt} (CH_3)_2CHCH_2COOH$$

4. Prepare adipic acid, starting with succinic acid.

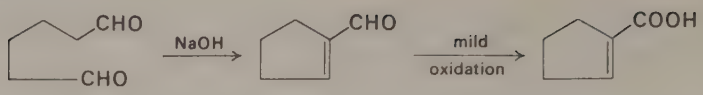
$$\begin{matrix}CH_2COOH\\|\\CH_2COOH\end{matrix} \xrightarrow{LiAlH_4} \begin{matrix}CH_2CH_2OH\\|\\CH_2CH_2OH\end{matrix} \xrightarrow{HBr} \begin{matrix}CH_2CH_2Br\\|\\CH_2CH_2Br\end{matrix} \xrightarrow{KCN}$$

$$\begin{matrix}CH_2CH_2CN\\|\\CH_2CH_2CN\end{matrix} \xrightarrow{H_2O/H^+} \begin{matrix}CH_2CH_2COOH\\|\\CH_2CH_2COOH\end{matrix}$$

5. Prepare  , starting with cyclohexanone.

(*a*) Since the starting material, cyclohexanone, has a six-membered carbocyclic ring, and the desired product has a five-membered ring, it is clear that some kind of ring contraction will have to be effected. One way to do this is to open the cyclohexanone ring and then reclose the resulting open-chain intermediate to form a five-membered ring. Since both the starting material and the final product have a total of six carbon atoms each, the —COOH group of the product will represent one of the original six carbon atoms of the starting material.

(*b*) It will be seen that an aldol condensation can effect the desired change, in the following way:



(*c*) The dialdehyde can be obtained by the ozonolysis of cyclohexene or by the periodic acid cleavage of cyclohexane-1,2-diol; and since this diol is most readily prepared from cyclohexene, the synthetic problem consists of the preparation of the latter compound. This can be accomplished by the series

$$\text{cyclohexanone} \xrightarrow[\text{or } LiAlH_4]{NaBH_4} \text{cyclohexanol} \xrightarrow[\text{heat}]{H_3PO_4} \text{cyclohexene}$$

23-26 Analytical procedures involving carboxylic acids and derivatives

Neutralization equivalent. The determination of the molecular weight of an organic compound is always of great value in the determination of its composition and structure. Molecular weights can be measured in many ways, some of them simple and reasonably accurate, others more accurate but requiring costly and elaborate equipment. Carboxylic acids lend themselves to a rapid and accurate determination of their equivalent weight (the molecular weight per —COOH group) by virtue of the fact that they can be titrated to sharp end points with standard alkali. The end point may be determined with an indicator, such as phenolphthalein, or with a pH meter. The following examples will illustrate the procedure.

Benzoic acid, C_6H_5COOH, has a molecular weight of 122. Its neutralization will require 1 equivalent of NaOH for 122 g or 1 milliequivalent (10 ml of 0.1 *N* NaOH) for 122 mg.

Thus, a sample of 0.244 g of benzoic acid will require 20 ml of 0.1 *N* NaOH for neutralization:

$$\text{Neutral equivalent} = \frac{\text{mg of acid used}}{\text{meq of alkali required}} = \frac{244}{20 \times 0.1} = 122$$

Succinic acid is a dibasic acid, and two equivalents of alkali will be required for the neutralization of one mole of the acid. It has a neutral equivalent (59) of one-half of its molecular weight (118). Hence, a sample of 0.356 g of succinic acid will require 30.0 ml of 0.201 *N* NaOH for neutralization:

$$\text{Neutral equivalent} = \frac{356}{30 \times 0.201} = 59$$

A sample of 0.278 g of an unknown acid required 18.8 ml of 0.156 *N* NaOH for neutralization:

$$\text{Neutral equivalent} = \frac{278}{18.8 \times 0.156} = 95$$

The unknown acid could be a monobasic acid with a molecular weight of 95, a dibasic acid with a molecular weight of 190, a tribasic acid with a molecular weight of 285, and so on.

Saponification equivalent. The saponification of an ester requires one equivalent of alkali for each —COOR group:

$$RCOOR' + NaOH \longrightarrow RCOO^-Na^+ + R'OH$$

The analytical procedure consists in saponifying a weighed sample of the ester with a measured excess of standard alkali, and titrating the alkali that is not consumed in the reaction.

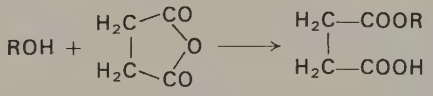
For example, 0.300 g of an ester is saponified with 5.0 ml of 1.00 *N* NaOH. After the saponification is complete the mixture is titrated with 0.100 *N* HCl to a phenolphthalein end point; 30 ml of HCl is required:

Equiv. NaOH initially used: 5 meq
Equiv. HCl required: 3 meq
Equiv. NaOH consumed by the ester: $5 - 3 = 2$ meq

$$\text{Saponification equivalent} = \frac{300 \text{ mg}}{2 \text{ meq}} = 150 \text{ g/equiv.}$$

The compound could be a monoester with a molecular weight of 150, or a diester with a molecular weight of 300, and so on.

The determination of neutralization equivalent or saponification equivalent cannot, of course, be applied unless the compound contains a titratable or a saponifiable group (usually —COOH or —COOR). It is often possible, however, to convert a compound into a *derivative* that can be titrated or saponified. There are numerous devices that can be resorted to. For example, an alcohol can be treated with succinic anhydride to yield the half-ester of succinic acid:



(86)

This derivative is an acid, and can be titrated. Since the molecular weight of the succinic-acid-derived portion of the molecule is known, its neutral equivalent affords the molecular weight of the alcohol.

Another procedure that is sometimes useful is to convert an alcohol into an ester with a known acyl halide, and then to determine the saponification equivalent of the ester. It must be borne in mind that derivatives prepared for such purposes must be carefully purified before they are analyzed.

Carbon-methyl determination. One of the most useful analytical devices available to the organic chemist is the determination of carbon-linked methyl groups. One method depends upon the fact that when a compound containing *C*-methyl groups is oxidized with chromic acid under vigorous conditions, the methyl groups are not oxidized, but remain in the final solution as acetic acid, while the remainder of the molecule is converted largely to carbon dioxide. The acetic acid can be isolated from the solution (by steam-distillation) and titrated. The method thus serves as a means of determining the number of carbon-linked methyl groups in an organic compound, and is commonly referred to as the *C-methyl* or *Kuhn-Roth determination.*

The procedure consists of heating a weighed sample with an oxidizing mixture (chromic acid in aqueous sulfuric acid) for a standard period of time (about an hour), distilling the mixture into a receiver, and titrating the contents of the receiver with standard alkali. The results are calculated and expressed as the *C-methyl number*, which is the number of carbon-linked methyl groups per molecule of compound.

Acetic acid is not produced quantitatively from methyl groups in all combinations, but if the behavior of model compounds is taken into account, the *C*-methyl number can nearly always be used as a measure of the number of methyl groups that are present. The list in Table 23-9 gives some values for the *C*-methyl number found for compounds of several types. It will be noted that methyl groups in saturated environments give low values, while those adjacent to a carbonyl group or a carbon-carbon double bond give values near 1.

It should be noted, however, that since the advent of nuclear magnetic resonance spectroscopy, by means of which methyl groups are readily detected, the Kuhn-Roth determination now has rather limited use.

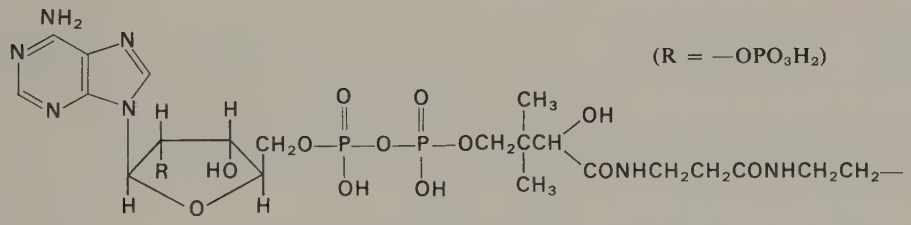
Table 23-9
The C-methyl numbers for some compounds

Compound	*C-methyl number*
acetic acid	0.97 to 1.0 (recovered)
acetone semicarbazone	0.96
crotonic acid	0.94
n-butyric acid	0.93
pivalic acid	0.89
2-butylhexanoic acid	1.64 (82% of two)
methyl isopropyl ketone	1.75 (88% of two)
methylmalonic acid	0.89
malonic acid	0.00
succinic acid	0.00
methylsuccinic acid	0.33 (resistant to oxidation)

23-27 Biological acylation

The formation of esters in biological systems would not be expected to proceed by the reaction of free carboxylic acids with alcohols, for neither the rates nor the equilibria of such reactions appear to be favorable for efficient esterification in the absence of suitable catalysts and with low concentrations of reactants. The reversal of esterase action might be regarded as a possible means of bringing about esterification, but this does not in fact constitute an important synthetic pathway.

The *biological acylating agents* are acid derivatives that show a reactivity approaching that of acid anhydrides and halides in the reactions described above. They are *thiol esters* of the general constitution RCOSR′. The most ubiquitous of these is *acetyl coenzyme A* (acetyl CoA), usually designated by the expression $CH_3COSCoA$, in which the portion "CoA" has the structure



CoA

(acetyl coenzyme A = CoA—S—$COCH_3$ or $CH_3COSCoA$)

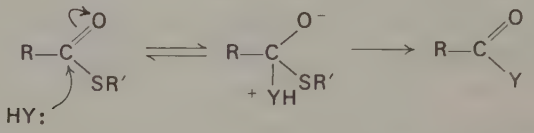
Because the reactivity at the carbonyl carbon atom of the acetyl group depends not upon the details of the complex structure of the remainder of the molecule, but upon the fact that the compound is a thiol ester, the abbreviated terminology will be used in the discussion to follow.

It is at first sight surprising that a thiol ester should display such a high degree of reactivity. For one thing, if we compare the IR stretching frequency of the C=O bond in acid chlorides, esters, amides, and thiol esters, we find the following:

Compound	*IR C=O stretch* (cm^{-1})
alkyl-COCl	1800–1820
alkyl-COOEt	1730–1740
alkyl-$CONH_2$	1680–1695
alkyl-$COSCH_3$	1690–1695

It appears that the degree of single-bond character in C=O is, as is to be expected, least in —COCl, greatest in —$CONH_2$. It will be noticed that in the series acid

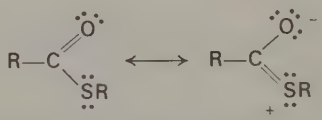
chloride, ester, and amide, the reactivity to nucleophilic attack increases with increasing C=O stretching frequency. By this reasoning alone, the thiol ester would be expected to be the least reactive of the four, and comparable to the amide. The experimental facts are, however, that in the reaction



(87)

thiol esters are very reactive; *that is, they are excellent acylating agents.* It is apparent from this that the facile conclusion based upon the IR data is faulty. It has been suggested that the capacity of sulfur to utilize 3*p* electrons in $C{=}\overset{+}{S}{-}R$ double-bond formation is less than that of oxygen in $C{=}\overset{+}{O}R$ delocalization, thus reducing resonance stabilization in the ground state of the thiol esters (as compared with the oxygen esters) and consequently reducing the activation energy required for passage to the tetrahedral transition state of the initial addition product. The discussion of the reactivity of carboxylic acid derivatives in Section 23-21, illustrated by Figure 23-2, is pertinent here. It would appear that thiol esters occupy a position in the energy levels of Figure 23-2 nearer to acid anhydrides than to esters.

Since sulfur can utilize 3*d* orbitals in bond formation, the structure of thiol esters can be represented by delocalization of the following kind:



It is further to be noted that the C—S stretching frequency of the C—SR bond in *thiol esters* is markedly higher (800–1000 cm^{-1}) than in *thiol ethers* (600–700 cm^{-1}), indicating a considerable degree of double-bond character in the C—SR bond of thiol esters.

Studies with model thiol esters have shown that they react rapidly with amines (while the corresponding oxygen esters react slowly). The following model thiol esters bear a structural resemblance to acetyl CoA at the —COSR portion, and are reactive acetylating agents:

$$\left.\begin{aligned} &CH_3CONHCH_2CH_2\underline{SCOCH_3} + H_2NOH \xrightarrow{\text{fast}} CH_3CONHCH_2CH_2SH + CH_3CONHOH \\ &CH_3CONHCH_2CH_2\underline{OCOCH_3} + H_2NOH \xrightarrow{\text{slow}} CH_3CONHCH_2CH_2OH + CH_3CONHOH \end{aligned}\right\} \quad (88)$$

$$CH_3CONHCH_2CH_2CONHCH_2CH_2\underline{SCOCH_3} + NH_3 \xrightarrow[25^\circ]{\text{fast}} CH_3CONHCH_2CH_2CONHCH_2CH_2SH + CH_3CONH_2 \quad (89)$$

The standard free energy of hydrolysis of thiol esters is markedly greater than that of the comparable *O*-esters:

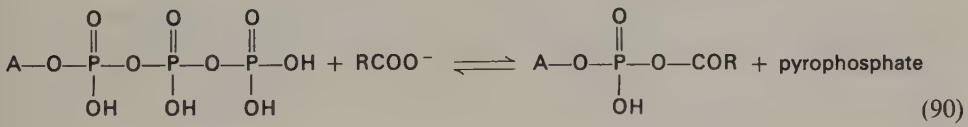
$$CH_3COOEt \qquad -\Delta F^\circ_{hydrol.} = 4700 \text{ kcal/mole}$$

$$CH_3COSCoA \qquad -\Delta F^\circ_{hydrol.} = 7520 \text{ kcal/mole}$$

These observations lead to the conclusion that thiol esters will react readily under physiological conditions with hydroxyl-containing compounds (or other nucleophiles) to yield acylated derivatives. Their reaction with carbon anions will be dealt with in Chapter 24.

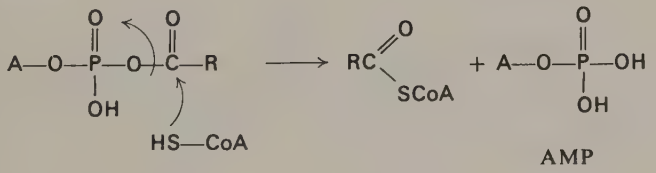
23-28 Thiol (coenzyme A) esters

The abundance, in biological systems, of *N*-acyl and *O*-acyl compounds derived from a wide variety of carboxylic acids suggests that biological mechanisms exist for transforming carboxylic acids into their reactive coenzyme-A thiol esters. A number of such mechanisms are known. One manner of formation of acetyl CoA and fatty acid–CoA esters will be described in Chapter 39. A more general mechanism exists, in which an intermediate acetic-phosphoric anhydride is the agent that acetylates coenzyme A (CoASH). The precursor of this intermediate is adenosine triphosphate (ATP):



(90)

ATP (A = adenosine)



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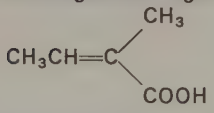
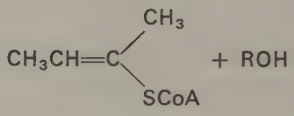
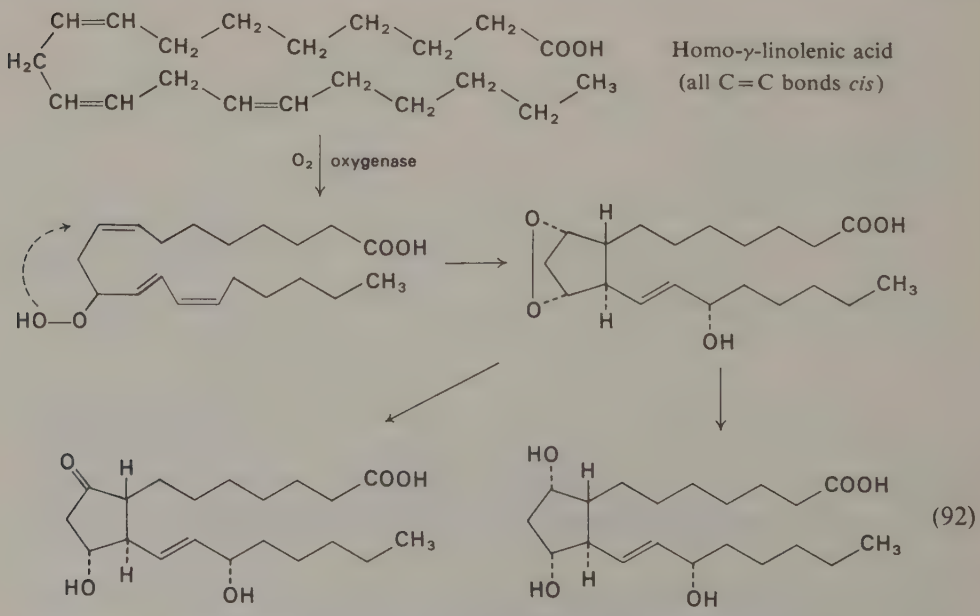
The compounds shown at the top of the following page are natural esters and amides that probably arise in living cells by reaction between an acyl CoA and an alcoholic hydroxyl group or an amino group. It should be pointed out that not all of these specific CoA esters have been identified, but the presumptive evidence for their existence is strong.

The extension of carbon chains by reaction between acyl-CoA thiol esters and nucleophilic (anionic) carbon atoms is described in Chapter 24.

Ester	*ex* RCO—SCoA
benzyl cinnamate $C_6H_5CH{=}CHCOOCH_2C_6H_5$	$C_6H_5CH{=}CHCO{-}SCoA$ + benzyl alcohol
hippuric acid $C_6H_5CONHCH_2COOH$	$C_6H_5CO{-}SCoA$ + glycine
fats and oils	stearoyl-, oleyl-, lineoyl-SCoA, etc. + glycerol
waxes, e.g., $CH_3(CH_2)_{12}COOCH_2(CH_2)_{24}CH_3$	$CH_3(CH_2)_{12}CO{-}SCoA$ (myristyl-CoA) + $CH_3(CH_2)_{24}CH_2OH$
numerous *O*-acetates	$CH_3CO{-}SCoA$ + alcohols
numerous esters of senecioic acid $(CH_3)_2C{=}CHCOOH$ and angelic and tiglic acids 	$(CH_3)_2C{=}CHCO{-}SCoA$ + ROH 
acetylcholine	$CH_3COSCoA$ + choline

23-29 Fatty acid derivatives with special physiological functions

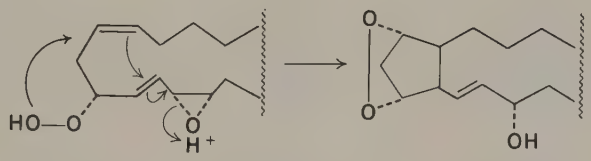
Prostaglandins. A group of modified fatty acids occurring in many body tissues, first isolated from seminal fluid, are the prostaglandins, of which a number have been isolated. All of them are very potent in their physiological activities, and are expected



(92)

to find applications in various areas of therapy. They affect blood pressure, heart rate, various metabolic activities, fertility, conception, and parturition.

Prostaglandin E_1 and $F_{1\alpha}$ (two of the most active) have the structures shown above. Their close relationship to the C_{20} fatty acid homo-γ-linolenic acid can be seen by comparing the structures; and their synthesis in the cell by the action of molecular oxygen (and enzymes called *oxygenases*) is suggested in the scheme shown in Eq. 92. A possible mechanism for the biosynthetic cyclization that forms the cyclopentane ring is

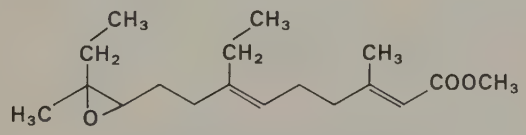


(93)

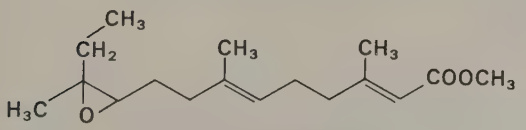
Epoxidation of carbon-carbon double bonds by oxygen/oxygenase systems is a common biological reaction. It can be seen that acid-catalyzed attack upon the (hypothetical) epoxide shown would initiate the steps leading to ring closure.

Numerous synthetic analogues of the prostaglandins have been prepared, some with potent physiological activity, and it is probable that important clinical applications of these substances will be found in the near future.

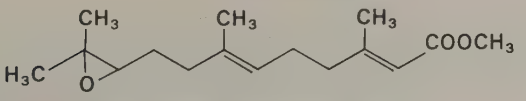
Insect hormones. A number of methyl esters of aliphatic carboxylic acids constitute a class of compounds responsible for regulating the postembryonic development of insects. Two such so-called "juvenile hormones," the physiological function of which is to maintain the larval stage and prevent metamorphosis, have the structures (*a*, *b*) shown below. A number of synthetic compounds of related structure [for example, (*c*)] show the same kind of activity:



(*a*) From giant silkworm moth

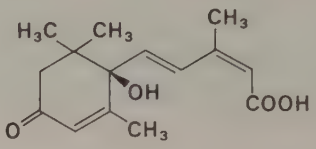


(*b*) From *Cecropia* moth

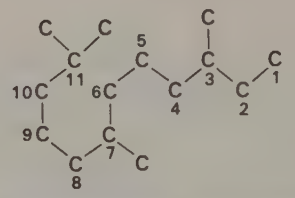


(*c*) Synthetic (biologically active)

Abscisic acid. Abscisic acid is a plant hormone that participates in the biological processes relating to the wilting and dropping of leaves from deciduous plants. Its structure has been shown to be



It can be seen by comparing the basic carbon chains of the insect juvenile hormones (JH) and abscisic acid (ABA) that they are all derived from the same fifteen-carbon-atom unit:



C_{15} (sesquiterpenoid) carbon skeleton

The secondary alterations, including the introduction of the "extra" carbon atoms in JH and ring closure and oxygenation of ABA, are changes brought about by specific biochemical systems in their respective organisms. The C_{15} skeleton shown is of wide occurrence in nature. Its origin and modifications will be described in Chapter 38.

Acids of cellular metabolism. The oxidative metabolism of cells of living organisms involves the formation, degradation, and synthetic utilization of a number of common carboxylic acids of low molecular weight. Many of them are constituents of familiar materials, from which some of them derive their names, for example, malic acid (*Malus*, apples) and citric acid (*Citrus* fruits). They originate in metabolic transformations depending upon another important property of acetyl CoA, which will be discussed in Chapter 37.

23-30 Synthesis and properties of dicarboxylic acids

The *alkanedioic* acids are a homologous series starting with oxalic acid (HOOC—COOH), proceeding by increments of $—CH_2—$ to longer chain lengths (Table 23-10).

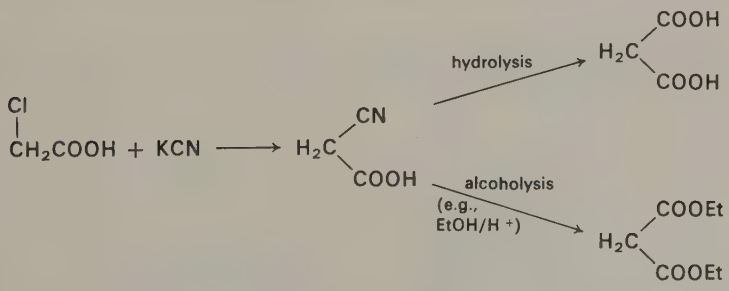
Table 23-10
Dicarboxylic acids (alkanedioic acids)

Compound	*Common name*	*Systematic name*
HOOC—COOH	oxalic (acid)	ethanedioic (acid)
$HOOC(CH_2)_nCOOH$		
$n = 1$	malonic	propanedioic
$n = 2$	succinic	butanedioic
$n = 3$	glutaric	pentanedioic
$n = 4$	adipic	hexanedioic
$n = 5$	pimelic	heptanedioic
$n = 6$	suberic	octanedioic
$n = 7$	azelaic	nonanedioic
$n = 8$	sebacic	decanedioic

Oxalic acid is a constituent (often as the sparingly soluble calcium salt) of many plants. Certain plants (for example, *Oxalis*) contain enough oxalic acid to be toxic to grazing animals, especially when their dietary calcium is low. The usual method of preparing oxalic acid is to heat sodium formate at 300–360°C in the presence of added sodium hydroxide:

$$2HCOONa \longrightarrow NaOOCCOONa + H_2$$

Malonic acid is found naturally in some plants and fungi, but is of infrequent occurrence. Its formation as the coenzyme A mono-ester (Section 24-7) is a fundamental step in the cellular metabolism of fatty acids. The synthesis of malonic acid and its esters is usually carried out by conversion of chloroacetic acid into cyanoacetic acid with potassium cyanide, followed by hydrolysis or alcoholysis:



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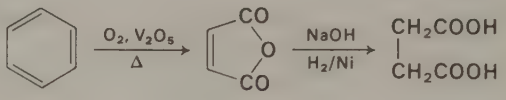
Substituted malonic acids can be prepared by *C*-alkylation of malonic esters; these reactions are described in Section 24-10.

Succinic acid is prepared industrially by the catalytic reduction (hydrogen, Raney nickel) of maleic anhydride, which is made by a catalytic oxidation of benzene:



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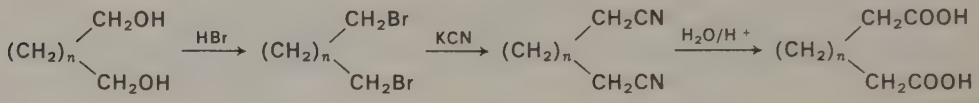
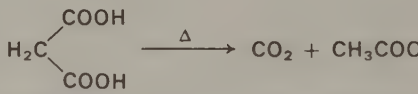
The higher dicarboxylic acids are readily prepared by lithium aluminum hydride reduction of $(CH_2)_n(COOR)_2$ to $(CH_2)_n(CH_2OH)_2$, followed by the steps



(96)

Malonic acid (like other 1,1-dicarboxylic acids and β-keto acids) is readily decarboxylated on moderate heating. Succinic and glutaric acids do not decarboxylate on heating; instead, they lose the elements of water to form the cyclic anhydrides. This reaction is general for dicarboxylic acids whose anhydrides are 5- or 6-membered cyclic compounds:



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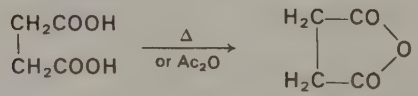
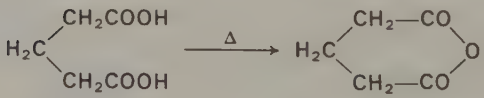


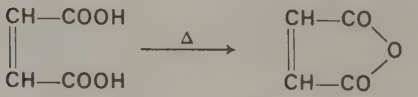
Succinic acid — Succinic anhydride

(98)



Glutaric acid — Glutaric anhydride

(99)



Maleic acid — Maleic anhydride

(100)

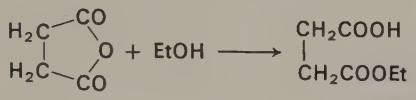
Phthalic acid — Phthalic anhydride

(101)

Further discussion of these and other ring-forming processes will be found in Chapter

27. Cyclic anhydrides with larger than 6-membered rings cannot be satisfactorily prepared by simple heating of the corresponding acids.

Cyclic anhydrides have many useful synthetic applications. For example, when succinic or phthalic anhydride is heated with an equimolar amount of an alcohol, the ring is opened with the formation of the half-ester of the dibasic acid:



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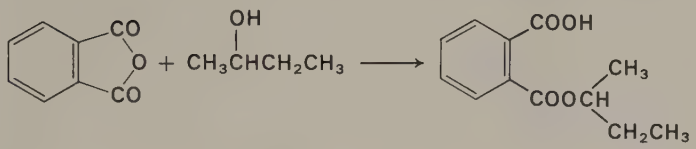
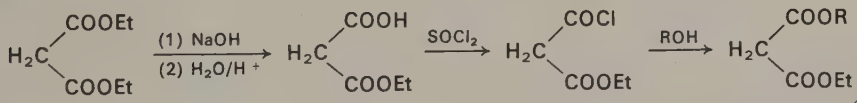


(103)

It will be recalled (Section 6-11) that the use of phthalic anhydride in this way is a part of a procedure for resolving an alcohol into its enantiomers. With an excess of the alcohol and with a mineral acid catalyst, the diester will be formed.

The mono-esters of dicarboxylic acids can also be prepared by controlled saponification of the diesters, using one equivalent of alkali. Ethyl hydrogen malonate (the half ethyl ester of malonic acid), which cannot be prepared by the anhydride-alcohol method, can be converted into the acid chloride, reaction of which with another alcohol yields the "mixed" diester. Other "half-esters" can be prepared and treated similarly:



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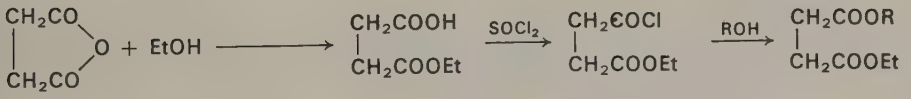


(105)

It may be recalled (Section 18-6) that the reaction of organocadmium compounds with acid chlorides derived from mono-esters of diabasic acids is a preparative route to keto esters.

Exercise 11

Show how the following could be synthesized: (*a*) 3,3-dimethylpentanedioic acid, (*b*) 4-ketohexanoic acid, (*c*) 2-butene-1,4-diol, (*d*) 1,6-dibromohexane. NOTE: Use as starting materials any compounds that could be regarded as reasonably available.

Problems

1. Name each of the following acids in two ways:
   (*a*) CH_3CH_2COOH
   (*b*) $BrCH_2COOH$
   (*c*) $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCOOH$
   (*d*) $HOCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH$
   (*e*) $CH_2{=}CHCH_2CH_2COOH$
   (*f*) $CH_2{=}CHCH_2COOH$
   (*g*) $(CH_3)_2CHCOOH$
   (*h*) $(CH_3)_2CH\underset{\displaystyle CH_2CH_3}{\underset{|}{C}}HCOOH$
   (*i*) $(CH_3CH_2)_3CCOOH$

2. Write the structural formulas for the following: (*a*) ethoxyacetic acid, (*b*) dichloroethanoic acid, (*c*) acetyl chloride, (*d*) α,β,γ-tribromo-*n*-butyric acid, (*e*) 2-bromo-3-heptenoic acid, (*f*) acetyl cyanide, (*g*) perfluoropropionic acid, (*h*) 2-hexenoyl chloride.

3. Write the equations for the reactions of propionic acid with (*a*) water, (*b*) ammonia, (*c*) ethylamine, (*d*) sodium ethoxide, (*e*) ethanol (with a trace of sulfuric acid), and (*f*) trimethylamine.

4. Describe the saponification of isopropyl acetate with sodium hydroxide by writing the sequence of steps through which the reaction proceeds.

5. Explain base-catalyzed ester interchange by describing the nature of the reaction between ethyl propionate and methanol in the presence of sodium methoxide.

6. Write the reaction of isobutyryl chloride with (*a*) ethanol, (*b*) isobutyl alcohol, (*c*) sodium acetate, (*d*) water, (*e*) hydrazine, (*f*) hydroxylamine, and (*g*) methylethylamine.

7. Write the reactions that would be involved in the following transformations:
   (*a*) *n*-butyl bromide into pentanoic acid
   (*b*) acetyl chloride into acetic anhydride
   (*c*) propionyl chloride into *n*-butylamine
   (*d*) ethylene dibromide into succinic acid (butanedioic acid)
   (*e*) tristearin into a soap

8. Which of the following compounds will give a positive hydroxamic acid test? Write the relevant reactions: (*a*) ethyl acetate, (*b*) methyl formate, (*c*) sodium acetate, (*d*) acetyl chloride.

9. Outline a practical experimental procedure that could be used to separate each of the following mixtures into its pure individual components:
   (*a*) di-*n*-butyl ether, pentanal, *n*-butyric acid, *n*-octane
   (*b*) diethylamine, 1-propanol, acetic acid
   (*c*) 2-hexanone, 3-hexanone, propionic acid

10. Show how trimethylacetic acid can be prepared from acetone in a three-step synthesis.

11. How many ways can you devise for the conversion of 1-bromobutane into pentanoic acid?

12. Plants native to northern latitudes have a ratio of saturated/unsaturated fats which differ from the ratio in tropical plants. Which should have the higher saturated/unsaturated ratio? Why?

13. Write equations showing three ways of converting acetic acid into its methyl ester. Which way would you adopt as the most practical, assuming you started with (*a*) one gram of the acid; (*b*) 100 grams of the acid? Explain the reasons for your choices.

14. Oxidation of cyclohexanone with chromic acid yields adipic acid. Would the oxidation of 3-methylcyclohexanone be an equally practicable method of preparing α-methyl adipic acid? Why?

15. A mixture of methoxyacetic acid and a large excess of acetic anhydride was heated to boiling and slowly distilled through a fractionating column. What compounds were contained in the distillate, and in what order did they appear? Support your conclusion by writing the appropriate equations for what took place.

24

Ester condensation reactions

Among the carboxylic acid derivatives, esters are singled out for further discussion in this chapter because they engage in a special kind of reaction of wide application in organic synthesis and of special importance in biological systems. *Ester condensations* are reactions of the general aldol type; they proceed by the attack of an α-carbanion upon the carbonyl group of an ester.

These reactions, *Claisen and Dieckmann condensations* (usually referred to as "name reactions"), lead to keto esters, which are also reagents of wide use in synthesis.

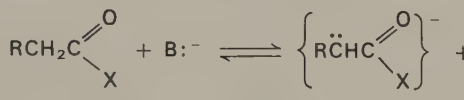
The biological reactions of esters are of central importance in the metabolism of living organisms. Among these reactions are the hydrolysis of natural esters (fats and oils) in digestion, the ester condensation reactions by which small molecules (acetic acid derivatives) are elaborated into complex cellular constituents, and a variety of related processes. Many of these involve the thiol esters described in the preceding chapter. Although these natural processes occur under the catalytic mediation of specific enzyme systems, they will be seen to involve the same mechanisms and they can be discussed in the same terms as the non-biological reactions to which they correspond.

In this chapter are also described the properties and uses of the keto esters that

are formed by Claisen and related condensation reactions. Special attention is again given to the greatly enhanced acidic character of C—H bonds when flanked by two carbonyl groups. This was discussed in Chapter 22 and may be reviewed again at this time.

24-1 Esters as "active methylene" compounds. Claisen condensations

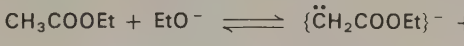
The α hydrogen atoms of carboxylic acid derivatives, like those of aldehydes and ketones, are "active" hydrogens and are subject to ionization by strong bases. The general reaction



(1)

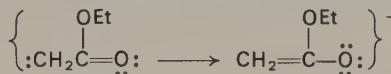
is experimentally practicable for esters (X = OR′), but only in special cases can it be realized with acid halides, anhydrides, and amides.*

The reaction of ethyl acetate with sodium ethoxide yields the enolate anion:



(2)

which, although the negative charge is delocalized in the familiar manner,



(3)

reacts as though the carbon anion were the principal contributing form. That is, in reactions with electrophilic centers the nucleophilic center of the anion is usually at the carbon atom, not the oxygen atom.

This carbanion† is the conjugate base of a very weak acid; it is therefore a very strong base and an effective nucleophile. Its reaction with un-ionized ester‡ proceeds in the expected manner, namely, by nucleophilic attack upon the ester carbonyl group:

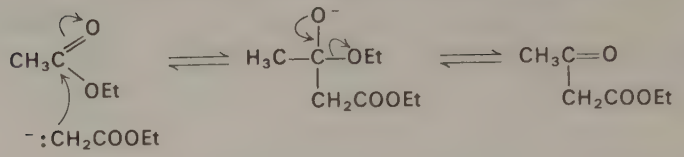
---

* In the reaction of RCOOR′ with an alkoxide, it is best to use the alkoxide (NaOR′) corresponding to the alkoxy group (—OR′) of the ester. If a different alkoxide (NaOR″) is used, ester interchange will occur, and a mixture of esters (RCOOR′ and RCOOR″) will be formed. The final products will be mixtures containing both —OR′ and —OR″ groups.

† Although the anion is a resonance-stabilized species with a delocalized charge, it will often be convenient to refer to it simply as the carbon anion, or carbanion.

‡ It must be kept in mind that under the usual experimental conditions only a small fraction of the ester is deprotonated, so the remaining ester is available for reaction with the carbanion.

$$CH_3COOEt + EtO^- \rightleftharpoons {}^-:CH_2COOEt + EtOH \qquad (4)$$



(5)

The final product in this expression is the β-keto ester ethyl acetoacetate, CH_3COCH_2COOEt. All of the steps shown in this overall process are reversible, but a further step drives the reaction to completion. Because the $—CH_2—$ group of the β-keto ester, flanked by two carbonyl groups, is sufficiently acidic ($pK_a = 10.7$) to undergo essentially complete ionization in the presence of the strong base used (EtO^-),

$$CH_3COCH_2COOEt + EtO^- \rightleftharpoons (CH_3CO\ddot{C}HCOOEt)^- + EtOH \qquad (6)$$

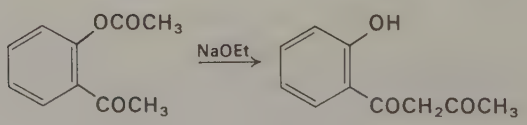
the overall equilibrium is shifted almost completely to the right. The final product of the reaction is the sodium salt (if sodium ethoxide is used) of the β-keto ester, from which the ester is recovered by acidification. The reaction, known as the *Claisen ester condensation*, thus results in the *C-acylation* of the starting ester.

C-Acylation of other active methylene groups can be accomplished in a similar way. Since ketones and nitriles are more readily converted into their anions than is ethyl acetate (pK_a of ethyl acetate = 26; acetonitrile = 25; acetone = 20; acetophenone = 19), their acylation proceeds as shown in the following examples. The last of these is the acylation of a methyl ketone by *intramolecular* reaction with an ester grouping, with the formation of a cyclic diketone.

$$\begin{aligned} CH_3COCH_3 + EtO^- &\rightleftharpoons CH_3COCH_2{:}^- + EtOH \\ CH_3COCH_2{:}^- + CH_3COOEt &\longrightarrow CH_3COCH_2COCH_3 + EtO^- \end{aligned} \qquad (7)$$

$$\begin{aligned} C_6H_5COCH_3 + EtO^- &\rightleftharpoons C_6H_5COCH_2{:}^- + EtOH \\ C_6H_5COCH_2{:}^- + CH_3COOEt &\longrightarrow C_6H_5COCH_2COCH_3 + EtO^- \end{aligned} \qquad (8)$$

$$\begin{aligned} C_6H_5CH_2CN + EtO^- &\rightleftharpoons (C_6H_5\ddot{C}HCN)^- + EtOH \\ (C_6H_5\ddot{C}HCN)^- + CH_3COOEt &\longrightarrow C_6H_5CH(COCH_3)—CN + EtO^- \end{aligned} \qquad (9)$$



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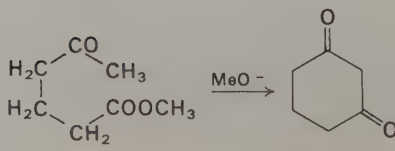


(11)

Exercise 1

Reactions (10) and (11) are written to show the overall result. Formulate each of these in detail to show the sequence of steps.

Claisen condensation reactions involving esters of the general structure RCH_2COOR'* lead to β-keto esters of the general structure $RCH_2COCHCOOR'$ (with R on the α-carbon). "Self-condensations" of this kind are successful with esters of propionic to pentanoic, hexanoic, lauric, myristic, and higher acids.

Exercise 2

Show the complete sequence of events in the reaction of ethyl hexanoate with sodium ethoxide to form the β-keto ester.

24-2 Oxalylation and formylation

An ester that contains no α hydrogen atoms can act *only* as the carbonyl component in a Claisen condensation. When, in addition, the ester possesses an exceptionally reactive carbonyl group (for electronic or steric reasons), it is a highly effective acylating agent.

Two esters often used in this way are those of formic and oxalic acids. Both of these are highly susceptible to nucleophilic attack, and react with α-carbanions to form *C*-formyl and *C*-oxalyl compounds. In the following groups of examples, the first reaction is shown in detail, the others as overall reactions:

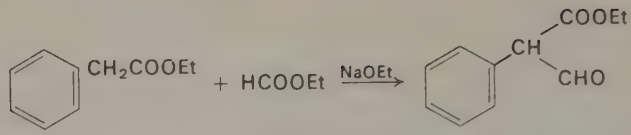
C-formylation

$$CH_3COCH_3 + OEt^- \rightleftharpoons CH_3COCH_2:^- + EtOH$$

$$CH_3COCH_2:^- + \underset{\text{Ethyl formate}}{HCOOEt} \rightleftharpoons CH_3COCH_2CHO(OEt)^- \longrightarrow$$

$$CH_3COCH_2CHO + EtO^- \rightleftharpoons (CH_3\ddot{C}OCHCHO)^- + EtOH \quad (12)$$

* Any ester that is conveniently available, in most cases an ethyl or methyl ester, may be used.



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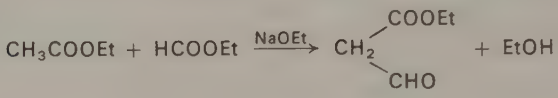
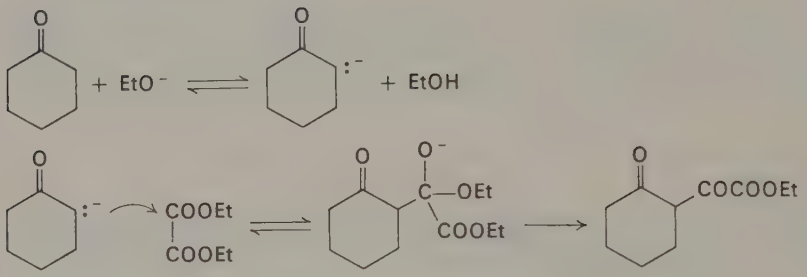


(14)

C-oxalylation



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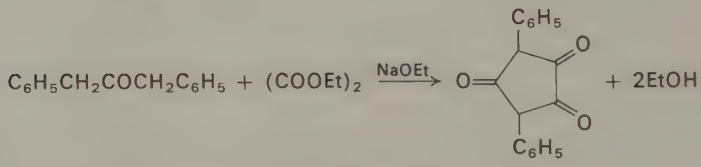

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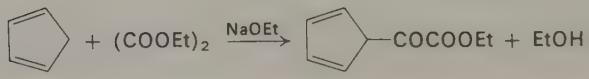


(17)

Exercise 3

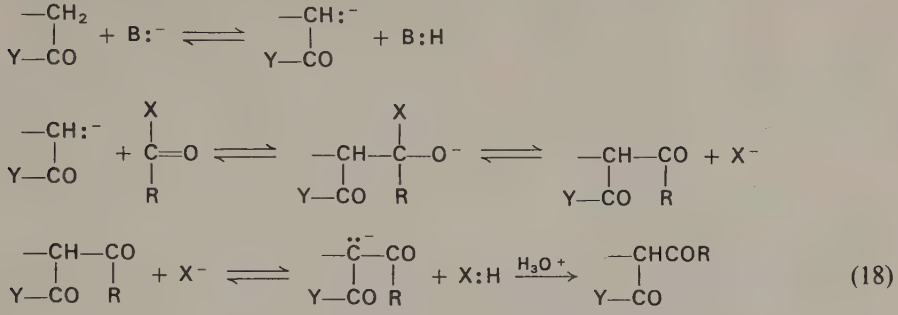
Write out the sequence of steps in each of the foregoing examples of oxalylation and formylation reactions. (NOTE: In the case of cyclopentadiene, refer to Chapter 22.)

Other esters that lack α hydrogen can also be used as acylating agents: for example, diethyl carbonate $CO(OEt)_2$ and ethyl benzoate.

Exercise 4

Formulate the sodium-alkoxide-catalyzed condensation of (*a*) acetophenone ($C_6H_5COCH_3$) and ethyl benzoate, (*b*) cyclopentanone and diethyl carbonate, (*c*) acetophenone and dimethyl carbonate.

The above reactions can be summarized in the following partial formulations:



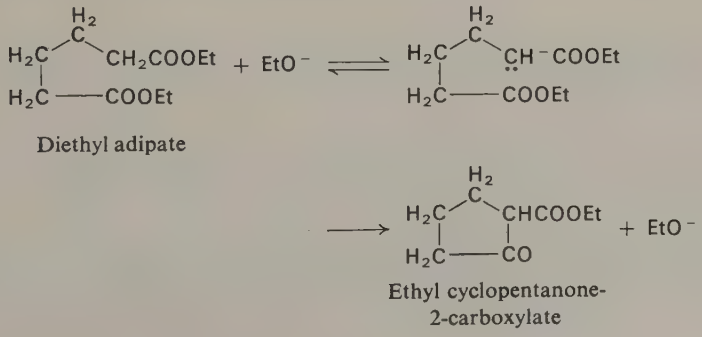
(18)

If Y = alkyl or aryl, final product is a 1,3-diketone (β-diketone)
If Y = alkoxyl, final product is a β-keto ester
X = $-OCH_3$ or $-OCH_2CH_3$

24-3 Cyclization by ester condensations. The Dieckmann reaction

When the two reacting functions—the activated α methylene group and the ester group—are present in the same molecule, their interaction results in the formation of a cyclic compound. As in the case of cyclic aldol condensations, certain steric requirements must be met for such cyclizations to be practicable. In general, five- and six-membered rings are readily formed. Smaller rings are subject to the strain imposed by the distortion of normal bond angles and, because the Claisen condensation is reversible, are not formed as stable final products. Seven-membered rings can be formed, usually in poorer yields than five- and six-membered rings, but the formation of larger rings (eight or more members) by Claisen condensations is usually not synthetically practicable.

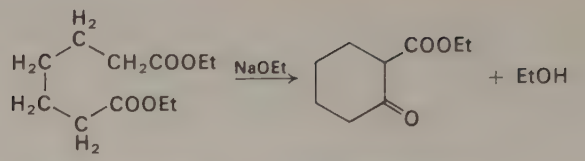
The simplest example of this intramolecular Claisen reaction (called the *Dieckmann reaction*) is the formation of a cyclopentanone or cyclohexanone derivative from the appropriate dicarboxylic acid ester:



Diethyl adipate

Ethyl cyclopentanone-2-carboxylate

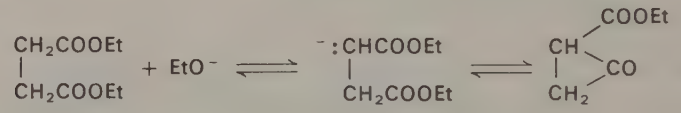
(19)



Diethyl pimelate — Ethyl cyclohexanone-2-carboxylate (20)

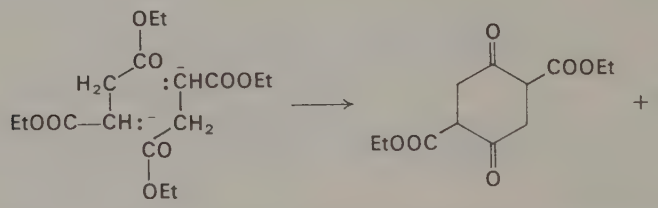
Some examples of cyclization given in the preceding section correspond to this reaction.

What happens if the only possible course for the Dieckmann condensation is one that leads to a ring of an unfavorable size? Diethyl succinate, for example, might be expected to undergo intramolecular condensation to give the three-membered cyclic keto ester:



(21)

This highly strained ring system does not persist under the reversible conditions of the reaction, and the cyclization ultimately takes the more thermodynamically (energetically) favored course in which two molecules of the ionized ester react to form a six-membered ring:



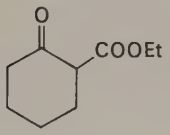
(22)

When *intramolecular* cyclization is not favored and no suitable *intermolecular* cyclization alternative exists, the reaction is seldom useful; it may lead to polymeric products by repeated intermolecular condensation.

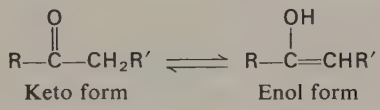
24-4 Properties of β-diketones and β-keto esters. Tautomerism

Compounds containing the 1,3-diketo (β-diketo) system —$COCH_2CO$— differ from simple aldehydes and ketones in several ways. The —CH_2— group, flanked by two carbonyl groups, shows enhanced acidity because of the possibility for enhanced charge delocalization and consequent stabilization in the anion. Reprotonation of the carbanion can occur either on carbon or oxygen, the two possible reprotonated forms being known as *tautomers.*

Table 24-1
Enolic content of some carbonyl compounds

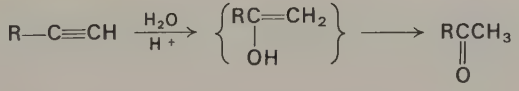
Essentially no enol (simple aldehydes, ketones, esters)	*Partly enolic* (β-keto esters)	*Largely enolic* (β-keto aldehydes, β-diketones)
CH_3COCH_3	CH_3COCH_2COOEt	$CH_3COCH_2CHO \rightleftharpoons (CH_3COCH{=}CHOH)$
CH_3CH_2CHO		$CH_3COCH_2COCH_3 \rightleftharpoons (CH_3COCH{=}C(OH){-}CH_3)$
CH_3CH_2COOEt		

In monocarbonyl compounds the enol form is unstable with respect to the carbonyl form, so that in ordinary aldehydes and ketones the equilibrium



Keto form Enol form (23)

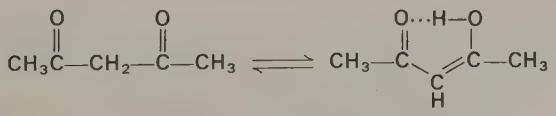
is normally far to the side of the carbonyl compound (the keto form). Reactions that would be expected on formal grounds to lead to the formation of simple enols actually yield the keto forms. For example, the hydration of an acetylene, by a process that corresponds to hydration of an olefin, yields the ketone:



(24)

β-Diketones and β-keto esters, on the other hand, usually consist, in solution, of an equilibrium mixture of enol and keto forms.* The percentage of the enol form in such mixtures is strongly influenced by the molecule's overall structure. Some generalizations can be made, as Table 24-1 shows.

The high proportion of the enolic form in β-dicarbonyl compounds is due in part to the stabilization of the enol by intramolecular hydrogen-bond formation:



(25)

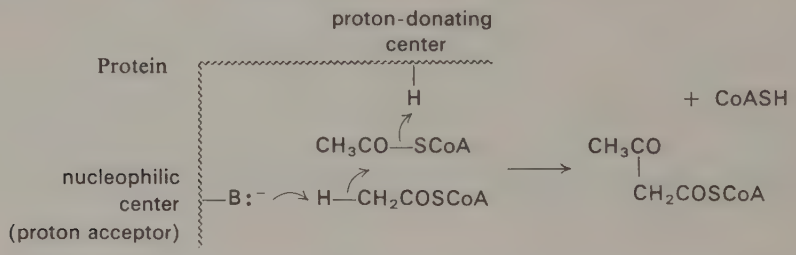
* It is to be emphasized that tautomerism is not the same as resonance. The keto and enol forms of a carbonyl compound are distinct compounds, differing in the position of a hydrogen atom, and not simply in the disposition of the bonds or the location of a charge.

24-5 Claisen-like condensation reactions in biological systems

Some of the most fundamental and important reactions in cellular metabolism are the biological counterparts of the Claisen and related condensations. The central reactants in these reactions are thiol esters ($RCH_2CO—SCoA$), in particular, acetyl coenzyme A ($CH_3CO—SCoA$).

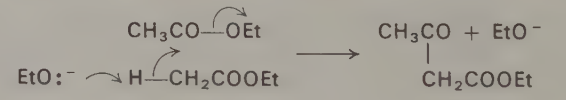
The reactivity of the carbonyl group of acetyl CoA has been discussed in Chapter 23. Associated with this high degree of carbonyl reactivity is an activation of α hydrogen of the acetyl group. Although Claisen condensations of esters ordinarily require strongly basic reagents, such as alkali alkoxides or amides, the reactivity of acyl CoA esters in biological systems suggests that formation of the α-carbanion can be accomplished by the relatively mildly basic centers present as constituent elements of a polypeptide (protein).

The earlier discussion (Section 23-28) of the role of acyl CoA (thiol esters) as acylating agents applies here as well, for the Claisen condensation is a *carbon-acylation* with an α-carbanion acting as the nucleophile. The self-condensation of acetyl CoA is a well-known biological reaction, and can be represented as follows:



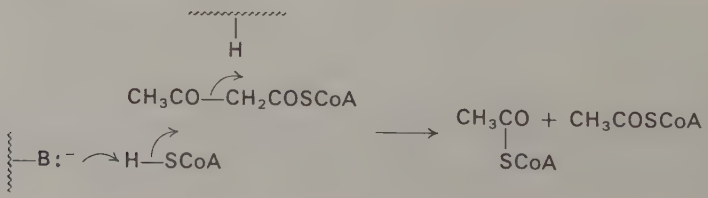
(26)

This is clearly the exact counterpart of the self-condensation of ethyl acetate, the overall process of which may be represented in a corresponding manner:



(27)

The reversal of the biological *C*-acylation can be formulated in terms that show its correspondence to the reversal of the Claisen condensation (prior to the final ionization of the β-dicarbonyl compound):



(28)

The degradation of long-chain fatty acids takes place by a comparable mechanism, the final stage of which is the cleavage of a β-keto acyl CoA by the nucleophilic CoA—SH. The initial stages of this process are outlined below, but it is only the final cleavage (*d*) that pertains directly to the present discussion.

$$(a)\quad RCH_2CH_2CH_2CH_2CO{-}SCoA \overset{(1)}{\rightleftharpoons} RCH_2CH_2CH{=}CHCO{-}SCoA$$

$$(b)\quad RCH_2CH_2CH{=}CHCO{-}SCoA \overset{(2)}{\rightleftharpoons} RCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CO{-}SCoA$$

$$(c)\quad RCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CO{-}SCoA \overset{(3)}{\rightleftharpoons} RCH_2CH_2COCH_2CO{-}SCoA$$

$$(d)\quad RCH_2CH_2COCH_2CO{-}SCoA + CoASH \overset{(4)}{\rightleftharpoons} RCH_2CH_2CO{-}SCoA + CH_3COSCoA$$

$$(e)\quad RCH_2CH_2CO{-}SCoA \xrightarrow[\text{as above}]{\text{repetition}} RCO{-}SCoA + CH_3COSCoA \qquad (29)$$

NOTE: (1), (2), (3), and (4) represent enzymatic systems catalyzing the individual reaction stages.

This kind of degradation of stearic acid ($CH_3(CH_2)_{16}COOH$), for instance, yields nine molecules of acetyl CoA. The further oxidative degradation of acetyl CoA in the citric acid cycle (Section 37-13) provides energy and synthetic starting materials needed for metabolic activity.

24-6 Chain extension by *C*-acylation

In principle at least, the initial condensation of acetyl CoA to give acetoacetyl CoA can be followed by successive similar reactions to build up a chain of $—CH_2CO—$ units:

$$CH_3CO{-}SCoA + CH_3CO{-}SCoA \longrightarrow CH_3COCH_2CO{-}SCoA + CoASH \qquad (30)$$

$$CH_3COCH_2CO{-}SCoA + CH_3COSCoA \longrightarrow$$

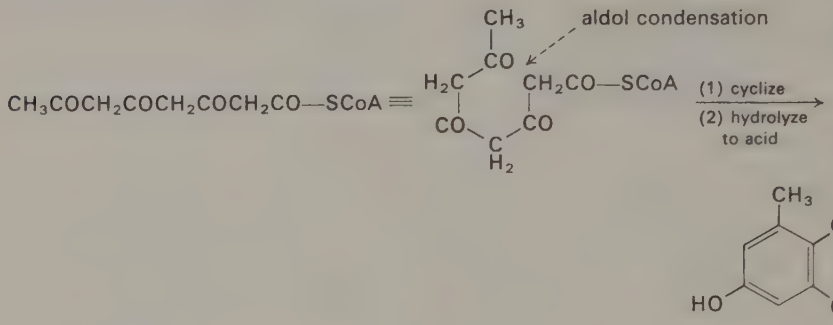
$$CH_3COCH_2COCH_2CO{-}SCoA + CoASH \xrightarrow{\text{etc.}} CH_3(COCH_2)_nCO{-}SCoA \qquad (31)$$

NOTE: Although it is mechanistically adequate, this expression is simplified; the actual biological system may involve an enzyme-bound acyl group formed by the transfer of RCO— from RCOSCoA to the —SH group of an enzyme:

$$Enzyme{-}SH + RCOSCoA \longrightarrow Enzyme{-}S{-}COR + CoASH$$

There is little doubt that such condensations occur in specialized systems in the cell. The polyketo compounds are not known as such, for so highly reactive a system of β-diketo linkages would be prone to undergo aldol-like condensation reactions with the formation of cyclic compounds; this process appears actually to occur in nature.

Natural compounds formed in this way are of wide distribution and of diverse structural type; two examples are given here:



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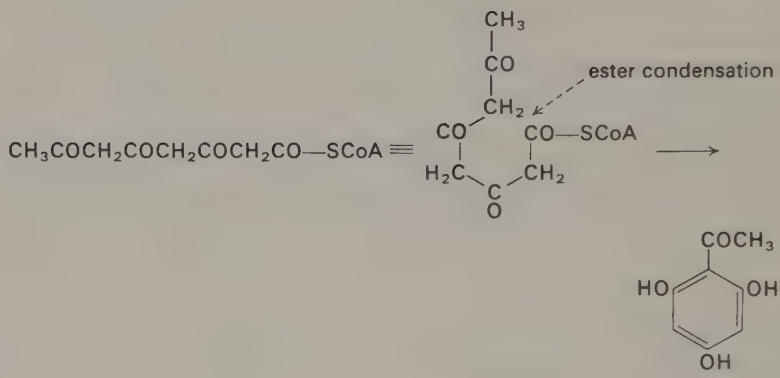
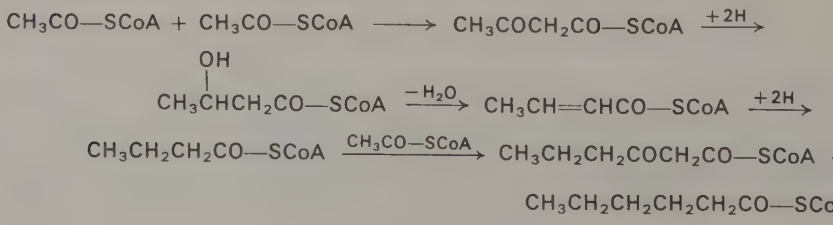


(33)

24-7 Activation of acetyl CoA. Malonyl CoA

The repeated acylation of acetyl CoA, with intermediate reduction of $—COCH_2—$ to $—CH_2CH_2—$, corresponds to a reversal of the successive steps in the cleavage of a fatty acid and could be envisioned as a means of synthesizing fatty acids. This means of synthesizing long saturated chains of carbon atoms does not, however, appear to be the usual way in which the higher fatty acids are formed in nature. Although the naturally occurring lower fatty acids can be synthesized this way



(34)

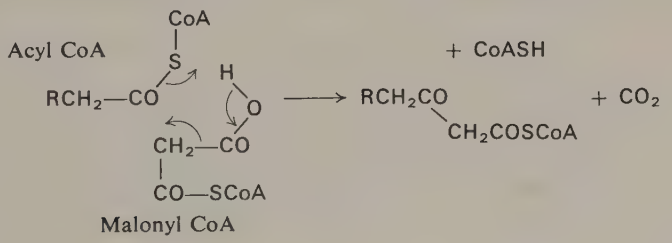
the synthesis of such larger acids as lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), and so on follows a course that is a modification of this.

The synthesis of higher fatty acids does indeed utilize acetyl CoA, but also two additional reactants: an enzymatic system requiring the cofactor *biotin*, and carbon dioxide. The overall process involves the *activation* of the α methylene group of acetyl CoA by conversion of acetyl CoA into the CoA ester of malonic acid:

$$CH_3CO{-}SCoA + CO_2 \xrightarrow[\text{enzyme}]{\text{biotin}} \underset{\displaystyle \underset{\displaystyle COOH}{|}}{CH_2CO{-}SCoA} \qquad (35)$$

Malonyl CoA

It should be at once apparent that the $-CH_2-$ group of malonyl CoA is a much more reactive methylene group than that of acetyl CoA, for it is flanked by two carboxyl carbonyl groups. Condensation with an acyl CoA proceeds exactly as before, except with a greater degree of reactivity. It is probable that loss of CO_2 accompanies, rather than follows, the condensation step. The details may be represented as follows:



(36)

The general reaction

$$RCH_2CO{-}SCoA + CH_3CO{-}SCoA \xrightarrow[\text{biotin}]{CO_2} RCH_2COCH_2COSCoA + CoASH \qquad (37)$$

occurs with a great many modifications in natural processes. The group RCH_2- in the above expression need not be simply the methyl group as in acetyl CoA, but may be of any of a wide range of structural types. Natural compounds derived from many diverse "starter" acyl CoA esters can arise from such initial steps as the following:

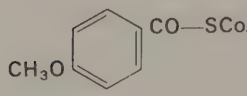
$$CH{=}CHCO{-}SCoA + \text{malonyl CoA} \longrightarrow$$

$$CH{=}CHCOCH_2CO{-}SCoA + CO_2 + CoASH \qquad (38)$$

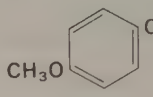
$$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO{-}SCoA + \text{malonyl CoA} \longrightarrow$$

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCH_2CO{-}SCoA + CO_2 + CoASH \qquad (39)$$

$$CH_3CH_2CO—SCoA + \text{malonyl CoA} \longrightarrow CH_3CH_2COCH_2CO—SCoA + CO_2 + CoASH \quad (40)$$



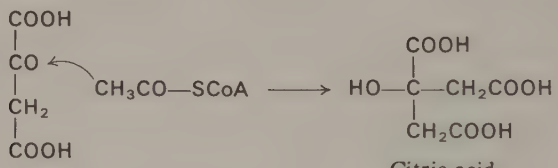
$$+ \text{malonyl CoA} \longrightarrow$$



$$+ CO_2 + CoASH \quad (41)$$

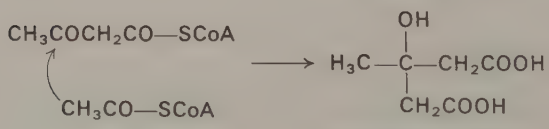
24-8 Aldol-like condensations of acetyl CoA

The potential nucleophilic reactivity at the α carbon atom of acetyl CoA is further shown in several important biological reactions. In all of these the addition, to a carbonyl group, of a carbon anion derived from an activated $—CH_3$ group resembles an aldol addition reaction. Omitting the various ionic intermediate steps that have already been described, the overall reactions may be represented as follows:*



(42)

Citric acid



(43)

β-hydroxy-β-methyl-glutaric acid

β-Hydroxy-β-methylglutaric acid exists as the free acid in some natural sources, but the reaction in which it is initially formed, as the CoA ester, is more commonly recognized as the starting point for the elaboration of a compound of great importance in biological systems. The formation of *mevalonic acid*, and its eventual conversion into isopentenyl pyrophosphate and γ,γ-dimethylallyl pyrophosphate, provides the biological precursors for the synthesis of terpenes, carotenoids, and steroids (see Chapter 38):

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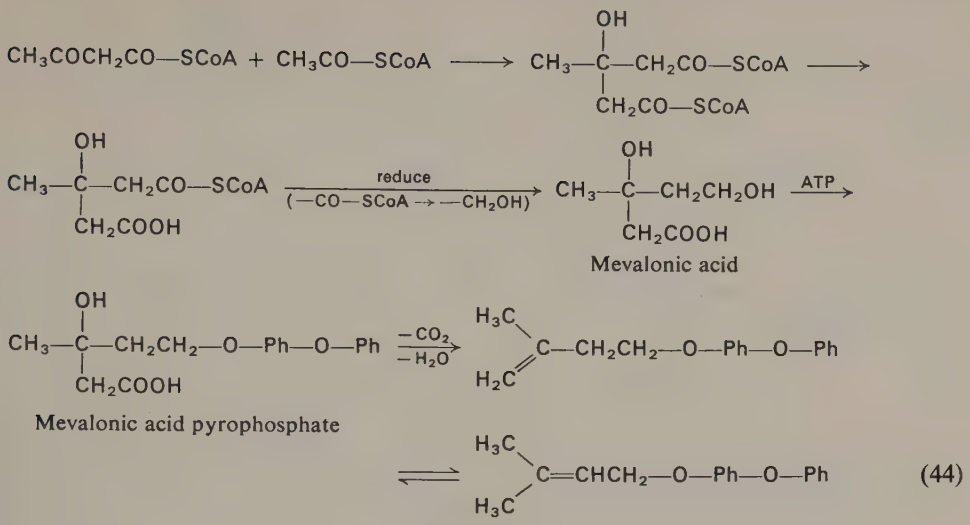
* It is possible that in these reactions the intermediate RCO—SCoA esters react with —SH groups on the enzyme protein, so that the Enzyme —S—COR esters are the actual reactants. This has been alluded to in Section 24-6.



(44)

24-9 β-Keto esters and malonic esters in synthesis

The acidic properties of the $—CH_2—$ group of ethyl acetoacetate ($pK_a = 10.7$), diethyl malonate ($pK_a = 13.3$), and similarly constituted β-dicarbonyl compounds are sufficient to make possible their complete conversion to the carbon anions* by the moderately strong base alkoxide ion:

$$CH_3COCH_2COOEt + EtO^- \rightleftharpoons (CH_3COCHCOOEt)^- + EtOH \qquad (45)$$

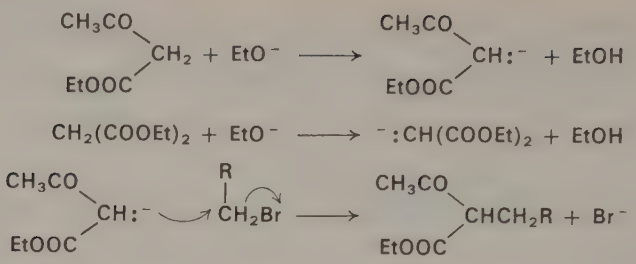
The enolate (α-carbon) anion, as the conjugate base of a very weak acid, is a strong base and can act as an effective nucleophile. The alkylation of β-dicarbonyl compounds, described in the following section, is a general reaction of wide application in organic synthesis and of common occurrence in biological reactions.

24-10 Carbon alkylation of β-dicarbonyl compounds

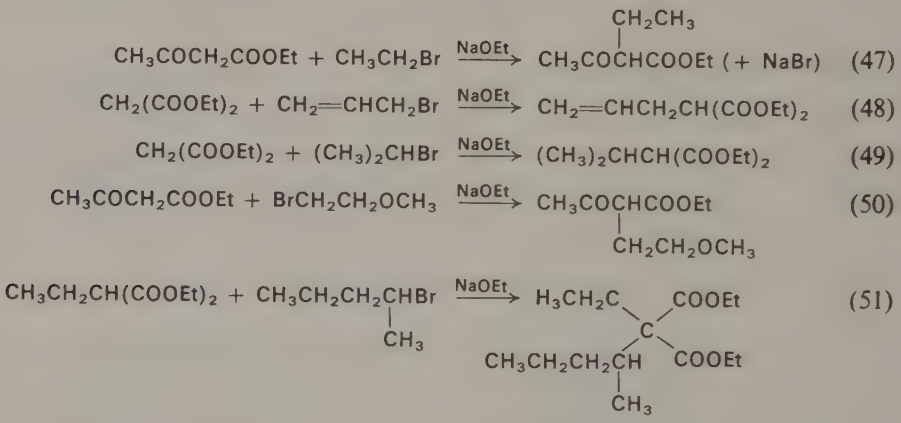
The reaction of the anion of ethyl acetoacetate or diethyl malonate with an alkyl halide proceeds as follows:

---

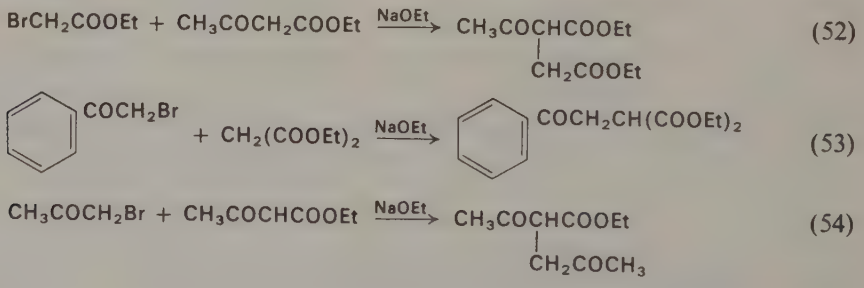
* Since α-carbon anions are resonance hybrids of the type $(—\ddot{C}H—\overset{|}{C}=\ddot{O}: \leftrightarrow —CH=\overset{|}{C}—\ddot{\underset{\cdot\cdot}{O}}:)$, as was pointed out in Section 24-1, they can just as properly be called *enolate ions*, and are often referred to in this way.



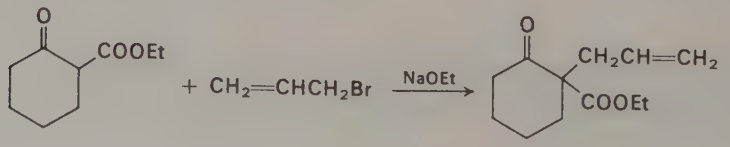
It can be seen that the alkylation step is a typical nucleophilic displacement reaction. Some examples are:

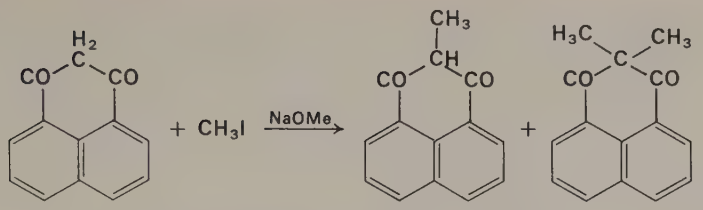


Other compounds containing displaceable halogen atoms can be used in place of simple halides:

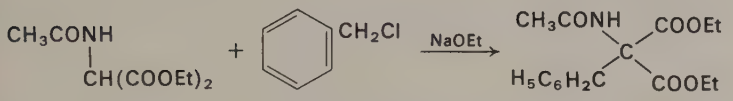


and most compounds containing the structural unit —COCHCOOR or —COCHCO— can be alkylated in a similar way:





(56)



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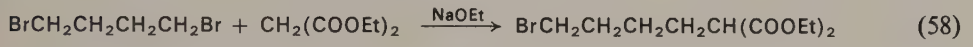
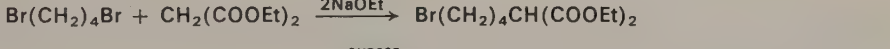


(58)

The monoalkylation of malonic ester with 1,4-dibromobutane, shown in (58), would be successful as it is written only if it were carried out with carefully regulated amounts of the reagents. By varying the proportions of reagents and the reaction conditions, two further reactions can occur: (*a*) alkylation of a second molecule of malonic ester; or (*b*) internal alkylation with cyclization. Each of these can be realized under appropriate experimental conditions:



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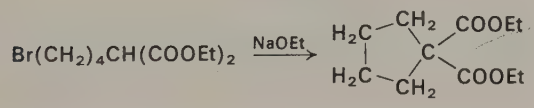


(60)

The formation of the cyclopentane dicarboxylic acid diester is a *dialkylation*. Since malonic and acetoacetic esters have two replaceable hydrogens on the active methylene group, both can be substituted in the kinds of reactions described above to form products of the general formulas $\mathrm{\overset{R}{\underset{R'}{C(COOEt)_2}}}$ and $\mathrm{CH_3COC(R)(R')COOEt}$.

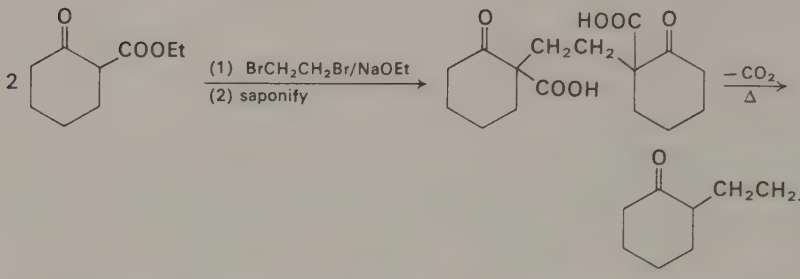
24-11 Decarboxylation of β-keto acids and 1,1-dicarboxylic acids

Compounds containing the structural element $\mathrm{-CO-\overset{|}{\underset{|}{C}}-COOH}$ are readily decarboxylated on heating at moderate temperatures, often at or below the melting point. β-keto acids and 1,1-dicarboxylic acids of this kind are prepared by saponification of

the corresponding esters. Thus, the decarboxylation reaction, when coupled with alkylation of the β-keto esters or malonic esters, provides a valuable synthetic procedure:

$$CH_2(COOEt)_2 \xrightarrow[(2)\ \text{saponify}]{(1)\ RCH_2Br/NaOEt} RCH_2CH(COOH)_2 \xrightarrow[\Delta]{-CO_2} RCH_2CH_2COOH \qquad (61)$$

$$CH_3COCH_2COOEt \xrightarrow[(2)\ \text{saponify}]{(1)\ BrCH_2COOEt/NaOEt} CH_3COCHCOOH \xrightarrow[\Delta]{-CO_2} CH_3COCH_2CH_2COOH \qquad (62)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_2COOH$$



(63)

$$CH_2(COOEt)_2 \xrightarrow[(2)\ \text{saponify}]{(1)\ BrCH_2CH_2Br/NaOEt} \text{(COOH)}_2\text{C}_3\text{H}_4 \xrightarrow[\Delta]{-CO_2} \text{C}_3\text{H}_5\text{COOH} \qquad (64)$$

Exercise 5

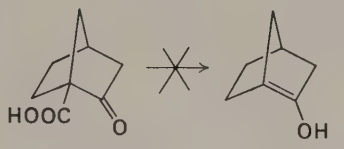
Starting with diethyl malonate or ethyl acetoacetate, show how you could use the procedures described above to prepare (*a*) β-phenylpropionic acid, (*b*) succinic acid, (*c*) 4-pentenoic acid, (*d*) octanedioic acid, and (*e*) 2-methyl-4-ketopentanoic acid.

The decarboxylation reaction is subject to certain structural requirements that reveal the mechanism of the transformation. β-Keto (or malonic) acids undergo the reaction, but acids in which the second carbonyl group is α, γ, or in any position other than β are not decarboxylated under comparably mild conditions.* It appears that the role of the β carboxyl group is as shown in the following equation. An intermediate enol is formed; as was pointed out earlier, this tautomerizes to the more stable keto form:

$$H_3C{-}C(=CH_2){-}CO{-}O{-}H \longrightarrow CO_2 + \{H_3C{-}C(=CH_2){-}OH\} \longrightarrow CH_3COCH_3 \qquad (65)$$

* Decarboxylation in these cases can often be accomplished by other means, sometimes under severe conditions, but in any case by mechanisms quite different from those that operate in the case of β-keto and 1,1-dicarboxylic acids.

When for structural reasons an enol cannot form, the compound is not decarboxylated on simple heating. For example, in the following bicyclic keto acid the expected enol would necessarily possess a bridgehead double bond, which is structurally prohibited in any but large rings:



(66)

Thus, decarboxylation would not occur under the relatively mild conditions sufficient to decarboxylate typical β-keto esters.

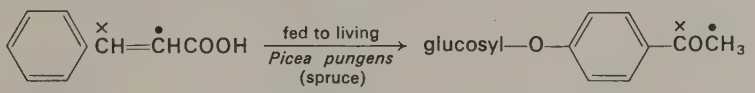
Mono-esters of malonic acid can be smoothly decarboxylated by heating, to yield the corresponding carboxylic acid ester.

24-12 Decarboxylation as a metabolic process

The appearance in natural sources of compounds containing terminal $—COCH_3$ groups suggests their origin by decarboxylation of β-keto acids:

$$RCOCH_2COSCoA \xrightarrow{H_2O} RCOCH_2COOH \longrightarrow CO_2 + RCOCH_3$$

Reaction schemes of this kind are supported by the structural correspondence between the methyl ketone and the carboxylic acid from which it is derived, and by isotopic labeling experiments. For example, the following transformation has been established by the use of ^{14}C-labeled precursors (the introduction of the glucosylated hydroxyl group is not pertinent to the reaction under discussion here):

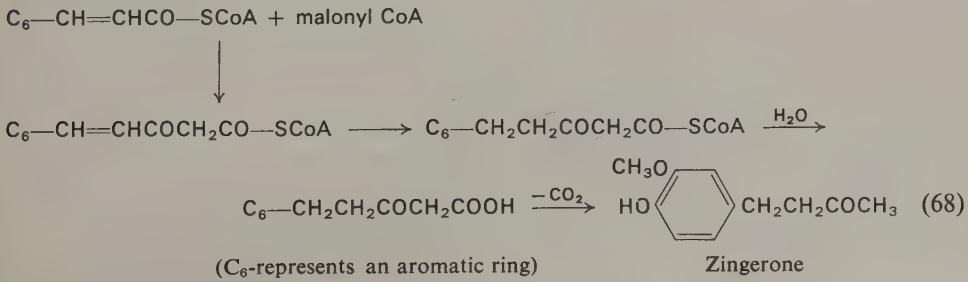


(67)

×, • = ^{14}C-labeled carbon atoms

This transformation probably occurs by way of (*a*) β-hydroxylation of the cinnamic acid; (*b*) oxidation of the —CHOH— group to —CO—; (*c*) decarboxylation.

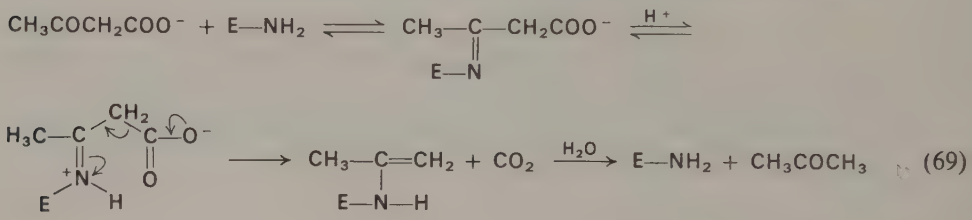
Another naturally occurring methyl ketone, zingerone, probably arises by the following route:



(68)

(C_6-represents an aromatic ring) Zingerone

The most common natural product of this kind of decarboxylation reaction is acetone, which is metabolically produced from acetoacetic acid; it accumulates in the blood of persons suffering from certain metabolic abnormalities, for example, diabetes. This reaction, catalyzed by an enzyme, has been studied in detail, and has been found to proceed by a mechanism that involves the formation of a Schiff base between the keto group of the acid and an amino group of the polypeptide portion of the enzyme. The mechanism of the reaction is a variant of that shown above:



(69)

Exercise 6

Show the sequence of steps in the acid-catalyzed hydrolysis of an enamine $R{-}C(NR_2){=}CH_2$ to the ketone $RCOCH_3$ and HNR_2.

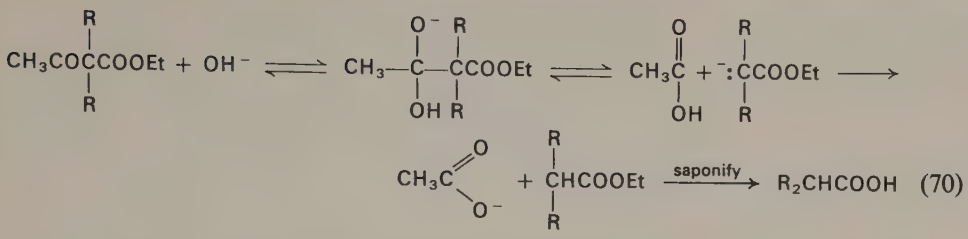
24-13 Base-catalyzed cleavage of β-keto esters

β-Keto esters can react with basic reagents (for example, OH^-) in a number of ways. They may

(*a*) simply ionize by loss of a proton from the active methylene group;
(*b*) undergo saponification by attack of OH^- at the ester carbonyl group; or
(*c*) undergo nucleophilic attack by OH^- at the keto carbonyl group.

Since reaction (*a*) is a *reversible* ionization reaction, processes (*b*) and (*c*) can also occur in compounds containing the $-COCH_2COOR$ grouping. Thus, acetoacetic and malonic esters can be saponified to the corresponding acids.

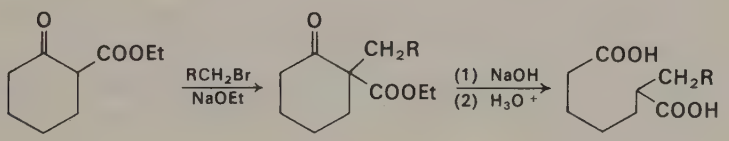
When the central carbon atom of a β-dicarbonyl compound is disubstituted, ionization cannot occur, and attack by hydroxide ion occurs at one or the other of the carbonyl groups. Attack at the β keto group takes the following course:



(70)

This cleavage reaction has been used for the preparation of carboxylic acids (R_2CHCOO— in the preceding example) but it is not generally satisfactory, because of the concomitant saponification of the keto ester. Dicarboxylic acids of the type $R_2CHCOOH$ are usually better prepared by the dialkylation of diethyl malonate followed by saponification and decarboxylation.

The cleavage reaction can be usefully applied to cyclohexanone derivatives because of the enhanced reactivity of the carbonyl group in the ring to nucleophilic attack:



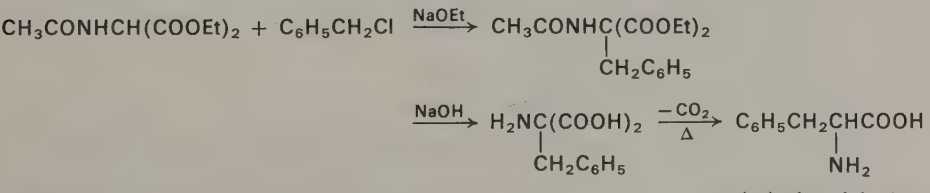
(71)

Exercise 7

Formulate the details of the cleavage of the cyclohexanone derivative shown in the preceding example, leading finally to the dicarboxylic acid.

24-14 Synthesis of amino acids by *C*-alkylation reactions

The *N*-substituted malonic ester $CH_3CONHCH(COOEt)_2$ (diethyl acetamidomalonate) is a versatile synthetic source of α-amino acids by alkylation of the ester in the usual way, followed by saponification (which includes hydrolysis of the amide grouping) and decarboxylation. Two examples of this method, showing the synthesis of phenylalanine and aspartic acid, are the following:



(72)

$$CH_3CONHCH(COOEt)_2 + ClCH_2COOEt \xrightarrow{NaOEt} CH_3CONHC(CH_2COOEt)(COOEt)_2$$

$$\xrightarrow[(2)\ \text{decarboxylation}]{(1)\ \text{saponification}} H_2NCH(CH_2COOH)COOH \quad (73)$$

(±)-aspartic acid

Problems

1. Write out the following alkylation reactions:
   (*a*) alkylation of ethyl acetoacetate with methyl bromide
   (*b*) alkylation of ethyl malonate with *sec*-butyl bromide
   (*c*) alkylation of ethyl malonate with bromoacetone
   (*d*) alkylation of ethyl cyclohexanone-2-carboxylate with ethyl iodide
   (*e*) alkylation of methyl acetoacetate with ethyl bromoacetate

2. Devise practical syntheses for the following compounds, starting with any monoester, 1,1-diester, or β-keto ester, and any necessary organic halogen compounds:
   (*a*) *n*-amyl methyl ketone (2-heptanone)
   (*b*) levulinic acid (4-oxopentanoic acid)
   (*c*) ethylsuccinic acid
   (*d*) 2-ethyl-5-methylcyclohexanone
   (*e*) cyclopropylcarbinol
   (*f*) 2-isobutyl-1,4-butanediol [since the desired product is obtainable by the $LiAlH_4$ reduction of isobutylsuccinic acid, the synthetic problem is reduced to the preparation of the latter; see (*c*)]
   (*g*) 2,2-dimethyl-1,3-butanediol

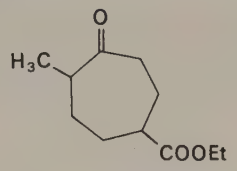
3. Write the structure of the anion formed by the action of a base on each of the following compounds. In each case remove only the most acidic proton: (*a*) CH_3CHO, (*b*) CH_3COCH_3, (*c*) $(CH_3)_3CCOCH_3$, (*d*) $CH_3COCH_2COCH_3$, (*e*) $(CH_3CO)_3CH$, (*f*) $CH_2(COOCH_3)_2$, (*g*) $CH_3CH(COOCH_3)_2$, (*h*) $CH(COOEt)_3$, (*i*) dicyclopentyl ketone

4. Write the sequence of steps involved in the following ester condensations:
   (*a*) ethyl propionate with ethyl propionate (that is, self-condensation)
   (*b*) ethyl formate with acetone
   (*c*) ethyl oxalate with cyclohexanone
   (*d*) diethyl carbonate with diethyl ketone

5. What would be the product of the cyclization of ethyl α-methyladipate?

6. What would be the product of the reaction between the enamine derived from diethyl ketone and methyl acrylate (methyl propenoate)?

7. When ethyl 2-methylcycloheptanone-5-carboxylate



(IR bands at 1710, 1735 cm^{-1}) is treated with sodium ethoxide in ethanol it is transformed into an isomeric ester with IR bands at 1735 and 1740 cm^{-1}. Write a mechanism for the reaction that accounts for this change.

25

The Michael and Mannich reactions

Were the study of organic chemistry merely the accumulation of facts and the memorization of methods of synthesis, the Mannich and Michael reactions would simply take their place among many hundreds of useful synthetic procedures. They are singled out for special attention because they provide excellent examples of how the general principles of reactions of the aldol family apply to processes that appear at first sight to be quite different in character.

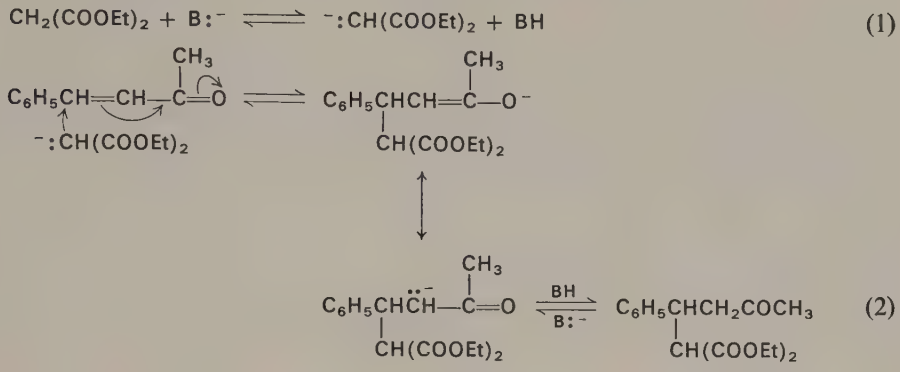
Both the Michael and the Mannich reactions are themselves of great synthetic value; the examples given in this chapter illustrate their versatility in the preparation of many different compound types. But their instructive value in the study of the principles of organic reactivity outweighs their importance as practical procedures, and it is to these mechanistic principles that the discussion in this chapter is chiefly directed.

25-1 The Michael reaction

In Section 21-1 was described the addition of nucleophilic reagents (ROH, RNH_2, RSH, and so on) to α,β-unsaturated carbonyl compounds. The reaction proceeds in

the same manner when the nucleophile is an enolate anion (carbon anion), in which case the special name *Michael reaction* is used.

A representative example of the reaction is the following, showing the ionic character of the stages through which the addition proceeds:*

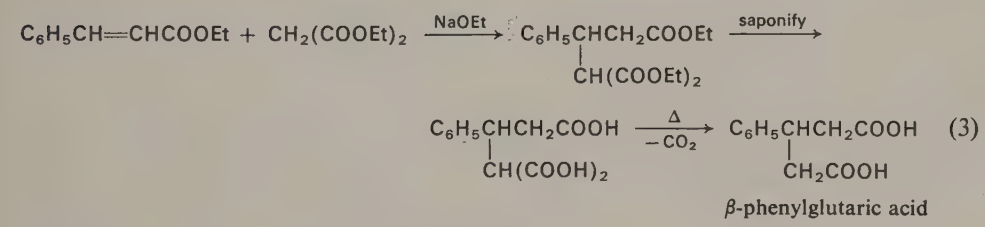


(1)

(2)

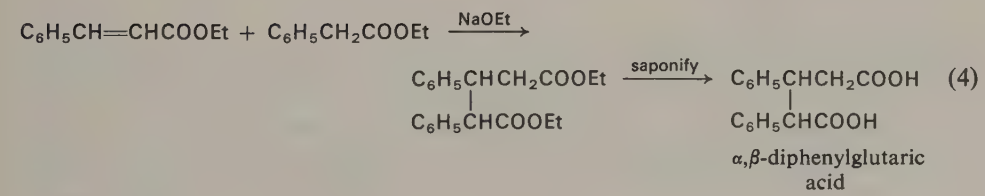
It can be seen from this expression that (*a*) the basic reagent is not consumed in the reaction, so that only a catalytic amount is required (about 0.1 equivalent is ordinarily used); and (*b*) the reaction is reversible, although in most cases like the above, the yield can be improved by using an excess of one of the reactants, usually the active methylene component.

The Michael reaction is a versatile synthetic device. A new carbon-carbon bond is formed, and the product is often capable of further transformation:



(3)

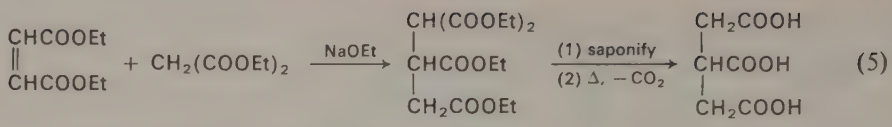
β-phenylglutaric acid



(4)

α,β-diphenylglutaric acid

* The basic catalyst, shown as $B:^-$ in these reactions, may in practice be any of several reagents: sodium alkoxides in alcoholic solution or basic amines such as triethylamine or piperidine.



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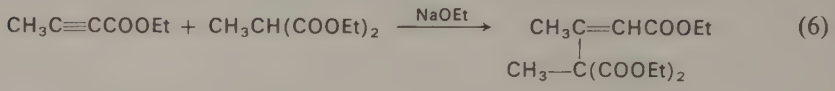
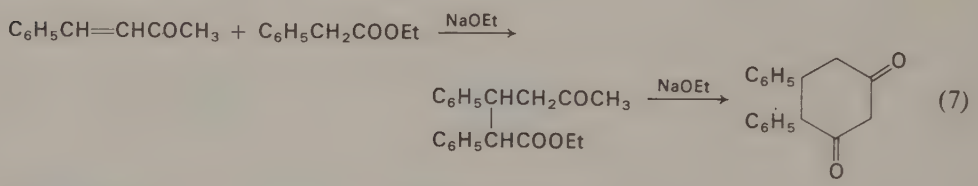


(6)

Since the products are diketones, keto esters, or diesters, ring closures may ensue in the presence of the basic catalyst; or the products may be isolated and then subjected to ring closure. The use of the Michael reaction to form cyclic compounds is discussed in greater detail in Chapter 27.



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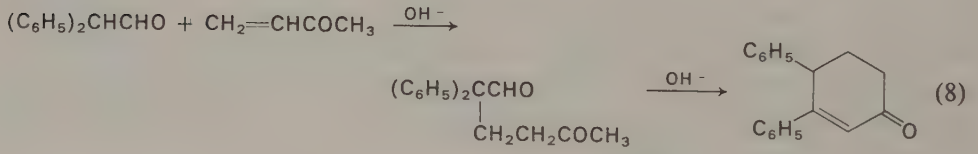
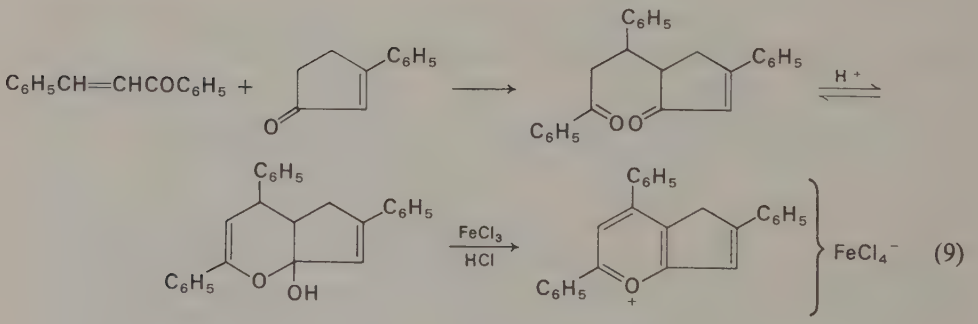


(8)



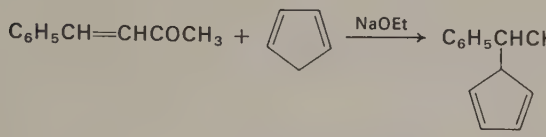
(9)

Exercise 1

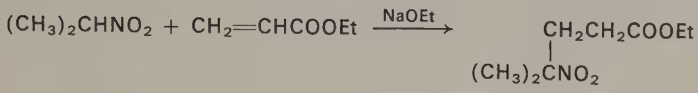
Formulate all of the preceding reactions, showing the details of the various steps as in (1) and (2).

Carbanions derived from active methylene compounds of many kinds can add in this manner to conjugated carbonyl compounds. Michael additions not only of

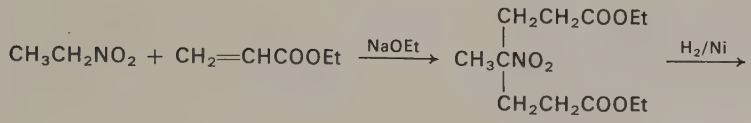
malonic esters, acetoacetic esters, and so on, but also of aliphatic nitro compounds, cyclopentadiene, and simple ketones can be brought about:

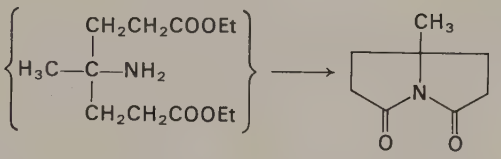


(10)



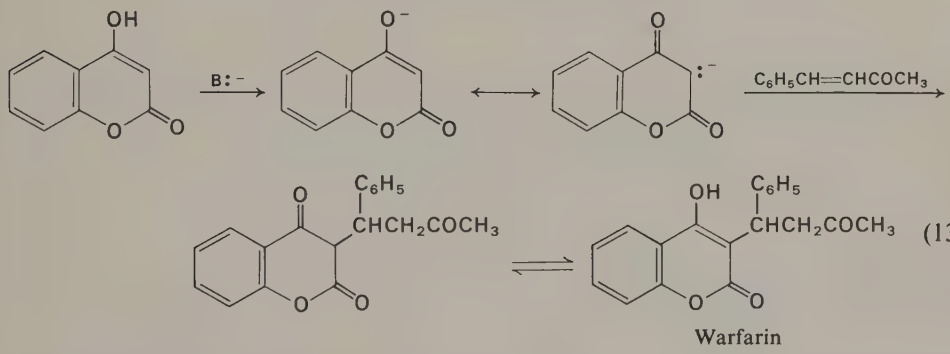
(11)





(12)

A valuable compound is formed by the Michael addition of benzalacetone to 4-hydroxycoumarin. Abstraction of the proton from 4-hydroxycoumarin yields an anion that is a resonance hybrid of an enolated anion and a carbanion:

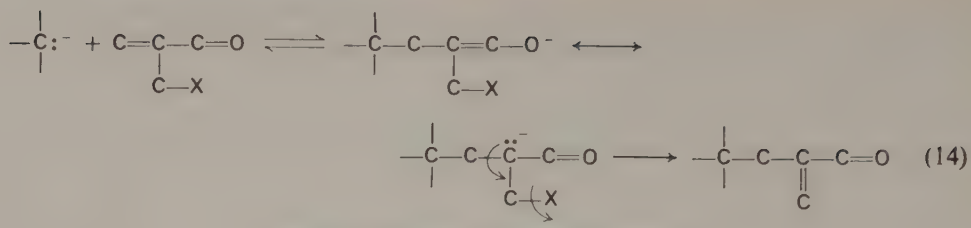


Warfarin

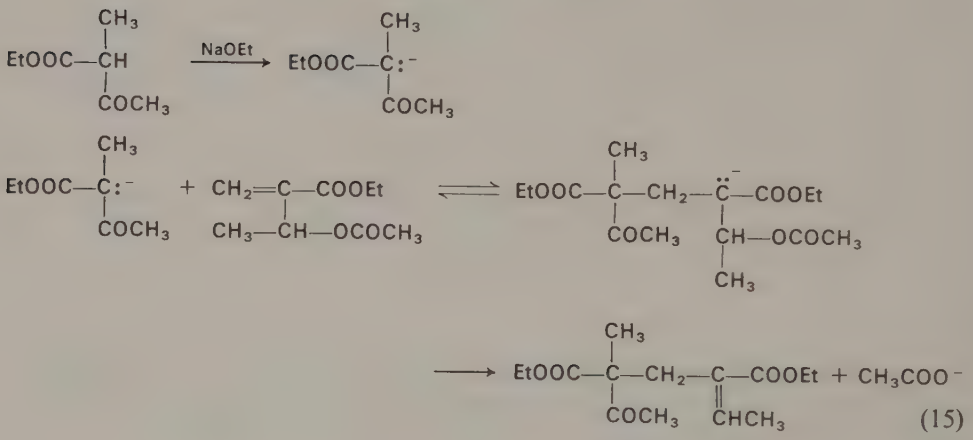
(13)

The product of this reaction, called *Warfarin*, is a blood anti-coagulant. It lowers the clotting power of the blood, and thus it finds clinical use in the treatment of cardiovascular disease associated with intravascular blood clotting (for example, cardiac infarction). It is widely used as a rat poison. When ingested by a rat it causes internal hemorrhage and death.

The adduct produced in the first stage of the Michael reaction is an enolate-carbanion, the anionic center of which may act in an internal displacement (that is, an elimination) reaction:



(e.g., X = halogen, —OCOR, —OTos) (14)



(15)

Exercise 2

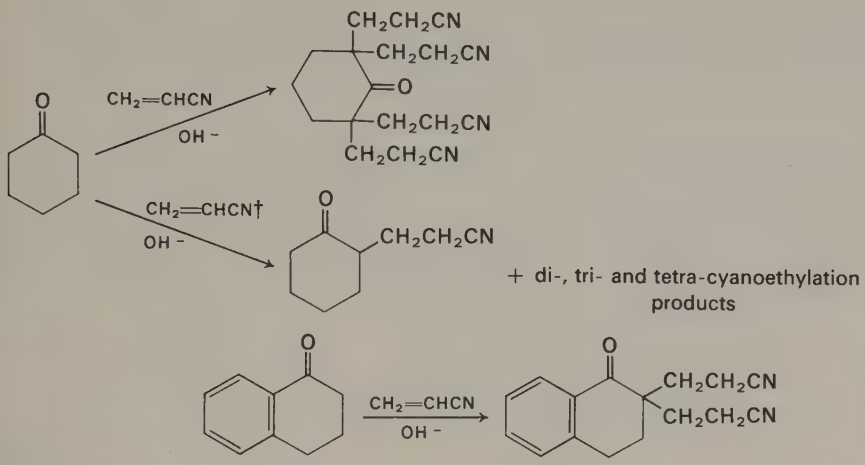
Show how the Michael reaction could be used as one of the steps in the synthesis of (*a*) 5,8-dinitrododecane-2,11-dione, (*b*) 5-ketohexanoic acid, (*c*) 1,3,5-triphenylpentane-1,5-dione, and (*d*) 5,5-dimethylcyclohexane-1,3-dione.

25-2 Cyanoethylation

Acrylonitrile, $CH_2{=}CHCN$, participates very readily in the Michael reaction, and undergoes addition of active methylene compounds of many kinds. The reactivity of acrylonitrile in this way is so great that it is difficult and often impracticable to interrupt the reaction until all of the active hydrogen atoms have been replaced. The reaction is called *cyanoethylation*, because the products contain the grouping $-CH_2CH_2CN$.* The use of a limited amount of acrylonitrile (that is, a large ratio of

* A basic catalyst often used for cyanoethylation, as well as for other Michael reactions, is the quaternary ammonium hydroxide $C_6H_5CH_2\overset{+}{N}(CH_3)_3OH^-$ (Triton B).

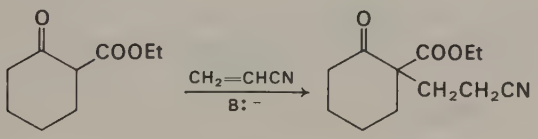
active methylene compound to acrylonitrile) may result in fair yields of the mono-adduct:



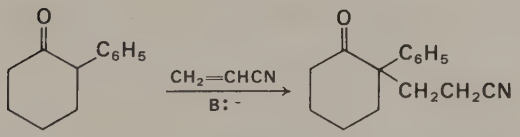
(16)

(17)

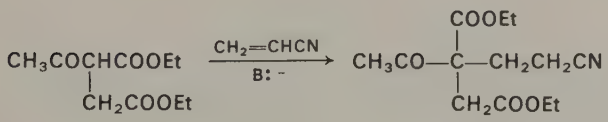
When one of the α hydrogen atoms is more acidic than others, preferential cyanoethylation can be accomplished:



(18)

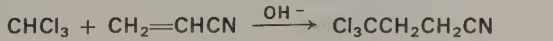


(19)



(20)

It is interesting to note that the ability of chloroform under the influence of a strong base to provide the carbanion $Cl_3C:^-$ can be demonstrated by the cyanoethylation reaction:

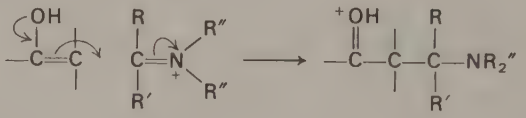


(21)

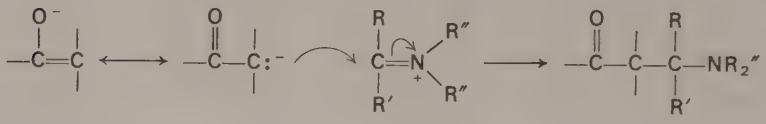
† 5:1 excess of the ketone.

25-3 The Mannich reaction

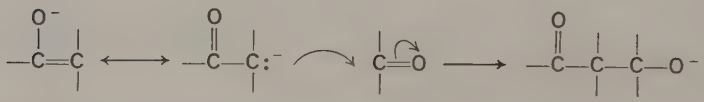
The *Mannich reaction* consists of the addition of an anionic carbon atom or an enol to an iminium salt or a protonated Schiff base. The mechanism of the reaction is completely analogous to the addition of a carbanion or enol to a protonated carbonyl group:



or (22)

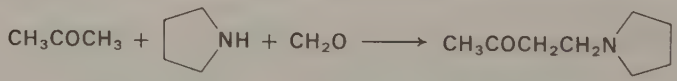


or (23)

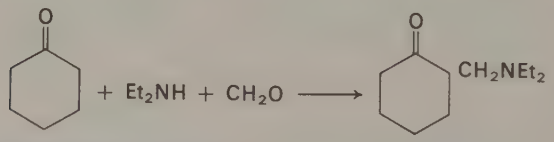


In its most common form, the Mannich reaction involves a ketone, formaldehyde, and a secondary amine (for example, dimethylamine), as in the following:

$$C_6H_5COCH_3 + (CH_3)_2NH + CH_2O \longrightarrow C_6H_5COCH_2CH_2N(CH_3)_2 \quad (24)$$

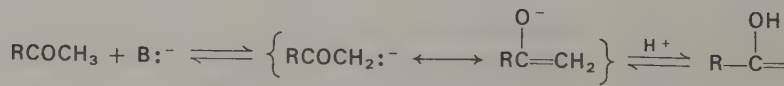


(25)

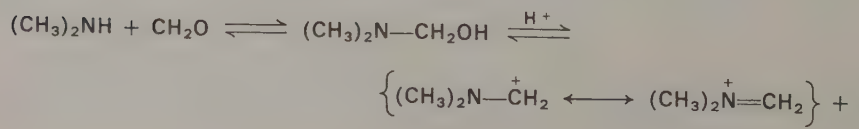


(26)

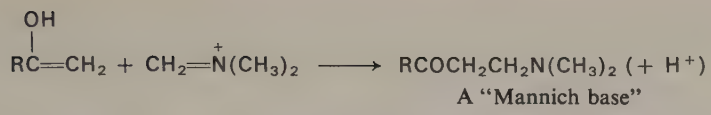
Several (nearly equivalent) mechanisms have been proposed for the reaction, but the following most satisfactorily accommodates the requirements imposed by experimental results from a variety of types of reactions:



(27)

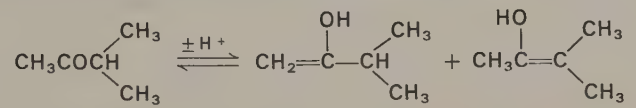


(28)

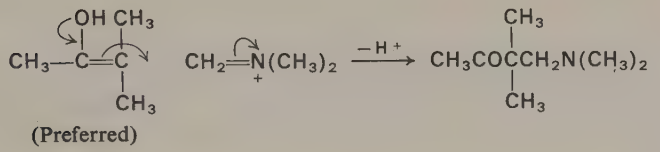


(29)

Under the slightly acidic conditions of the Mannich reaction, the nucleophilic form of the ketone that adds to the electrophilic imonium ion appears to be the enol produced by proton transfer as shown in the following equations. This conclusion is supported by the observation that the condensation takes place preferentially at the more highly substituted α carbon atom. Of the two possible enolic forms of methyl isopropyl ketone, the one with the more highly substituted double bond is the one that would be expected to be the more stable. The reaction in fact yields chiefly the Mannich base derived by condensation at the isopropyl group:

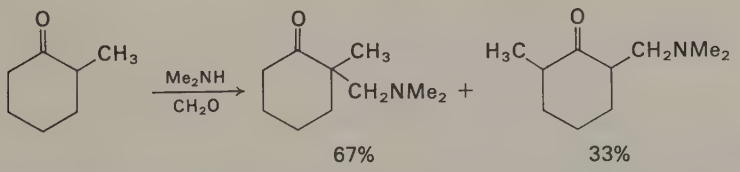


(30)



(31)

It is found, however, that this selectivity is not absolute, for 2-methyl-cyclohexanone yields both isomeric Mannich bases:



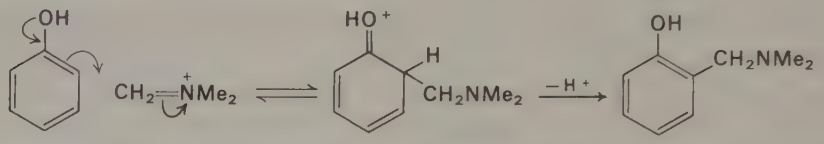
(32)

Since the equilibria ketone $\rightleftharpoons$ [carbanion $\leftrightarrow$ enolate ion] $\rightleftharpoons$ enol exist under the conditions of the reaction, one cannot dismiss from consideration a course in which the attacking nucleophile is the [enolate ion $\leftrightarrow$ carbanion] itself rather than the unionized enol, or in which *both* enol and enolate ion attack the electrophilic imonium salt.

25-4 Non-ketonic carbanions in Mannich reactions

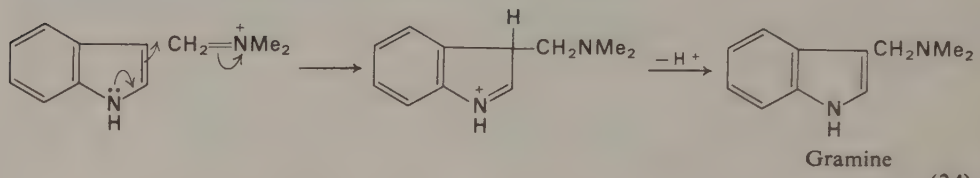
The anionic (nucleophilic) carbon atom required in the Mannich condensation can be provided in other ways than by the keto $\rightleftharpoons$ enol system described in the foregoing discussion. Moreover, it should be recognized that the imonium ion $(CH_2{=}NR_2)^+$

is an electrophilic species and can attack positions at which a transition state makes electrons available. Mannich reactions with phenols can be regarded as electrophilic substitution onto the aromatic ring:



(33)

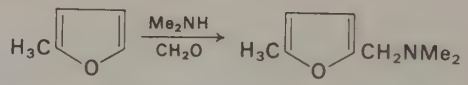
The nucleophilic 3 position in the indole ring system can be attacked in a comparable way to give 3-dialkylaminomethyl derivatives of indole:



(34)

The 3-dimethylaminomethylindole in this example is the naturally occurring alkaloid *gramine*, found principally in grasses (family Gramineae). The use of gramine in the synthesis of the important plant hormone 3-indoleacetic acid (*auxin*) is described in Section 25-6.

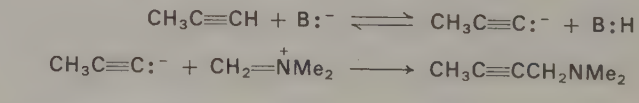
Furans take part in a reaction closely related to that between indole, formaldehyde, and dimethylamine:



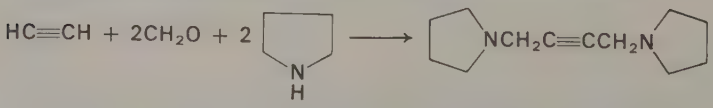
(35)

It will be recalled (Chapter 6) that the methiodide of the Mannich base formed in (35) is a strongly muscarine-like compound.

The anions derived from terminal acetylenes (1-alkynes) are also capable of acting as the nucleophilic agents in Mannich condensations:



(36)



(37)

25-5 Experimental conditions for Mannich reactions

Since the reactions [formaldehyde + dialkylamine ⇌ imonium salt] and [ketone ⇌ anion ⇌ enol] are subject to acid-base catalysis—that is, require both proton donors

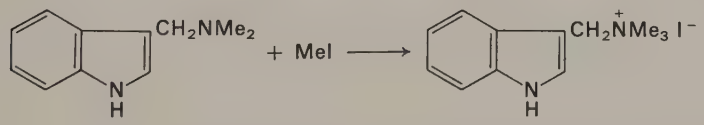
and proton acceptors—they are most effectively realized in a medium that is neither strongly basic nor strongly acidic. The reaction is usually carried out in alcoholic solution with the secondary amine hydrochloride. Since the amine (for example, dimethylamine) is a base of only moderate strength, its salt is dissociated in solution to provide both the protonated ($Me_2NH_2^+$) and non-protonated (Me_2NH) species. These provide a medium in which the proton-transfer equilibria required for the reaction can occur. If the free amine is used as the reagent, a small amount of acid is added to the solution.

It should be apparent from what has been said that it is not always possible to define categorically the state of ionization of the reacting nucleophile, for it may vary between the extremes of the neutral (for example, indole) and the anionic (for example, the acetylenic anion) species, or it may be an equilibrium mixture of anion and enol (for example, ketones and phenol).

25-6 Quaternary salts of Mannich bases

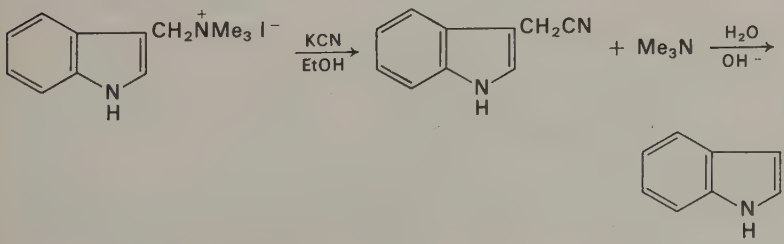
Mannich bases are tertiary amines and can be quaternized by reaction with appropriate alkyl halides. The most common examples of this are the trimethylammonium salts formed by the reaction of the *N*,*N*-dimethyl Mannich bases with methyl iodide:

$$CH_3COCH_2CH_2NMe_2 + MeI \longrightarrow CH_3COCH_2CH_2\overset{+}{N}Me_3\ I^- \qquad (38)$$



(39)

Conversion of the secondary amino group into the quaternary ammonium group makes it susceptible to displacement by nucleophilic attack or elimination. Treatment of gramine methiodide with potassium cyanide yields 3-indoleacetonitrile, hydrolysis of which gives the corresponding acid, a growth-regulating hormone of plants:

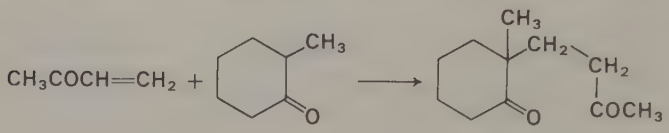


(40)

3-indoleacetic acid (IAA)

A valuable synthetic procedure in which the Mannich and Michael reactions are combined consists in (*a*) treating a quaternized Mannich base with a basic reagent (for example, sodium ethoxide) to eliminate trimethylamine and form the vinyl ketone; and (*b*) adding the vinyl ketone to a ketone by a Michael addition reaction:

$$CH_3COCH_2CH_2\overset{+}{N}Me_3 \underset{}{\overset{EtO^-}{\rightleftharpoons}} CH_3C\ddot{O}\overset{-}{C}HCH_2\overset{+}{N}Me_3 \longrightarrow CH_3COCH{=}CH_2 + Me_3N \qquad (41)$$



(42)

The further extension of this sequence to a final ring closure is described in Section 22-15, along with the formation of cyclic compounds by aldol condensations.

Exercise 3

An early use of the Mannich reaction was in the synthesis of the alkaloid *arecoline*, an active principle of betel nuts. Look up the structure of arecoline and devise a route for its synthesis, starting with methylamine, acetaldehyde, and formaldehyde. The final steps are an oxidation of an aldehyde to an acid, and esterification of the acid.

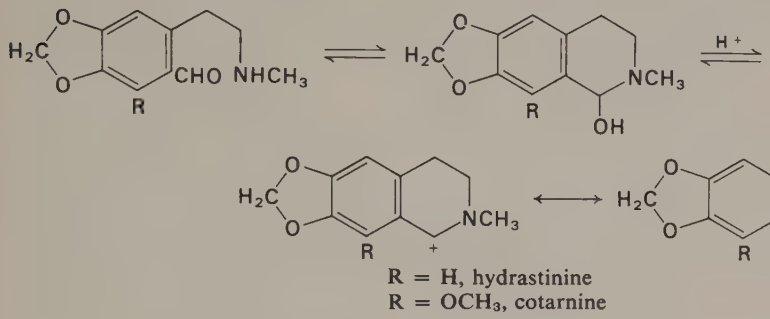
25-7 Pseudo-bases as electrophilic reagents

The product formed in the first stage of the addition of a secondary amine to an aldehyde is an α-hydroxy amine. Compounds of this class are called *pseudo-bases* because of the ease with which they are converted by acids into -onium ions. Protonation of the hydroxyl group facilitates its displacement by the non-bonding electron pair of the adjacent nitrogen atom to form the *imonium* ion:

$$RCHO + R'_2NH \rightleftharpoons RCHNR'_2 \overset{H^+}{\rightleftharpoons} RCHNR'_2 \rightleftharpoons RCH{=}\overset{+}{N}R'_2 + H_2O \qquad (43)$$

Two pseudo-bases of this kind, known as degradation products of alkaloids, are hydrastinine (obtained from the alkaloid hydrastine by oxidation), and cotarnine

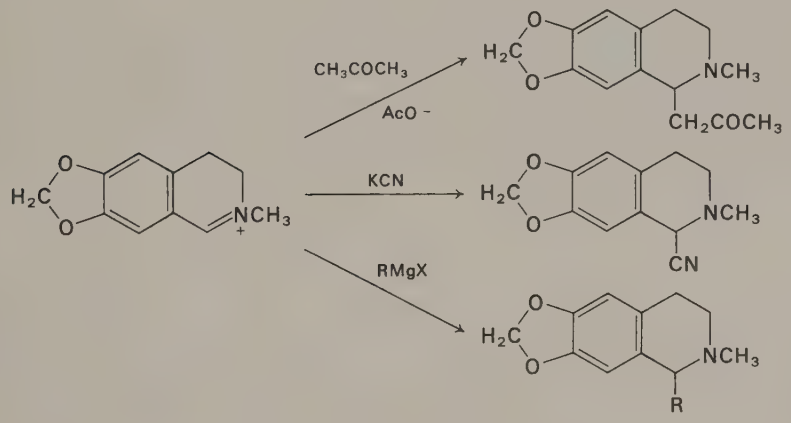
(from the alkaloid narcotine). They have the following structures, which are in hydroxyamine/imonium-salt equilibrium at intermediate pH values:



(44)

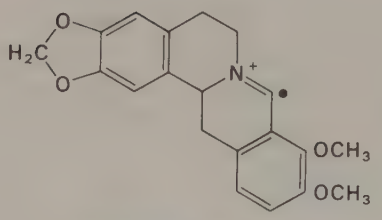
R = H, hydrastinine
R = OCH_3, cotarnine

At high acid concentrations (low pH) they exist principally as the imonium salts; at high pH they exist in the unionized pseudo-base form. Both hydrastinine and cotarnine condense with nucleophilic reagents; the total process resembles the Mannich reaction except that hydrastinine and cotarnine are not formed by intermolecular reaction between separate molecules of aldehyde and amine; they may be recognized as nitrogen analogues of cyclic hemiacetals:

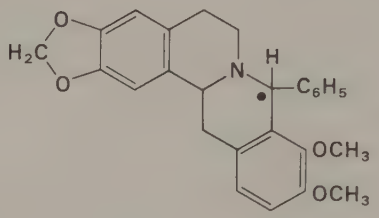


(45)

The reaction of the imonium salt with a Grignard reagent, one of the preceding examples, has been used in a procedure devised to establish the location of a labeled (radioactive) carbon atom in a complex molecule. The final stage of this reaction sequence is a vigorous permanganate oxidation. Since benzoic acid survives this oxidation, while the remainder of the molecule is destroyed, the labeled carbon atom is found in the carboxyl group of the benzoic acid recovered as the final product, thus fixing its position in the original compound:



Berberine (• = ^{14}C)



(46)

25-8 Imonium ions in transition complexes

Electrophilic attack upon a compound of the general type RCH(X)Y, where Y can stabilize the intermediate carbonium ion $R\overset{+}{C}H—Y \leftrightarrow RCH{=}Y^+$, provides a reaction pathway that can take many forms, including the Mannich reaction.

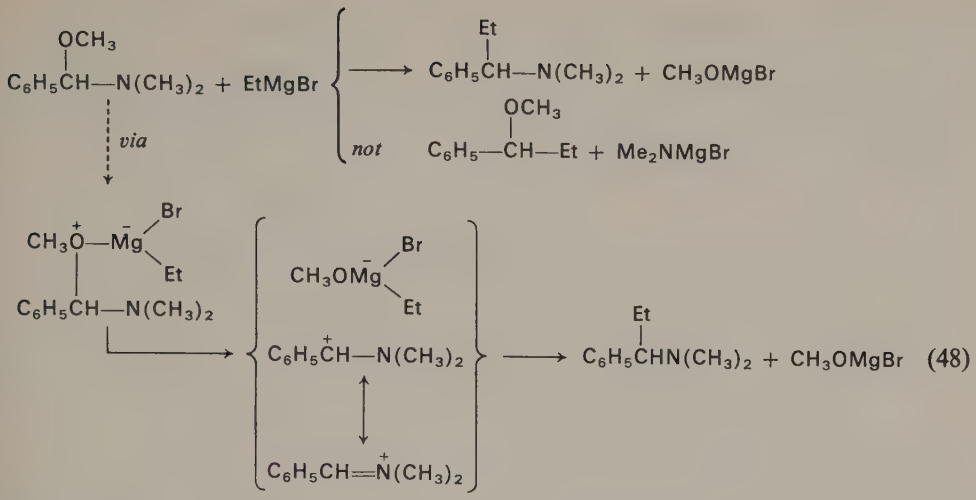
Reactions belonging to this general class have been encountered earlier, in the synthesis and reactions of acetals and hemiacetals (Sections 12-9 and 12-10). It will be recalled that the intermediate carbonium ↔ oxonium ion in these reactions is a participant in the equilibria

$$R—CHO + CH_3OH \rightleftharpoons RCH(OH)—OCH_3 \overset{H^+}{\rightleftharpoons} RCH(OH_2^+)—OCH_3 \rightleftharpoons \overset{+}{R}CH—OCH_3 + H_2O$$

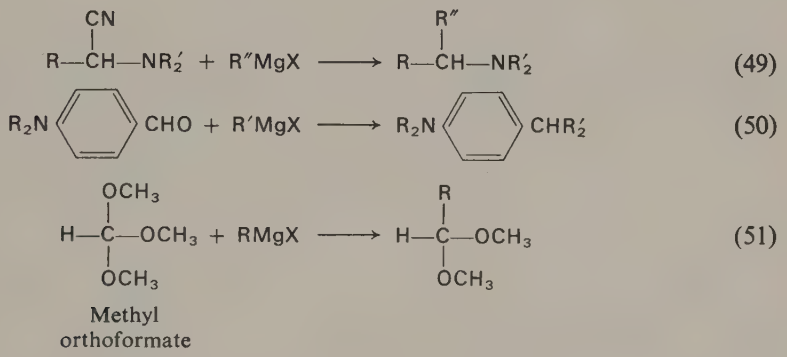
$$\left(\overset{+}{R}CH—OCH_3 \longleftrightarrow RCH{=}\overset{+}{O}CH_3\right) \overset{CH_3OH}{\rightleftharpoons} RCH(\overset{+}{O}(H)CH_3)(OCH_3) \overset{-H^+}{\underset{H^+}{\rightleftharpoons}} RCH(OCH_3)_2 \qquad (47)$$

where Y in the general expression above is —OCH_3.

The capacity of Y in stabilizing $R\overset{+}{C}H—Y$ depends upon its electron-donating properties, and the dialkylamino group surpasses the alkoxy group in this regard. This is clearly demonstrated by the reaction of an α-alkoxy amine with a Grignard reagent. Here it is the alkoxyl group that is replaced, not the dialkylamino group:



Other reactions allied to those just described are shown in the following general equations:



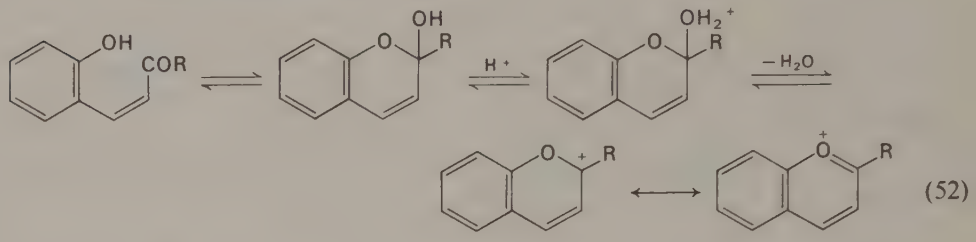
The reaction of a Grignard reagent with a trialkoxymethane (an orthoformic ester) is a valuable synthetic method for preparing aldehydes, for the product is an acetal and is easily hydroxylized with dilute acid to the aldehyde.

Exercise 4

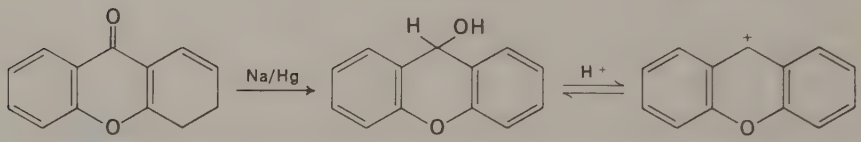
Write the reaction between *p*-dimethylaminobenzaldehyde and methylmagnesium bromide, showing the details of the separate states that lead to the final product, which has the composition $C_{11}H_{15}N$.

25-9 Related reactions of pseudo-bases and associated -onium ions

The term "pseudo-base" can be applied to any compound from which protonation and dissociation of a hydroxyl group yields a highly stabilized -onium ion. The following examples will illustrate this:

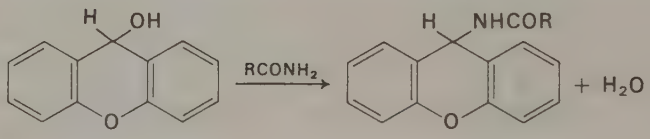


(52)



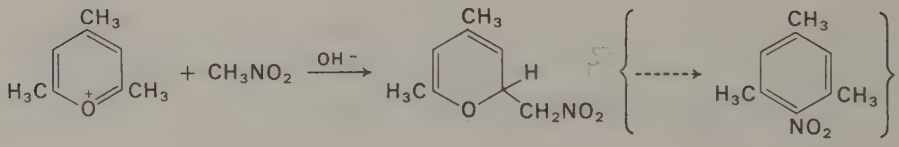
(53)

The cations derived from pseudo-bases such as these are capable of reacting with nucleophiles in a manner quite similar to the behavior of hydrastinine and cotarnine. For example, the reaction of 9-hydroxyxanthene with amides yields 9-acylaminoxanthenes, which are useful derivatives for the characterization of amides.



(54)

The cyclic oxonium salt 2,4,6-trimethylpyrylium (chloride) reacts with the carbanion derived from nitromethane:



(55)

Exercise 5

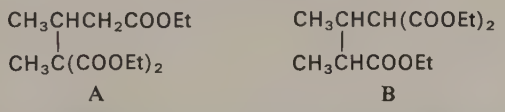
The reaction of nitromethane with a 2,4,6-trimethylpyrylium salt, of which the first step is shown in equation (55), proceeds through further base-catalyzed steps to give, finally, 2,4,6-trimethylnitrobenzene (nitromesitylene). Devise an acceptable route for this overall transformation.

Problems

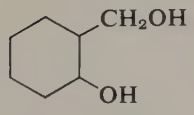
1. Write the complete equations for the following reactions:
   (*a*) ethyl acrylate + diethyl malonate →
   (*b*) benzalacetone + ethyl acetoacetate →
   (*c*) isobutyraldehyde (2-methylpropenal) + acrylonitrile →
   (*d*) bromoform + acrylonitrile →
   (*e*) diethyl fumarate + diethyl methylmalonate →

2. Show the final product obtained from the following initial reactants:
   (*a*) $(CH_3)_2CHCHO + CH_2{=}CHCOCH_3 + NaOEt \rightarrow$
   (*b*) 2,6-dimethylcyclohexanone + $CH_2{=}CHCOCH_3 + NaOEt \rightarrow$
   (*c*) $(CH_3)_2C{=}CHCOCH_3 + CH_2(COOEt)_2 + NaOEt \rightarrow$

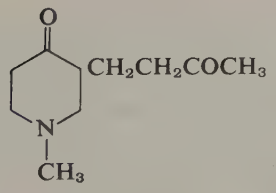
3. When diethyl methylmalonate, $CH_3CH(COOEt)_2$, is added to ethyl crotonate in the presence of an equimolal amount of sodium ethoxide, the product is **B**, not the expected **A**. How can you explain this result?



4. Write equations showing how the following compounds could be prepared, using the indicated starting material and other necessary reagents:
   (*a*) $CH_3C{\equiv}CCH_2NEt_2$ (from propyne)
   (*b*) $CH_3COCH_2CH_2NEt_2$ (from acetone)
   (*c*) $C_6H_5CHCOCH_3$ (from benzyl chloride, $C_6H_5CH_2Cl$)
   CH_3

   (*d*)  (from pimelic acid, $HOOC(CH_2)_5COOH$)

   (*e*) $CH_3COCHCH_2CH_2COOH$ (from ethyl acetoacetate)
   CH_2COOH

   (*f*)  (from $CH_2{=}CHCOOEt$ and $MeNH_2$)

   (*g*) α-aminoglutaric acid (from $CH_3CONHCH(COOEt)_2$)
   (*h*) $CH_2{=}CHCH_2CH_2NMe_2$ (from $CH_3OCH_2NMe_2$)
   (*i*) α,β-diphenylglutaric acid (from benzaldehyde)

26

Nuclear magnetic resonance and mass spectrometry

Of the formidable array of diagnostic techniques in the hands of the present-day organic chemist, nuclear magnetic resonance (NMR) and mass spectrometry (MS) are most often brought into play for the recognition of functional groups and the establishment of structure and stereochemistry. Along with ultraviolet and infrared spectroscopy, they permit a multi-faceted attack that can in many cases lead to complete solutions of structural problems without the need for additional experiments. Their usefulness in organic synthesis lies in the ease with which the progress of a synthetic sequence can be observed by examining the NMR spectra of the intermediates and of the final product.

Although these physical methods are almost universally used in organic chemistry, and have been used to illuminate in some way most facets of the subject, their treatment in an organic chemistry textbook must be limited in scope. Each of these physical methods is the subject of an extensive literature, and there are available many excellent monographs that describe the instrumental techniques and the interpretation of the data.

The description of the application of NMR and MS given in this chapter is intended to provide a basis upon which facility in their use can be developed. In nearly all physical methods of this kind there is no substitute for experience, and this can

only be gained by the continuing study of actual spectra. A number of spectra are shown in this chapter, and their detailed interpretation given. The student should not look at these spectra as a whole, but should follow the analysis provided for each of them, observing how clearly details of structure can be revealed by these powerful analytical tools.

26-1 Physical methods of studying organic compounds

In recent years the progress of organic chemistry has been greatly aided by the development of a number of techniques for the study of certain physical properties, the interpretation of which is central to the problem of determining the structure of organic compounds. The development of convenient and accessible instruments for the routine measurement of ultraviolet and infrared absorption spectra has had a profound influence upon the development of the science by making it possible to establish, by a single measurement requiring only small quantities of material, the presence of structural features that could otherwise be recognized only by means of elaborate chemical procedures.

New techniques are continually being added to those already available to the organic chemist, and with the development of reliable commercial instruments these new methods are coming into increasingly wide use in the laboratory. Among them may be mentioned the study of molecular asymmetry by means of *optical rotatory dispersion*, of free radicals by *electron paramagnetic resonance*, of total molecular structure by computer-aided methods of *X-ray crystallography*, and of structural elements of molecules by *nuclear magnetic resonance spectroscopy* and *mass spectrometry*. It is not possible to discuss all of these in useful detail here, so attention will be directed to those that have so far found the most general application to the problems of molecular structure: nuclear magnetic resonance and mass spectrometry.

26-2 Nuclear magnetic resonance

A bare nucleus such as a proton is a spinning charged body, which, because of its charge, generates a magnetic field. It may be likened to a tiny bar magnet, the axis of which corresponds to the axis of rotation. If an external magnetic field is applied, the proton tends to line up with the field in one of two ways: in a stable orientation, in which the north pole of the proton's field points away from the north pole of the static external field (parallel); or in an unstable orientation of higher energy, in which the proton is lined up against the field (antiparallel). The difference in the energy of these two orientations is small, and at ordinary temperatures there is only a small excess of protons in the more stable, parallel orientation.

A proton that is not lined up exactly parallel to the applied field performs a motion known as *precession*, in which the rotational axis describes a circle at right angles to the applied field. The wobbling of a spinning top or of a gyroscope whose axis of rotation is not perpendicular is a precessional motion. Quantum-mechanical calculations show that the frequency of the precessional rotation is equal to the frequency of electromagnetic radiation that is necessary to cause the nucleus to "flip" from parallel to antiparallel orientation. This transition can be brought about by applying a rotating magnetic field at right angles to the static field, and in phase with the precessing nucleus. When transition occurs, the frequency of precession and the frequency of the rotating magnetic field are equal, and they are in *resonance*. The resulting absorption of energy is detected by a radio frequency receiver, and is recorded.

The energy required for the transition of the nucleus from one energy level to the other is expressed by the equation

$$\text{Energy} = h\nu = 2\mu H$$

where h is Planck's constant, ν is the frequency of the electromagnetic radiation at which transition occurs under a constant static field strength H, and μ is the nuclear magnetic moment characteristic of the nucleus under consideration (H^1, C^{13}, F^{19}, and so on). With a static applied field of about 14,000 gauss, the electromagnetic radiation is in the region of radio frequency of about 60 megacycles.

Figure 26-1 is a schematic drawing of the system used for the measurement of nuclear magnetic resonance. It is possible to bring about resonance between the nuclei and the rotating magnetic field in either of two ways: by keeping the applied radio frequency constant, and varying the static field; or by keeping the static field constant, and "sweeping" with a varying electromagnetic field. The former method is the one used in the most common commercial instruments.

If the resonance frequency of a nucleus were simply a function of the applied field and of the magnetic properties of the nucleus, all of the protons* in an organic molecule would absorb at the same frequency, and the phenomenon would be of little practical importance. Fortunately, however, not all of the hydrogen atoms in an organic compound are in the same molecular environment, and the electrons in the bonds between the hydrogen atoms and other atoms in the molecule (usually the carbon-hydrogen, oxygen-hydrogen, and nitrogen-hydrogen bonus) screen each nucleus in such a way as to alter the effective magnetic field at the nucleus so that it is not exactly the same as the applied field. Consequently, hydrogen atoms in different environments are *shielded* to different degrees, and the various hydrogen atoms in a typical organic molecule resonate at different frequencies. The measurement of the

* For reasons outside the scope of this discussion, nuclei of carbon-12, carbon-14, oxygen-16, sulfur-32, and nitrogen-14 either have no magnetic moment or it cannot be detected with the instruments in general use. Nuclear magnetic resonance spectroscopy is largely confined to the hydrogen atoms of organic molecules, although fluorine-19 and carbon-13 are also studied.

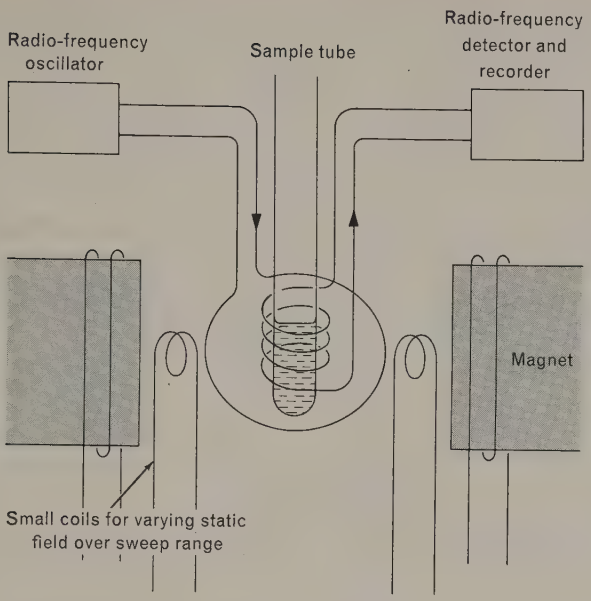


Figure 26-1
Essential components of a nuclear magnetic resonance spectrometer. The component that applies a rotating magnetic field is not shown.

nuclear magnetic resonance characteristics of a molecule is known as a *nuclear magnetic resonance spectrum.*

The spread of frequency over which protons of different kinds absorb is for most organic molecules about 700 cycles per second when the static field strength is 14,000 gauss. Since the measurement of the absolute values of frequencies that differ by only a few cycles per second from the applied radio frequency of about 60×10^6 cycles per second is difficult to carry out with the accuracy that would be required, frequencies are measured *relative* to an arbitrarily chosen value. The frequency that is chosen for reference is that of the protons of some reference compound, all of which are identical in their environment and absorb at one frequency. Any of a number of organic compounds can be used as the standard, but the most satisfactory reference compound for general use is tetramethylsilane, $(CH_3)_4Si$ (TMS), which gives a single sharp absorption for the twelve equivalent hydrogen atoms at a field strength that is higher than that for most other protons of organic molecules.

The most convenient way of using the reference compound is to add it directly to the solution of the substance under study. TMS is quite inert and seldom reacts with other compounds.

The procedure for carrying out the measurement of a nuclear magnetic resonance (NMR) spectrum is the following: the compound to be studied, dissolved in a solvent

that, ideally, contains no protons, is placed between the poles of the magnet. The TMS is added directly to the solution in an amount sufficient to give a prominent signal. The commonly used NMR instruments are designed to use a chart paper calibrated over a range of about 700 cycles per second (Hz); and the TMS signal is ordinarily adjusted to fall at the position on the chart marked 0 Hz. The field strength of the main static magnetic field is then altered continuously in a "sweep" that covers the 700-Hz range of the calibrated chart.* When resonance occurs, a sharp change in the signal detected by the radio-frequency receiver is recorded as a peak on the chart paper. The difference in frequency between the TMS peak and that of a proton absorption peak is known as the *chemical shift* of that proton.

Chemical shifts may be recorded in the units δ or τ. These are defined by the relationships

$$\delta = \frac{H - H_\tau}{H_\tau} = \frac{(\nu_{\text{proton}} - \nu_{\text{TMS}}) \times 10^6}{\text{oscillator frequency}} \qquad \text{(parts per million)}$$

where H_τ is the field strength at which the TMS signal appears, and H the field strength at which the proton signal appears. The TMS signal has $\delta = 0$, and a proton signal that appears at 600 Hz with an instrument operating at 60×10^6 Hz has $\delta = 10$. *Tau* values are simply equal to $10 - \delta$. Values of δ are in parts per million (ppm); they are dimensionless.

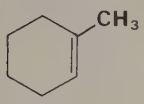
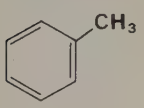
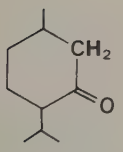
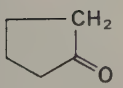
The most commonly used solvents are deuterochloroform, $CDCl_3$, and other deuterated compounds such as hexadeuteroacetone and hexadeuterodimethyl sulfoxide. Trifluoroacetic acid, the proton of which resonates outside of the range in which most other kinds of protons are found, and which is an excellent solvent for many compounds, is also useful.

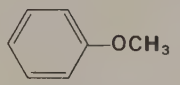
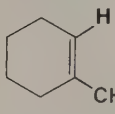
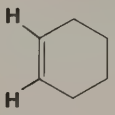
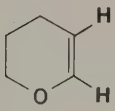
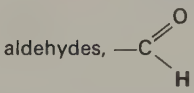
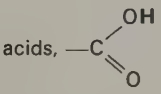
Chemical shifts depend upon the molecular environment of the proton in question; for most organic compounds the protons are found at δ values of about 0.5 to 12, the majority falling in the range of about 0.5 to 8. In Table 26-1 are given some representative values of the NMR absorption of a number of different kinds of organically bound protons.

The intensity of the absorption at any frequency is proportional to the number of protons, and is measured by the area of the relevant absorption peak. The actual number of protons in an organic molecule can be measured with considerable accuracy by measuring the areas under the absorption peaks (for example, by cutting each peak out of the chart paper and weighing the cut-out sections). If any one peak is known (or can be assumed) to represent a known number of protons, the number of protons in each of the other peaks can be determined. Modern instruments perform this measurement automatically by recording directly on the chart paper a tracing

* Field strength may be expressed either in terms of magnetic units (gauss) or electromagnetic frequency units [cycles per second (cps), or Hertz (Hz)].

Table 26-1
Representative values of chemical shifts for protons in organic compounds (tetramethylsilane $\delta = 0.00$)

Compound	*Chemical shift δ (ppm)*
Methyl groups CH_3—C	
$Si(CH_3)_4$	0.00
$CH_3CH_2CH_2CH_3$	0.85
CH_3CH_2OH	1.22
CH_3CH_2Cl	1.48
	1.60
CH_3COCH_3	2.17
CH_3COOH	2.10
CH_3CN	2.00
	2.32
Methylene groups C—CH_2—C	
	1.43
$CH_2{=}CHCH_2CH_2CH{=}CH_2$	2.12
	2.15
	2.00

Compound	*Chemical shift δ (ppm)*
Methyl groups CH_3—X	
CH_3OCH_3	3.27
	3.73
CH_3COOCH_3	3.67
$N(CH_3)_3$	2.12
CH_3Cl	3.00
CH_3Br	2.62
CH_3I	2.16
CH_3OH	3.47
Vinyl and aromatic protons	
	7.37
$(CH_3)_2C{=}CH_2$	4.60
$(CH_3)_2C{=}CHCH_3$	5.20
	5.30
	5.57
	*(a)* 6.24 *(b)* 4.54
Miscellaneous	
aldehydes, 	9.5–10
acids, 	11–11.5

that rises in steps as each proton absorption frequency is passed. The total rise of this line represents the total number of protons in the compound under study, and the number of protons in each "step" can be estimated if any one is known. Such integration records are shown in some of the figures to follow.

26-3 Interpretation of nuclear magnetic resonance spectra

The interpretation of nuclear magnetic resonance spectra is largely empirical, and is based primarily upon a knowledge of the characteristic chemical shifts for protons in different kinds of structural combination. Values such as those given in Table 26-1 are derived from extensive studies of compounds of known structure; they serve only as guides, for the detailed interpretation of NMR spectral features depends upon considerations of numerous secondary structural features. For example, the protons of the methyl group of acetone show absorption at $\delta = 2.2$ ppm, while those of the methyl group of acetophenone are found at $\delta = 2.6$ ppm. In both cases, the methyl group is present in the structural unit $—COCH_3$, but the effects of the remainder of the structure can be seen to influence the position of the absorption band.

Information gained from ultraviolet and infrared absorption spectra often provides valuable assistance in the interpretation of NMR spectra. For example, the presence of a sharp three-proton absorption peak in the region of $\delta = 3.7$ ppm usually indicates the presence of a methoxyl group, $—OCH_3$. But the methyl group of both methyl esters and methyl ethers is found in this region, and so the signal cannot ordinarily be interpreted in the absence of additional information. If the characteristic infrared carbonyl absorption of the ester grouping is absent, such an NMR signal can be attributed to the presence of a methyl ether grouping.

Spin-spin interactions. The absorption bands observed for single protons or for groups of protons in identical environments very often appear not as single sharp peaks in the recorded NMR spectrum, but as groups of separate peaks; that is, they exhibit "fine structure." In instruments incapable of high resolution, such groups of peaks may appear as broad, unresolved absorption bands, but present-day instruments are capable of sufficiently high resolution to resolve such bands into their separate components. Figure 26-2 is the NMR spectrum of acetaldehyde. It might be anticipated that acetaldehyde would show two proton absorption peaks: one, with an area corresponding to three protons, for the methyl group; and another, with an area corresponding to one proton, for the hydrogen atom of the formyl group. It is apparent that while the two "peaks" of areas 1 and 3 are present, both of these are multiplets: that of area 3 is a doublet; that of area 1 is a quadruplet.

The NMR spectrum of ethyl chloride, shown in Figure 26-3, shows two multiplets: one, of total area 3, is a triplet; the other, of area 2, is a quadruplet. Moreover,

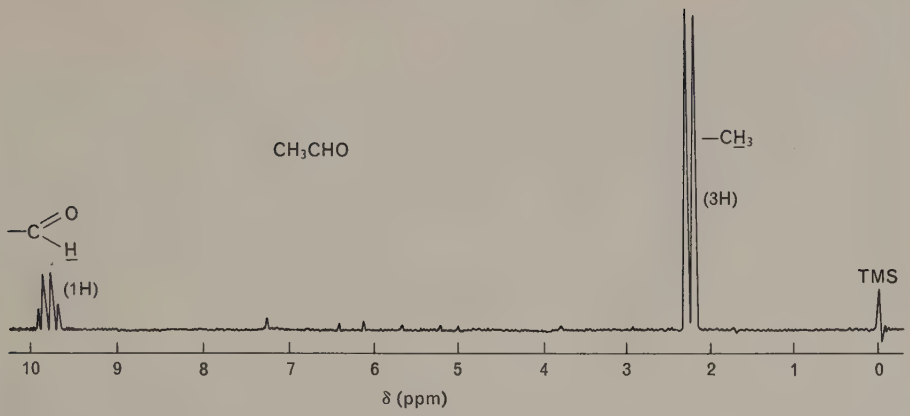


Figure 26-2
NMR spectrum of acetaldehyde, with TMS as internal standard. The three-proton signal for the methyl group is a doublet, owing to spin-spin coupling with the proton on the adjacent formyl group. The signal for the formyl hydrogen is a quadruplet, owing to spin-spin coupling with the three protons of the adjacent methyl group. Note the low-field position ($\delta = 9.8$) of the formyl hydrogen atom. (The NMR spectra illustrating this chapter were taken from the *Spectra Catalog*, Vol. 1, 1962, Varian Associates, Palo Alto, California.)

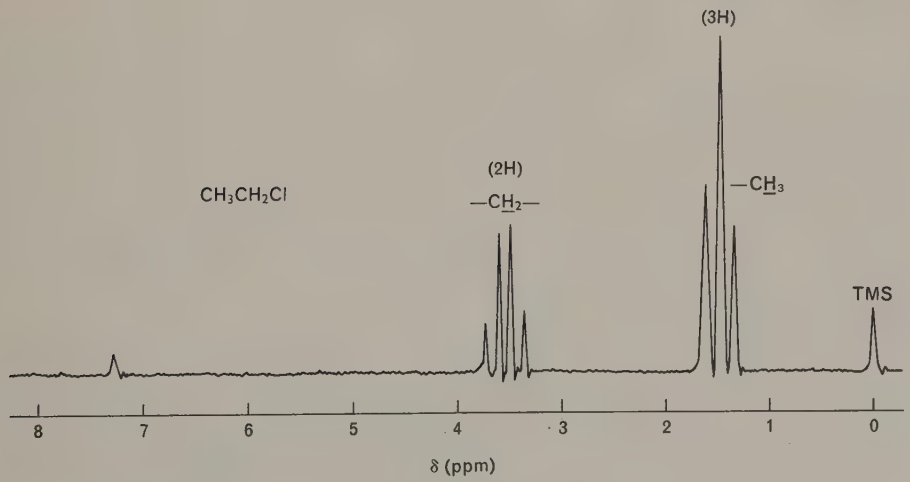


Figure 26-3
NMR spectrum of ethyl chloride. The quadruplet signal (two protons) for the —CH_2— group, adjacent to Cl, is at much lower field than the triplet signal (three protons) for the methyl group.

a detailed analysis of the triplet and of the quadruplet signals in the ethyl chloride spectrum discloses that the relative areas of the individual peaks are 1:2:1 in the triplet, and 1:3:3:1 in the quadruplet.

The reason for the splitting of the signals for the $—CH_2—$ and $—CH_3$ groups in the ethyl chloride spectrum can be found by examining the structure of the compound as it affects the environments of the protons of these groupings. Let us first consider the methyl group, the protons of which give rise to the triplet, of total area 3, at $\delta = 1.48$ (the "center of gravity" of the triplet signal). Adjacent to the $—CH_3$ group are the two protons of the $—CH_2—$ group, the spins of which may have three different arrangements, which can be represented by the symbols

$$\downarrow\downarrow \qquad \downarrow\uparrow \qquad \uparrow\downarrow \qquad \uparrow\uparrow$$

each of which represents a particular orientation of the proton magnets with respect to the applied field. Of these three orientations of the methylene-group protons, one reinforces, one opposes, and two neither oppose nor reinforce the field by which the $—CH_3$ protons are affected. Thus, there is one chance that the $—CH_3$ resonance will appear higher, one that it will appear lower, and two that it will be unaffected. Thus three peaks, in the observed ratio 1:2:1, appear in the signal for this methyl group.

The $—CH_2—$ absorption is affected by the neighboring methyl group in a similar way. The three $—CH_3$ protons can possess the spin orientations

$$\underset{1}{\uparrow\uparrow\uparrow} \qquad \underset{3}{\uparrow\downarrow\downarrow \; \downarrow\uparrow\downarrow \; \downarrow\downarrow\uparrow} \qquad \underset{3}{\uparrow\uparrow\downarrow \; \uparrow\downarrow\uparrow \; \downarrow\uparrow\uparrow} \qquad \underset{1}{\downarrow\downarrow\downarrow}$$

and affect the absorptions of the $—CH_2—$ protons in such a way as to give the four-line signal with the four peaks in the ratio 1:3:3:1.

The signals for the methyl group and the formyl hydrogen atom in the NMR spectrum of acetaldehyde (Figure 26-2) can be interpreted similarly. The methyl group gives rise to a doublet because of the influence of the adjacent proton of the —CHO group; and the formyl group proton, adjacent to the three protons of the methyl group, appears as a quadruplet.

The phenomenon represented in spectra by the splitting of the signals for single protons into multiplet signals is known as *spin-spin coupling*. The appearance of such multiplet signals and the separation, in cycles per second (designated by the symbol J, called the coupling constant), of the individual peaks in such signals, provides valuable information for the determination of organic structure. The signals for the aromatic protons in Figures 26-7 and 26-8 are typical of the splitting of signals for *ortho*-disposed aromatic protons and provide excellent evidence that the methyl and methoxyl groups (Figure 26-7) and the chloro and acetyl groups (Figure 26-8) are in the 1,4- rather than in the 1,2- or 1,3-positions. It is beyond the scope or intent of this presentation to discuss spin-spin coupling in great detail; examples of it may be

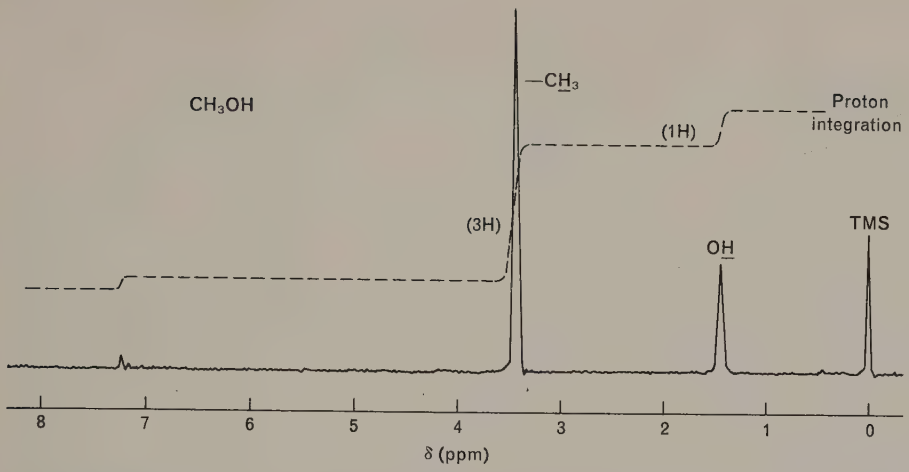


Figure 26-4
NMR spectrum of methanol. The spectrum shows two peaks: a three-hydrogen singlet for the —CH_3 group and a one-hydrogen singlet for the proton of the —OH group. The dotted line is the automatically recorded proton-integration curve. The small signal at about 7.3 ppm is from the proton in $CHCl_3$, usually present as an impurity in the $CDCl_3$ solvent.

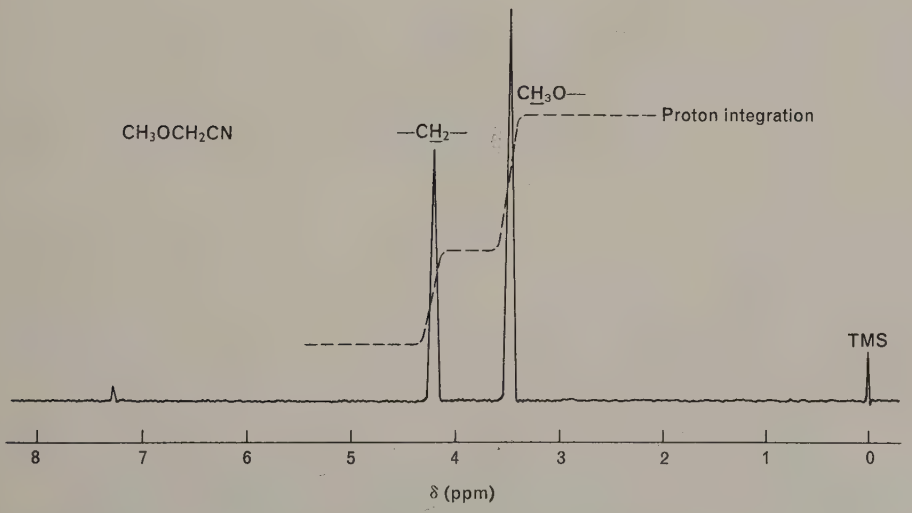


Figure 26-5
NMR spectrum of methoxyacetonitrile. Two signals, both singlets, with areas 2 (for —CH_2—) and 3 (for —CH_3) are seen. It will be noted that the signal for the methylene group is at a lower field than that for the methyl group; this is due to the additional shielding of the methylene group by —CN.

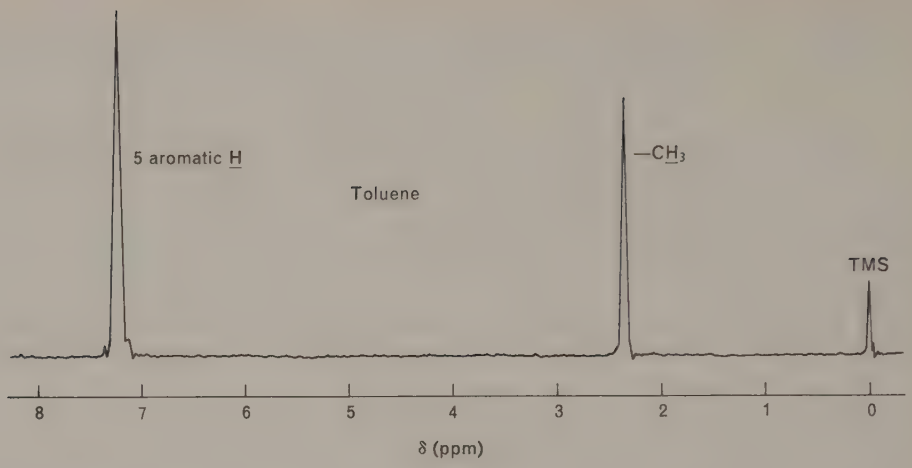


Figure 26-6
NMR spectrum of toluene. The five aromatic protons have essentially the same chemical shift and appear as a five-proton singlet. The only other signal is that of the methyl group.

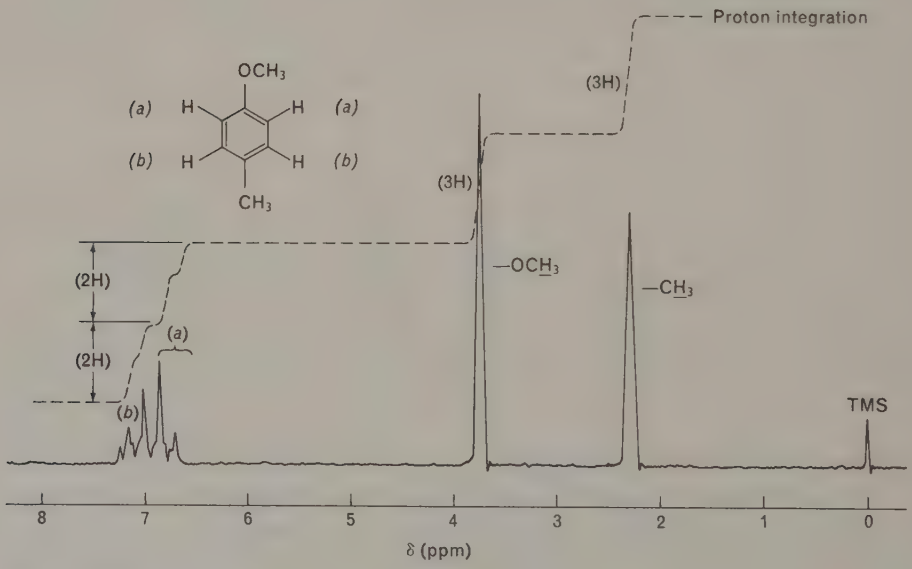


Figure 26-7
NMR spectrum of *p*-methoxytoluene. The nuclear methyl group and the methyl group of the methoxyl group appear as three-proton singlets. The ring protons form a coupling pattern characteristic of *ortho*-hydrogen atoms with different chemical shifts. Protons *ortho* to alkoxyl groups are found at higher field (lower values of δ) than those *ortho* to alkyl groups; this permits the quadruplet pattern found at $\delta \cong 7$ to be interpreted as shown. The proton integration tracing shows the two protons marked (*a*), the two marked (*b*), and the two three-proton signals for the two methyl groups.

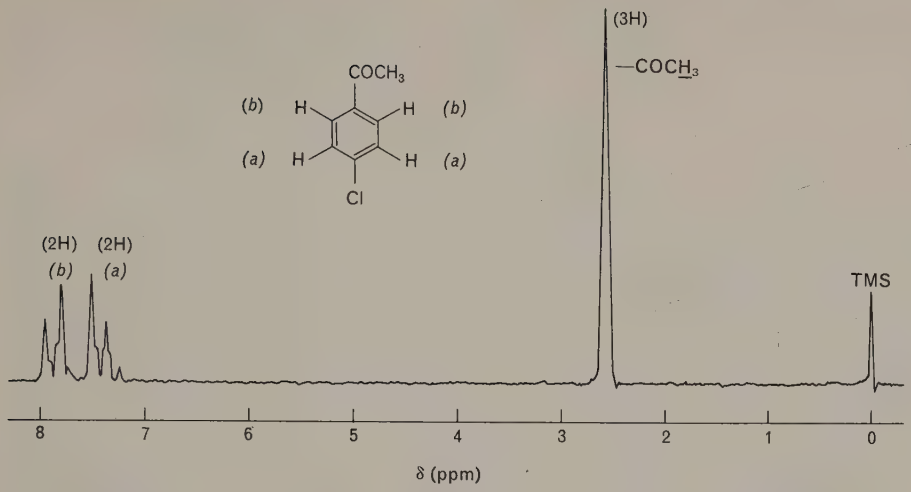


Figure 26-8
NMR spectrum of *p*-chloroacetophenone. The methyl group of —$COCH_3$ is responsible for the three-proton singlet at $\delta = 2.58$. Note the downfield shift of the nuclear protons (δ about 7 to 8) compared with those of *p*-methoxytoluene. The deshielding effects (downfield shift) of the *ortho* carbonyl and halogen groups are clearly evident. The coupling pattern of the *ortho*-disposed protons, resulting in the two doublets, is similar in form (and about the same in the separation of the peaks) to that shown for the protons of *p*-methoxytoluene.

discerned in some of the figures, which have been chosen as examples of NMR spectra of organic compounds containing protons in a variety of combinations. The legend of each figure describes briefly the chief characteristics of the spectrum and assigns to the several peaks the protons that they represent.

26-4 Mass spectrometry

The *mass spectrometer* is an instrument designed (*a*) to bring about the ionization and fragmentation of an organic molecule by bombarding it with high-energy particles, such as electrons, and (*b*) to analyze the resulting mixture of ionic fragments by determining their mass/charge ratio and measuring their relative abundance.

A mass spectrometer produces an intense beam of electrons, into which a sample of the compound to be studied is introduced. The resulting charged molecules and molecular fragments are accelerated in a beam toward a target, where the intensity and mass/charge ratio (m/e) of each species of ion is measured and recorded. The *mass spectrum* is a chart of the mass/charge ratio (most species of ions produced have unit charge) against the intensity of each species.

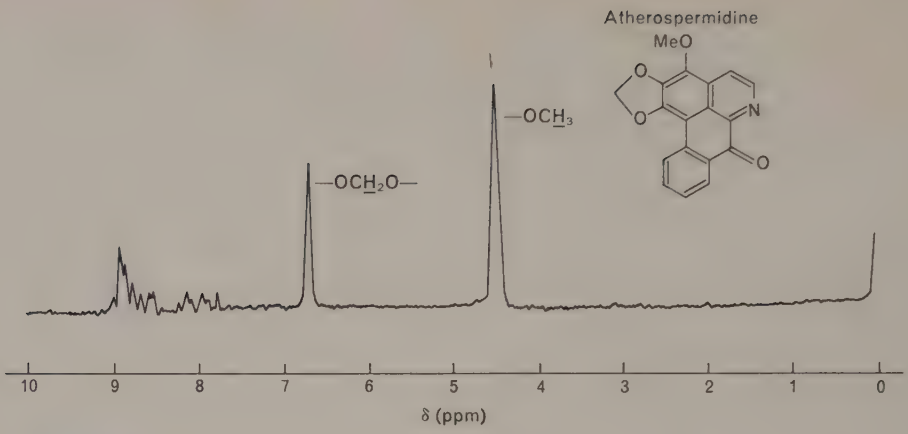


Figure 26-9
NMR spectrum of a naturally occurring alkaloid, atherospermidine. Note the simplicity of this spectrum, which is that of a rather complex molecule. The methoxyl group and the methylenedioxy group (—CH_2—) form sharp three- and two-proton singlets, respectively. The six aromatic protons are coupled in a complex manner and their signals are difficult to interpret in detail. It is apparent, however, that the six proton signals in the multiplets between 8 and 9 ppm represent aromatic protons. Compare this spectrum with that of liriodenine (Figure 26-10), which is identical with atherospermidine except for the presence of the methoxyl group in the latter. The proton in this position in liriodenine is not coupled with any other proton(s), and appears as the prominent singlet at $\delta \cong 7.7$ ppm. The remaining six protons of liriodenine and atherospermidine appear in substantially the same region and show nearly the same coupling characteristics.

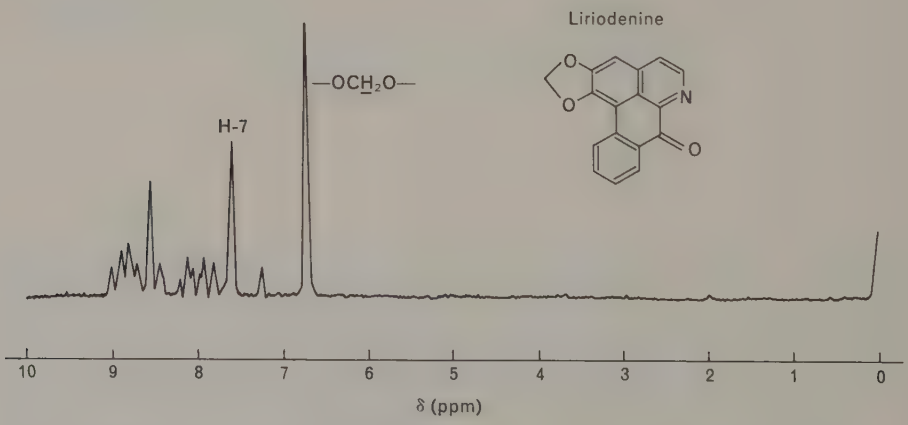


Figure 26-10
NMR spectrum of liriodenine. The only nonaromatic protons are those of the methylenedioxy group, which appear as a sharp two-proton singlet. The aromatic protons are found at values of 7 to 9 ppm, the sharp one-proton singlet being due to the single proton adjacent to the methylenedioxy grouping. See comments under Figure 26-9.

The bombardment of an organic molecule with high energy particles can result in the removal of a single electron from the molecule:

$$M + e \longrightarrow M^+ + 2e \qquad (1)$$

The resulting positively charged ion is called the *molecular ion*, and since its mass (m/e, where $e = 1$) can be measured accurately in a mass spectrometer, *mass spectrometry provides a valuable way of measuring molecular weights.* If the ion M^+ were stable, the mass spectrometer would give little information besides the molecular weight. But since the electron beam used has much greater energy than is needed to cause the initial ionization (1), the ion produced by impact has sufficient excess energy to decompose further into smaller fragments. These fragments may be positive ions (which are detected and recorded), uncharged free radicals, and neutral molecules. The latter two are not charged and are not detected by the measuring system of the instrument.

The fragmentation of the ions produced by the electron impact proceeds in accord with the usual principles of the relative stability of intermediate ions and radicals: tertiary carbonium ions, allylic carbonium ions, protonated carbonyl groups, and other stabilized -onium ions are usually produced in preference to alternative, less stable ions.

For an example, let us examine the behavior of some simple molecules in the mass spectrometer. Methanol, under electron bombardment, loses one of the nonbonding electrons on oxygen:

$$CH_3\ddot{O}{-}H + e \longrightarrow CH_3\dot{\ddot{O}}^+{-}H + 2e \qquad (2)$$

$m/e = 32\ (M^+)$

Further decomposition of M^+ proceeds by loss of a hydrogen atom, with formation of the oxonium ion:

$$\begin{matrix} H \\ | \\ CH_2{-}\dot{\ddot{O}}^+{-}H \end{matrix} \longrightarrow (CH_2{=}OH)^+ + H\cdot \qquad (3)$$

$m/e = 31\ (M - 1)$

Further breakdown of the initial ion can occur in the following way:

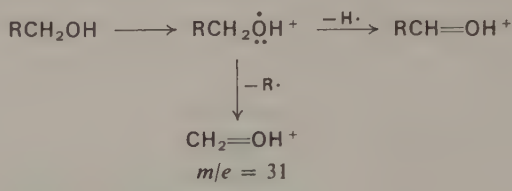
$$(CH_3{-}\dot{\ddot{O}}H)^+ \xrightarrow{-2H\cdot} H_2C{=}\ddot{O}\cdot^+ \qquad (4)$$

$m/e = 30\ (M - 2)$

$$\xrightarrow{-3H\cdot} H{-}C{\equiv}O{:}^+ \qquad (5)$$

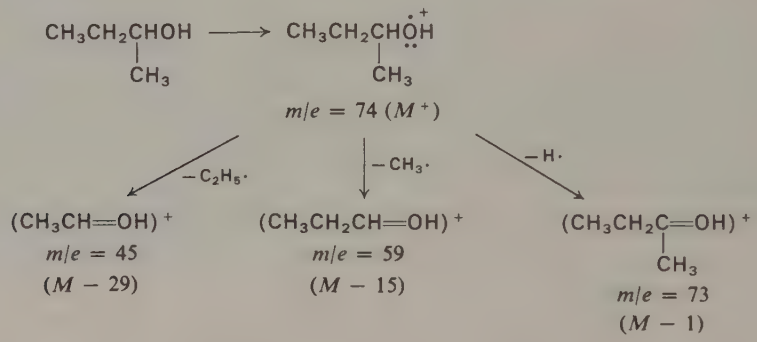
$m/e = 29\ (M - 3)$

More complex compounds give more complex fragmentation patterns. Ethanol and higher primary alcohols can decompose in the following way:



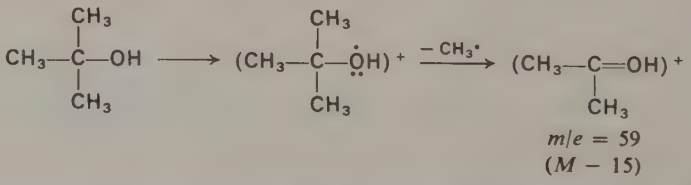
(6)

Secondary and tertiary alcohols are very apt to undergo fission because the carbonium (≡oxonium) ions produced after the initial ionization are more stable with increased substitution, making several courses of fission available. In the decomposition of the molecular ion of 2-butanol, the loss of H·, CH_3·, or C_2H_5· can occur, with the production of $M - 1$, $M - 15$, and $M - 29$ ion peaks:



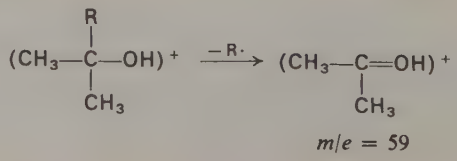
(7)

In tertiary alcohols the molecular ion is so much less stable than the product resulting from the loss of an alkyl radical that there is often no molecular-ion peak observed for M^+; its fission occurs in the following way:



(8)

The $m/e = 59$ ion peak is common for 2-methyl-2-alkanols, because the following decomposition can occur:



(9)

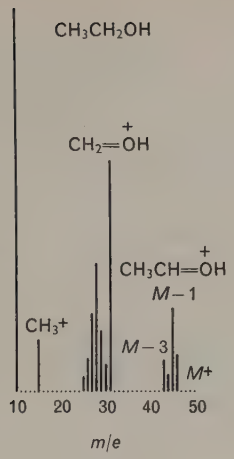


Figure 26-11
Mass spectrum of ethanol.

As the length of the chains in the alkyl groups of primary, secondary, and tertiary alcohols increases, more complex fission patterns (mass spectra) are observed. Figures 26-11 and 26-12 show the mass spectra of ethanol and 1-octanol. It is evident that many more prominent ion species are produced from the longer-chain alcohol.

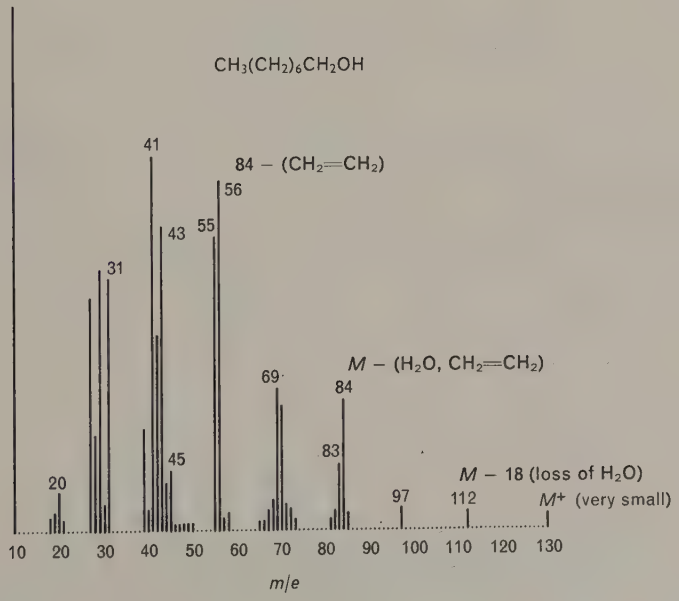


Figure 26-12
Mass spectrum of 1-octanol.

The sensitivity of the mass spectrometer to single-unit differences in the mass/charge number is responsible for the appearance of a number of small, but easily detectable, peaks corresponding to ions containing the isotopes ^{2}H, ^{13}C, ^{17}O, ^{18}O, ^{15}N, and so on. Although most of these isotopes occur naturally in very low abundances (^{2}H, 0.015%; ^{13}C, 1.11%; ^{17}O, 0.04%; ^{18}O, 0.20%), some of the common atoms contain high proportions of isotopes. For example, chlorine consists of ^{35}Cl and ^{37}Cl in the ratio of about three to one. The mass spectrum of ethyl chloride thus shows two distinct molecular ions, differing by two mass units. Among the prominent peaks in the ethyl chloride spectrum are $(C_2H_5{}^{35}Cl)^+ = 64$; $(C_2H_5{}^{37}Cl)^+ = 66$; $(CH_2{=}{}^{35}Cl)^+ = 49$; $(CH_2{=}{}^{37}Cl)^+ = 51$; $(^{35}Cl)^+$; $(^{37}Cl)^+$; and $(C_2H_5)^+ = 29$.

The introduction (by chemical synthesis) of deuterium (^{2}H) into an organic compound, and comparison of the mass spectra of the original and deuterated compounds, can give valuable clues about the nature of a fragmentation. For example, the mass spectrum of methyl formate, $HCOOCH_3$, shows the most abundant ion to have $m/e = 31$. This might be interpreted to mean that fragmentation gave $(CH_3O)^+$, for which $m/e = 31$. However, when methyl formate-*d* ($DCOOCH_3$) was studied, it was observed that the prominent peak at $m/e = 31$ was replaced by one at $m/e = 32$. This showed that the peak at 31 contained the hydrogen of the formyl group, which arose as follows:

$$\left(\begin{array}{l}\mathrm{H{-}C{-}O{-}CH_3}\\ \quad\|\\ \quad\mathrm{O}\end{array}\right)^{+} \longrightarrow \underset{m/e = 31}{(CH_2OH)^+} + H\cdot + CO \qquad (10)$$

$$\left(\begin{array}{l}\mathrm{D{-}C{-}OCH_3}\\ \quad\|\\ \quad\mathrm{O}\end{array}\right)^{+} \longrightarrow \underset{m/e = 32}{(CHDOH)^+} + H\cdot + CO \qquad (11)$$

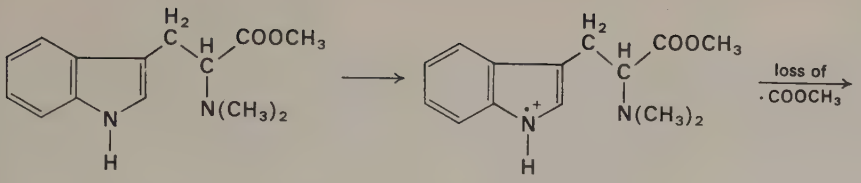
The mass spectrum of ethyl formate again shows the peak at $m/e = 31$, formed by the loss of $CH_3\cdot$ instead of $H\cdot$,

$$\left(\begin{array}{l}\mathrm{H{-}C{-}OCH_2CH_3}\\ \quad\|\\ \quad\mathrm{O}\end{array}\right)^{+} \longrightarrow \underset{m/e = 31}{(CH_2OH)^+} + CH_3\cdot + CO \qquad (12)$$

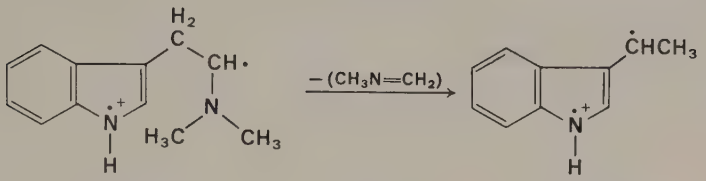
and isopropyl formate yields the corresponding fragment of $m/e = 45$:

$$\left(\begin{array}{l}\mathrm{H{-}C{-}O{-}CH{-}CH_3}\\ \quad\|\quad\quad\;\;|\\ \quad\mathrm{O}\quad\quad\mathrm{CH_3}\end{array}\right)^{+} \longrightarrow \underset{m/e = 45}{\begin{array}{l}(\mathrm{CHOH})^+\\ \quad|\\ \quad\mathrm{CH_3}\end{array}} + CH_3\cdot + CO \qquad (13)$$

More complex organic compounds may also be analyzed by mass spectrometry. In the mass spectrum of *N*,*N*-dimethyltryptophane methyl ester, prominent ion species are seen at $m/e = 246$ (M^+), 187, 144, 130, and 116. These are accounted for by the following fissions:



$m/e = 246\ (M^+)$



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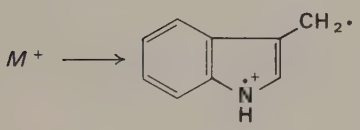
$m/e = 187$ $\qquad$ $m/e = 144$



and $(CH_3)_2\overset{+}{N}{=}CHCOOCH_3$ (15)

$m/e = 130$ $\qquad$ $m/e = 116$

The application of mass spectrometry to the elucidation of organic structures is rapidly assuming an importance comparable to that of nuclear magnetic resonance spectrometry. An extensive literature on the interpretation of mass spectra is bringing the technique within the purview of most organic chemists.

Instruction in the application and interpretation of ultraviolet and infrared spectroscopy (Chapter 17), nuclear magnetic resonance, and mass spectrometry is now an integral part of the study of organic chemistry. It is best undertaken as a special course of instruction. Many excellent introductory textbooks and monographs are available, all of which provide a great deal more information than can be offered in a general introductory textbook of organic chemistry. It is recommended that the student refer to one or more of these for additional instruction in these important areas, or include in his program a special course in spectrometry.

27

Cyclic compounds and cyclization reactions

In principle, any bond-forming reaction can be used to join two ends of a chain of atoms to form a ring. In practice there are conditions that affect the rate and the yield of such a cyclization reaction, and in some cases the relative balance between the desired cyclization process and undesired side reactions.

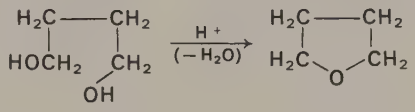
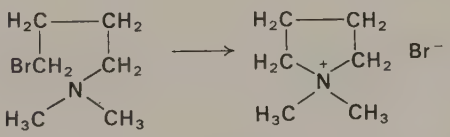
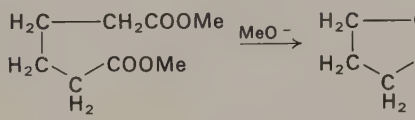
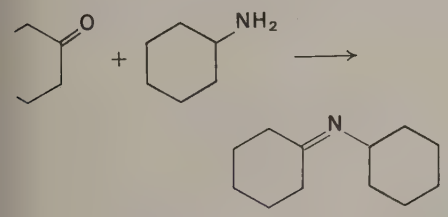
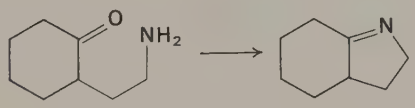
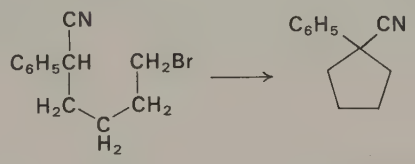
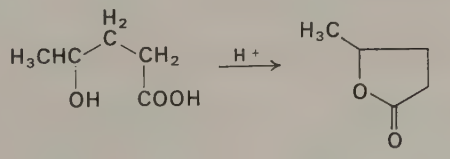
In this chapter we shall review some of the properties of cyclic compounds: their stability, ease of formation, configuration and conformation, and stereochemistry. The reactions that can be used for ring formation cannot be categorized. Reactions as diverse as esterification, ether formation, alkylation, and electrophilic and nucleophilic aromatic substitution can be used to effect ring closure.

These reactions have been discussed (or will be in chapters to follow), and their application to the formation of cyclic compounds will be readily apparent. Thus, our concern here will be not with types of reactions, but with the conditions for ring-forming reactions of all kinds.

Perhaps the largest distinct class of cyclic compounds, the aromatic compounds are not ordinarily considered from the standpoint of cyclization reactions. Although certain of the simpler members (benzene, toluene) are commercially prepared by cyclization of acyclic precursors, most of the chemistry of aromatic compounds deals with the reactions and transformations of compounds in which the basic ring system (benzene, naphthalene, and so on) is present to begin with.

27-1 Ring formation

Most organic reactions in which new bonds are formed by the interaction of functional groups in separate molecules can be applied to ring formation if the reactive functions are both present in the same molecule. The following equations show a number of typical bond-forming reactions, each in the *intermolecular* and the related *intramolecular* (cyclization) form:

Intermolecular	*Intramolecular (cyclization)*	
$H_3CH_2OH + CH_3CH_2OH \xrightarrow[(-H_2O)]{H^+} CH_3CH_2OCH_2CH_3$		(1)
$(CH_3)_3N + CH_3CH_2Br \longrightarrow (CH_3)_3\overset{+}{N}CH_2CH_3\ Br^-$		(2)
$H_3CH_2COOMe + CH_3CH_2COOMe \xrightarrow{MeO^-} CH_3CH_2COCHCOOMe$ (CH$_3$ on the CH)		(3)
		(4)
$H_5CH_2CN + CH_3CH_2Br \xrightarrow{NaNH_2} C_6H_5CHCN$ (CH$_2$CH$_3$ on the CH)		(5)
$H_3)_2CHOH + CH_3COOH \xrightarrow{H^+} CH_3COOCH(CH_3)_2$		(6)

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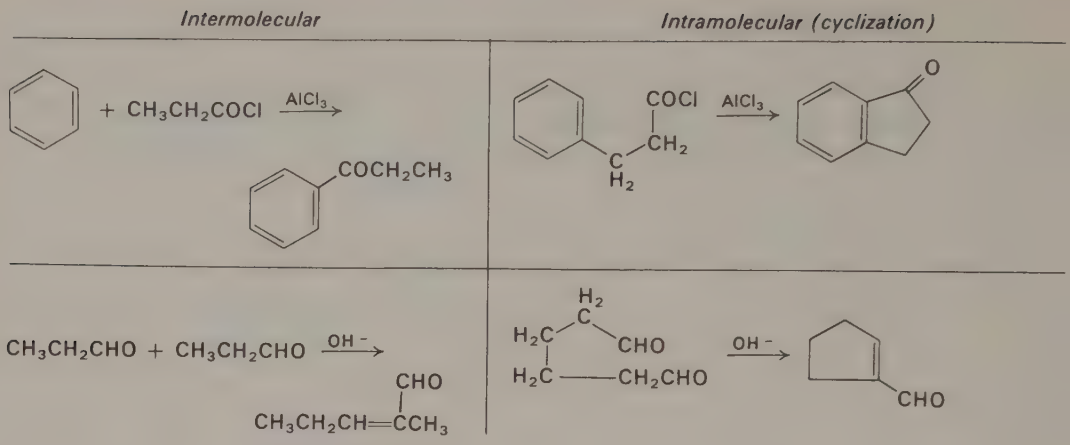


The generalization that any bond-forming process can be applied to ring formation must be qualified by the following provisions:

1. The cyclization reaction may be slow or may involve an unfavorable equilibrium because of strains imposed by the distortion of bond angles from their normal values in the process of ring closure (small rings).

2. The cyclization reaction may be slow if there is a low probability of the reactive functions coming into contact (large rings). In some cases ring formation is impossible because steric disposition of the reactive functions does not permit them to approach to within bond-forming distance.

3. If there are alternative pathways for the reaction of the two functions, and condition 1 or 2 obtains, the reaction that ensues may be *intermolecular* (polymerization) rather than *intramolecular* (cyclization). For example, if the reactive "ends" of a long chain cannot find each other, they will react with their complementary functions in other molecules to yield a long-chain polymeric product.

4. Cyclization reactions leading to 5- and 6-membered rings are usually fast, are not subject to unfavorable equilibria, and give good yields of the cyclic products.

27-2 Ring size and stability of cyclic compounds

Cyclic compounds are ordinarily classified as

(*a*) small rings: 3- and 4-membered
(*b*) common rings: 5-, 6-, and 7-membered
(*c*) medium rings: 8- to 12-membered
(*d*) large rings: 13-membered and larger.

Cyclopentane and cyclohexane rings (and heterocyclic rings of 5 and 6 members) are by far the most commonly encountered. They are readily formed by ring-closure reactions and have a high degree of stability. The bond angles between the atoms forming the ring are almost equal to the normal angles in acyclic compounds; thus they are nearly *strainless.*

Small rings (for example, cyclopropane and cyclobutane) are formed with a considerable distortion of the normal tetrahedral bond angles, although they are readily formed when the proximity of the reacting ends of a bifunctional precursor permits it. The C—C—C angle in cyclopropane is 60°, compared with 109.5° in propane; in cyclobutane the C—C—C angle is 90°. Deflections from the normal tetrahedral angles are given, for various ring sizes, in Table 27-1.

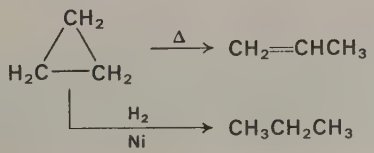
Table 27-1
Departures from tetrahedral bond angles in carbon rings

Ring size	*Departure of each bond in C—C—C from 109.5°*	*Heat of combustion per CH_2 (kcal/mole)* **
3	24.7°	168.5
4	9.7°	165.5
5	0.7°	158.7
6	0	157.4
7	0	158.3
9	~0	159.0
15	~0	157.1

* For *n*-alkanes, ~156.

An early "strain theory" assumed similar distortions (by spreading of the bond angles) in 6-, 7-, and higher-membered rings, based upon the erroneous postulate that these rings were planar molecules. Such rings are in fact strainless; they are not planar, but can pucker in such a way as to permit the assumption of normal bond angles.

For small rings the distortion of the bond angles has an effect on their reactivity, and cyclopropane derivatives react with many reagents to form non-cyclic products (although many cyclopropanes with functional substituents may also react quite normally at the functional group):



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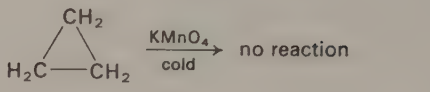

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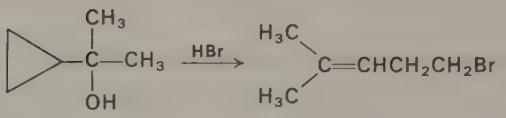

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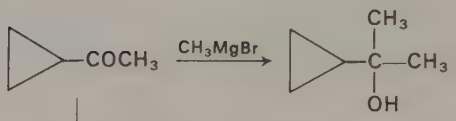
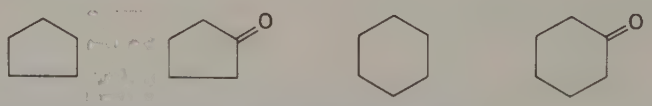


(12)

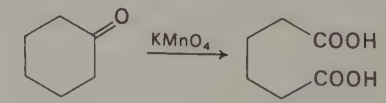
(13)

Cyclobutanes are somewhat more stable than cyclopropanes, but will undergo ring-opening reactions under more drastic conditions.

Five- and six-membered carbocyclic rings* are stable under most experimental conditions that involve heating, the action of halogens or acids, and hydrogenation. Reactions that are not simply reversals of the ring-forming processes can, however, lead to irreversible ring opening: oxidation and alkaline-cleavage/saponification open 5- and 6-membered rings because the products are not in a simple equilibrium with the original cyclic compounds. Similar comments apply to many heterocyclic ring compounds. For example, the compounds



are stable under the conditions of their formation, but:



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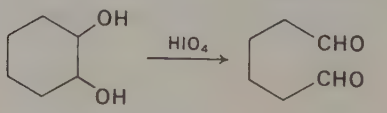
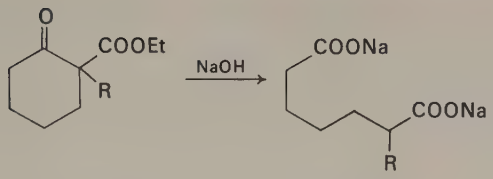


(15)

* The term "carbocyclic" refers to rings of which all the members of the cycle are carbon atoms. Rings in which one or more atoms is oxygen, nitrogen, or some other atom are called *heterocyclic* rings; the atoms other than carbon are often referred to as *hetero* atoms.



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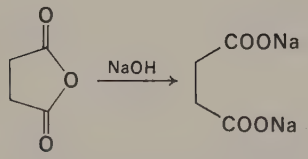

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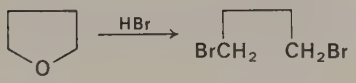

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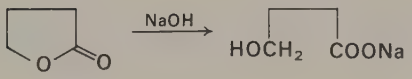

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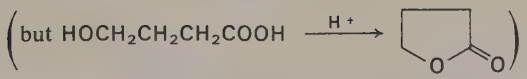


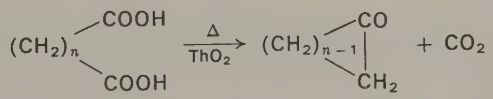
(20)

Very large rings, such as cyclopentadecane ($C_{15}H_{30}$), are quite stable. They and their functional derivatives are similar in reactivity to the corresponding alkanes. As will be shown in the discussion to follow, they are not "strained" molecules.

27-3 Factors affecting yield in cyclization reactions

The general conditions for ring formation, stated briefly in Section 27-2, derive partly from considerations of ring strain and probability, but also from the results of much experimental study. One of the earliest and most comprehensive investigations of a cyclization reaction was a study of the formation of cyclic ketones from dicarboxylic acids.

When a dicarboxylic acid of the general structure $HOOC(CH_2)_nCOOH$ is heated with a heavy metal oxide (for example, thorium oxide or cerium oxide), the following reaction occurs, leading to a cycloalkanone:



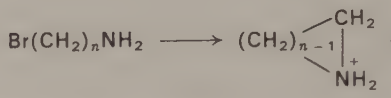
(21)

Adipic acid ($n = 4$) yields cyclopentanone; pimelic acid ($n = 5$) yields cyclohexanone, and so on.

The yields from this reaction are excellent when the products are 5- and 6-membered cyclic ketones. The yields fall when rings with more than 6 members are the products. It is found that C_7–C_8 rings are formed in moderate yields (10–20%), and for C_9–C_{13} rings the yields are very poor (~0.5%). Yields remain low for rings larger

than these, but rise to a maximum of about 5% at C_{13}, then fall slowly to a rather constant value of about 2% for larger rings.

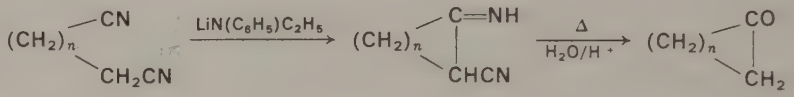
Other ring-forming reactions have been studied with similar objectives. The cyclic displacement reaction



$$\mathrm{Br(CH_2)_nNH_2} \longrightarrow \mathrm{(CH_2)_{n-1}}\begin{array}{l}\mathrm{CH_2}\\ \\ \mathrm{NH_2^+}\end{array} + \mathrm{Br^-} \qquad (22)$$

leads to yields that are in the order $n = 2 > 4 < 5 > 6 > 7$, but fails when $n = 9$ to 13. Cyclization to 3-, 5-, and 6-membered rings is fast.

Another useful route to cyclic ketones is the Ziegler reaction, carried out in dilute solutions:



$$\mathrm{(CH_2)_n}\begin{array}{l}\mathrm{CN}\\ \mathrm{CH_2CN}\end{array} \xrightarrow{\mathrm{LiN(C_6H_5)C_2H_5}} \mathrm{(CH_2)_n}\begin{array}{l}\mathrm{C{=}NH}\\ \mathrm{CHCN}\end{array} \xrightarrow[\mathrm{H_2O/H^+}]{\Delta} \mathrm{(CH_2)_n}\begin{array}{l}\mathrm{CO}\\ \mathrm{CH_2}\end{array} \qquad (23)$$

Yields reported for this reaction are: for C_7 ($n = 5$), 95%; $n = 6$, 88%; $n = 7$–9, negligible; $n = 10$, 8%; $n = 11$, 15%; $n = 12$–13, 60%.

These and other observations of a similar kind lead to the following generalizations:

1. The probability that the functional groups at the two ends of a chain will meet to form a ring is higher the shorter the chain. Thus, the *probability* of cyclic interaction is greatest for 3-membered rings and decreases with increasing chain length. The frequency with which the reactive chain ends approach to within bond-forming distance diminishes with increasing chain length; in the case of large rings the decrease in entropy necessary for favorable orientation of the open-chain precursor is so great that cyclization is very slow, and the reactions either do not proceed or take alternative courses.

2. The strain imposed by bond-angle distortion is highest in small rings, minimal in 5-, 6-, and 7-membered rings, somewhat increased in medium rings, and essentially absent in large rings.

3. Associated with bond-angle strain is an additional factor that appears in medium rings, shown by the consistently low yields of 9- to 12-membered rings. Because of the limited opportunity for configurational changes (that is, in flexibility) in 9- to 12-membered rings, it is inevitable that some of the substituents on such rings (for example, the hydrogen atoms of the $—CH_2—$ groups) are forced into close proximity, thus creating unfavorable repulsive forces, which can be accommodated by small distortions of the C—C—C bond angles. In large rings these forces are absent because the ring is flexible and can assume a shape in which internuclear interactions of this kind are minimal.

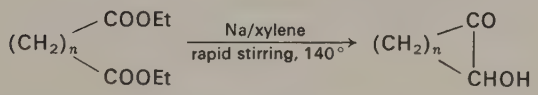
The yield of a cyclization reaction depends upon the resultant of all of these factors.

Modern improvements in experimental techniques have made it possible to prepare certain large ring compounds in good yields. Two such procedures are:

1. High-dilution methods. If the long bifunctional chain is present in very dilute solution, the probability of its reacting with another molecule (to give a polymer) is diminished, and the competing intramolecular reaction leading to ring closure is favored.

2. The use of reagents that attach to one or both of the reactive ends in some manner (which is sometimes not clear) to fix them at contiguous sites or to reduce the randomness between them. The acyloin condensation, shown below in the acyclic and cyclic cases, can be carried out in the presence of molten, finely divided sodium in aprotic solvents to give astonishingly high yields (40% in the usually unfavorable cases of C_9–C_{13} rings) of cyclic acyloins:

$$2RCH_2COOEt \xrightarrow{Na} \underset{\text{An acyloin}}{RCH_2\overset{\overset{O}{\|}}{C}\overset{\overset{OH}{|}}{C}HCH_2R} \tag{24}$$



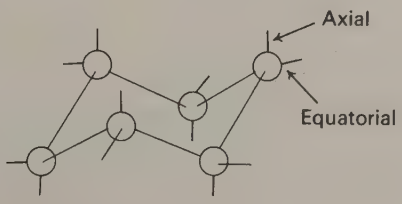
(25)

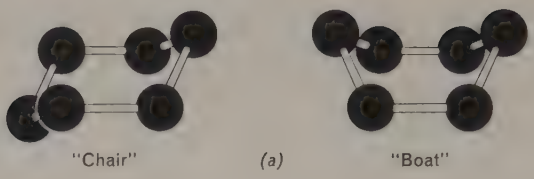
An application of this reaction is described in Section 27-13. It is possible that the formation of large ring compounds in living organisms is due to a catalytic enzyme, providing sites for the attachment of a substrate so that reacting functions are in close proximity or have limited mobility.

27-4 Configuration and conformation

A cyclohexane ring can exist in two principal *conformations*, in both of which the bond angles are the normal tetrahedral value of 109.5°. These are called the "boat" and "chair" forms, shown in Figure 27-1.

The chair conformation of cyclohexane is shown more clearly in the following drawing:





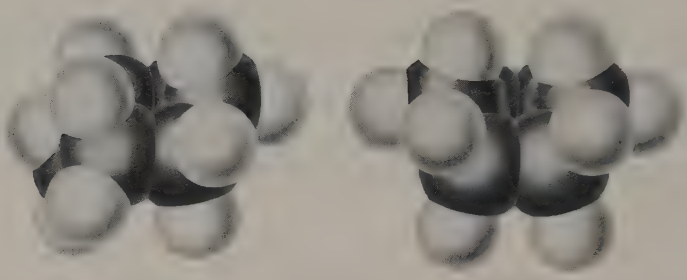
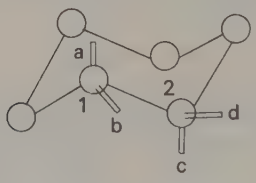
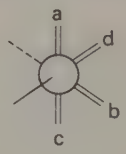


Figure 27-1
"Boat" and "chair" forms of cyclohexane; (*a*) carbon skeletons, only C—C bonds shown; (*b*) molecular models.

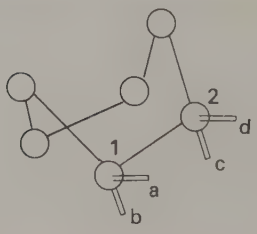
The twelve bonds (to hydrogen or other substituents) are disposed in two ways: six of them extend in the direction parallel to an axis drawn perpendicular to the ring, and are called *axial*; the remaining six extend parallel to the general plane of the ring in a kind of equatorial belt, and are called *equatorial*. It will be noticed that the chair conformation allows the most effective separation of adjacent substituents:



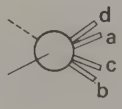
End-on view along bond joining 1-2



whereas in the boat form adjacent hydrogen atoms would "eclipse" each other:



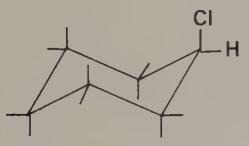
End-on view along bond joining 1-2



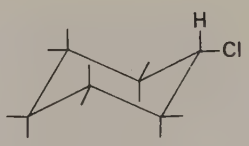
a-d and c-b are "eclipsed"

The interference caused by the eclipsing of adjacent substituents represents a degree of strain that, while not large, helps to determine which conformation is the more stable.

When the cyclohexane ring carries a substituent, a new question arises. Taking chlorocyclohexane as an example, and assuming that the ring is in the more stable chair form, is the chlorine atom axial or equatorial?



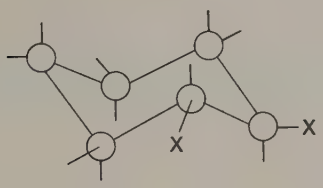
Chlorine axial



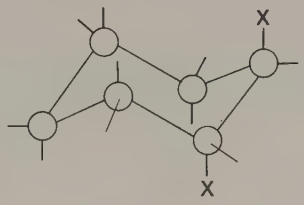
Chlorine equatorial

It is found experimentally by electron diffraction that the most stable conformation of chlorocyclohexane is the form in which chlorine is equatorial. In general, *in monosubstituted cyclohexanes the substituent is in the equatorial position.*

The reason for this is that an axial substituent and the two other axial hydrogen atoms or substituents offer some interference to each other; but when the substituent is equatorial no such interaction is present. In cyclohexane derivatives with more than one substituent, the maximum number of substituents are equatorial. Thus a *trans*-1,2-disubstituted cyclohexane prefers to assume conformation (26) rather than (27):



Diequatorial (26)



Diaxial (27)

In *cis*-1,2-, *trans*-1,3-, and *cis*-1,4-disubstituted cyclohexanes, one substituent is necessarily axial, the other equatorial.

Exercise 1

Draw conformational structures of *cis*-1,3- and *trans*-1,4-dimethylcylohexanes, with the methyl groups in equatorial positions.

It should be recognized that (26) and (27) have the same *configuration*; they are both *trans*-1,2-disubstituted. They differ in *conformation*.

27-5 Polysubstituted cyclohexanes

The 1,2,3,4,5,6-hexachlorocyclohexanes have been intensively studied because of the importance of one of the isomers as an effective insecticide (*Lindane*, *Gammexane*). The mixture of isomers prepared by the photochemical addition of chlorine to benzene comprises eight stereoisomers, of which only one can exist in enantiomeric forms (making a total of seven *meso*, one (+) and one (−) form). Five of them have been separated in pure form; they are designated α, β, γ, δ, and ϵ; of these, the γ form is the physiologically active insecticide.

Establishment of their conformations by X-ray crystallography and chemical studies has shown that they have the following disposition of the chlorine atoms: α = aaeeee; β = eeeeee; γ = aaaeee; δ = aeeeee; and ϵ = aeeaee (a = axial chlorine, e = equatorial chlorine; ring in the chair form). It will be noticed that the number of equatorial chlorine substituents always (except for γ) exceeds the number that are axial.

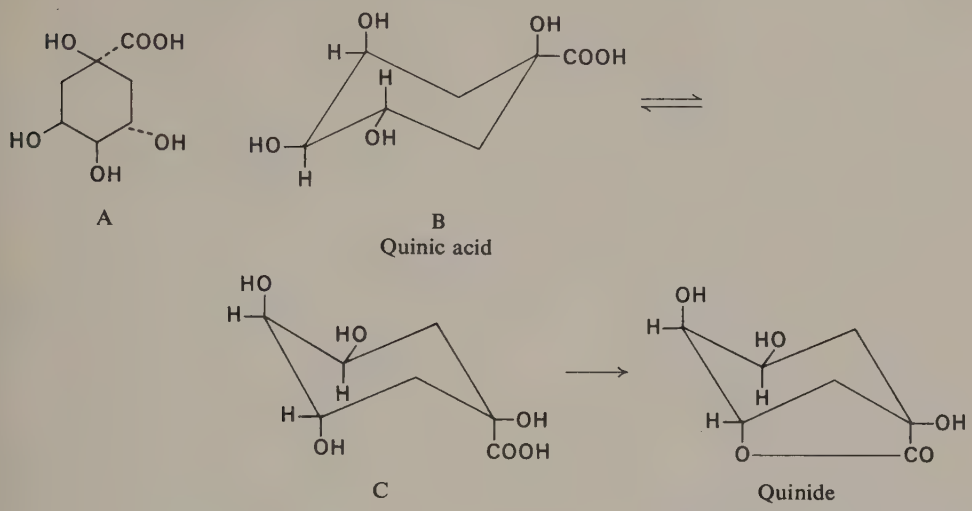
Exercise 2

Which of the isomers possesses no element of symmetry? Draw both enantiomers in conformational form. Draw the structure of the γ isomer (chair form) and indicate the element of symmetry.

27-6 Conformational change in the course of a reaction

Although it is reasonable to assume that the substituents in six-membered rings in the chair form will assume equatorial positions, the conclusion should be regarded as tentative unless experimental confirmation can be obtained. Moreover, because of the low energy barriers for change in conformation ("flipping" of the ring), substituents that are equatorial in their most stable conformations may change to an axial disposition if this is required for a reaction to occur. For example, the naturally occurring cyclohexane derivative quinic acid, with *configuration* A and presumed *conformation* B, forms the lactone, quinide, on heating. It is clear that the lactone can form only by

interaction of *axial* —OH and —COOH groups (C). Thus, if the preferred conformation is B, a change to C must occur before lactonization:



Exercise 3

The configuration of (−)-menthol (as the chloride) is shown in Section 10-8. Neomenthol is the epimeric alcohol. (*a*) Indicate the most probable conformations of these two alcohols, assuming the rings are in the chair forms. (*b*) When menthol and neomenthol are dehydrated by treatment with a strong acid, one gives nearly pure 2-menthene, the other gives a mixture of 2- and 3-menthenes. Which gives largely 2-menthene, and which gives the mixture? (*c*) Neomenthol dehydrates more readily than menthol. Explain, in terms of their conformations.

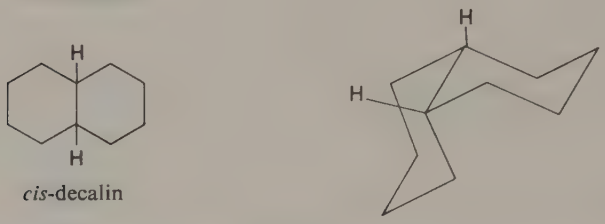
Additional influences may affect conformation. Substituents that are capable of forming hydrogen bonds, for example, may be constrained by such bonding to an axial-axial relationship, rather than to what might appear on other grounds a more favorable equatorial-equatorial disposition.

27-7 Bicyclic and polycyclic ring systems

The bicyclic ring system decahydronaphthalene (decalin, bicyclo[4,4,0]decane) can exist in two stereoisomeric forms. These are distinct compounds and are not simply

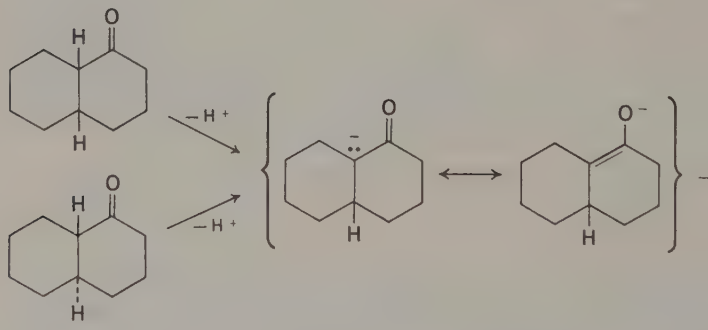
conformational isomers ("conformers"), for in one of them the two rings are *trans*-fused, in the other, *cis*-fused. Both of these exist in the chair forms:

trans-decalin (29)



cis-decalin (30)

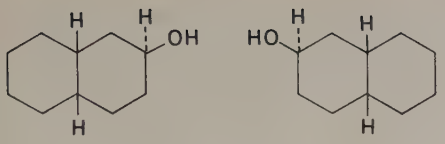
Of these, the *trans* ring system is known to be more stable than the *cis*. Although the two decalins themselves are not interconvertible by any simple equilibrium conversion, the 1-keto compounds (1-decalones) can be equilibrated by treatment with a base. The intermediate anion (enolate ion) can accept a proton to regenerate either the *trans*-fused or the *cis*-fused ketone. Since this is an equilibrium, the thermodynamically more stable isomer predominates. Experiment has shown that the ratio of *trans* to *cis* at equilibrium is about 20:1.



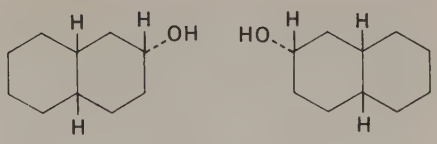
trans + *cis* (31)

~95% : ~5%

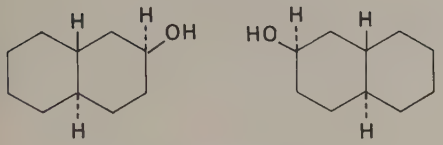
Because of the relatively stable conformation of polycyclic ring systems, they possess a degree of rigidity that imposes quite unambiguous configurations upon substituents present on the rings. The two *cis*-2-decalols (2-hydroxydecalins) and the two *trans*-2-decalols, for instance, have the following configurations. Note that each of these can exist in enantiomeric forms, making a total of eight (two (±)-*cis*-2-decalols and two (±)-*trans*-2-decalols):



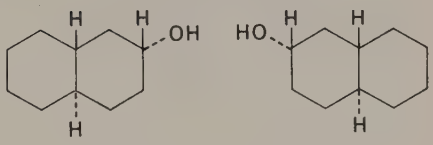
(±)-*cis*-2β-decalol (A)



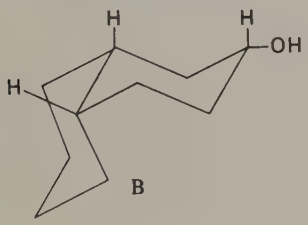
(±)-*cis*-2α-decalol (B)



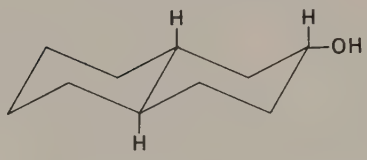
(±)-*trans*-2β-decalol (C)



(±)-*trans*-2α-decalol (D)



B



D

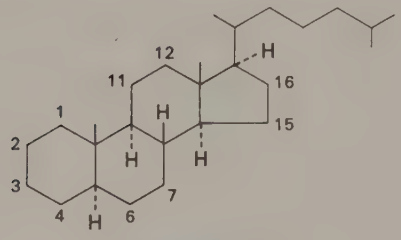
Exercise 4

Treatment of an alcohol such as one of the decalols with hot alcoholic sodium alkoxide may convert it into a mixture of epimers, the more stable epimer largely predominating. Of the alcohols A, B, C, and D, which would you expect to epimerize with such treatment and which would retain unchanged its configuration at >CHOH?

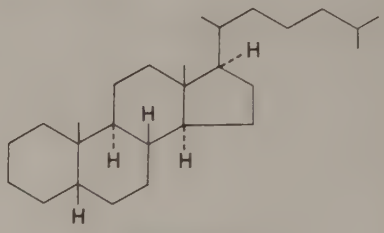
27-8 Designation of configuration. α and β orientation

The stereoisomeric forms of polycyclic compounds carrying substituent groups can be named by using the RS convention for all asymmetric centers, but in complicated systems this method is sometimes awkward or lacking in ready comprehensibility. When the absolute configuration of the whole system is known (or when this can be made an arbitrary assumption by fixing one center of asymmetry), a simpler system is widely used. The commonest of such polycyclic systems are those of the steroids. One basic steroid ring system, cholestane, has the configuration commonly drawn below

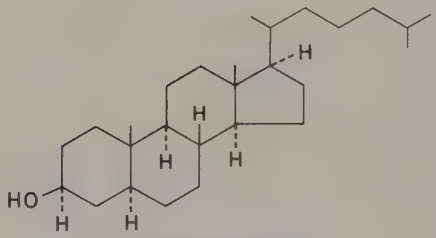
as A. Substituents above the plane of the molecule as drawn in this way are designated β; those below, α. Thus B is cholestan-3β-ol. Compound C is the A/B-*cis*-fused coprostane, and D is coprostan-3α-ol. Other examples are shown in the following:



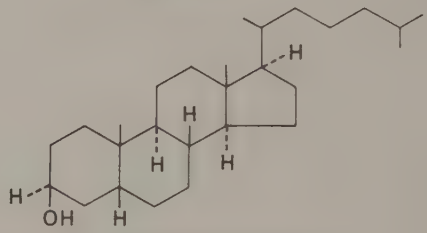
Cholestane (A)



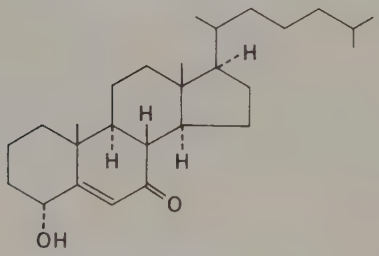
Coprostane (C)



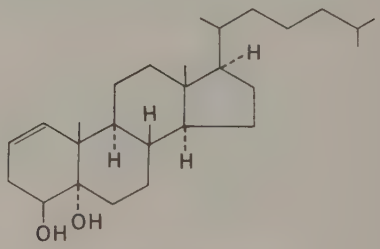
Cholestan-3β-ol (B)



Coprostan-3α-ol (D)



Cholest-5-en-4α-ol-7-one



Cholest-2-en-4β5α-diol

Exercise 5

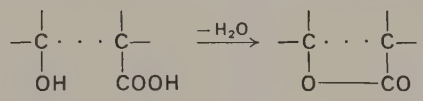
Draw these compounds in conformational notation.

Exercise 6

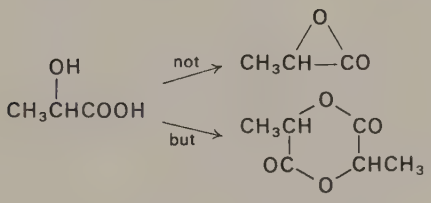
Draw the structures of (*a*) cholest-4-en-3β-ol, (*b*) cholest-1,4-dien-3-one, (*c*) 7α-chlorocholestan-3α-ol, (*d*) cholestan-3α,7α-diol-1-one, and (*e*) cholestan-3β-ol-11-one.

27-9 Lactones

Lactones are cyclic esters formed by the interaction of a carboxyl group and a hydroxyl group in the same molecule (32). Although 3- and 4-membered ring lactones are known, they are uncommon because of their ready ring opening by hydrolysis and because under the experimental conditions used for lactone formation by ring-closure of α- and β-hydroxy acids their precursors react in other ways. Attempts to form the 3-membered lactone from lactic acid lead to the 6-membered dilactone (33); and the β-hydroxy acids that would give 4-membered lactones are readily dehydrated (34):

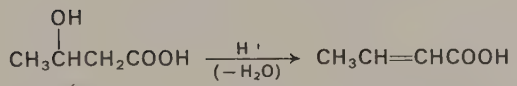


(32)



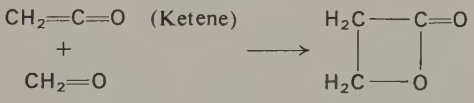
"Lactide"

(33)



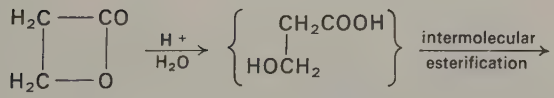
(34)

When β lactones are formed, by special means, they prove to be very reactive compounds. The high degree of angle strain in the 4-membered ring predisposes it to rapid ring-opening reactions. β-Propiolactone, formed by the addition of formaldehyde to ketene, reacts vigorously with strong acids to give a linear polymeric ester, and with nucleophilic reagents to give β-substituted propionic acids:



β-propiolactone

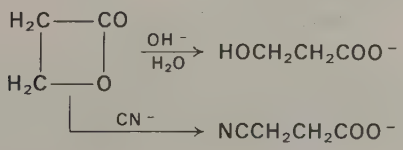
(35)



$$HOCH_2CH_2CO{-}O{-}(CH_2CH_2CO{-}O)_n{-}CH_2CH_2COOH$$

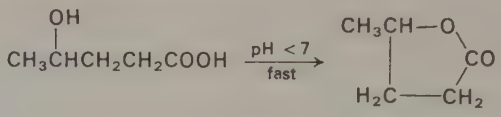
A polymeric ester

(36)



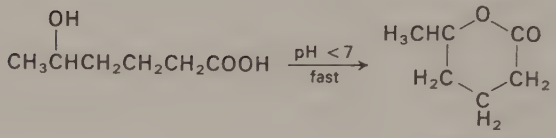
(37)

The formation of 5- and 6-membered lactones (usually called γ and δ lactones, respectively) occurs with such ease that the corresponding hydroxy acids often lactonize spontaneously in solutions at low pH:



(38)

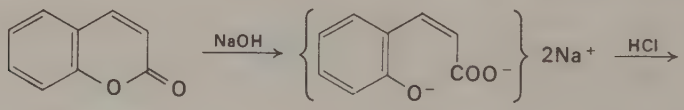
A γ-lactone



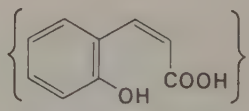
(39)

A δ-lactone

In some cases, when the configurational requirements are ideal, the free hydroxy acid is unknown in the free form, as it lactonizes immediately when the sodium salt is neutralized. The hydroxy acid corresponding to the lactone *coumarin* is an example:



Coumarin



(40)

Not isolable, re-forms lactone at once

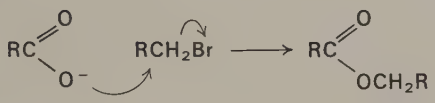
The rapid ring closure of, say, γ-hydroxybutyric acid to give the γ lactone is in contrast to the relatively slower *intermolecular* esterification of an alcohol and an aliphatic acid. In the latter (acyclic) case an important factor affecting the reaction rate is the necessary decrease in entropy accompanying the change from random distribution of the reactants to the orientation necessary for interaction of the functional groups. In the hydroxy acid the reacting functions are already "ordered" into positions leading to reaction, and the decrease in entropy of the system upon cyclization is minimal. In the case of coumarin, in which the carboxyl group of the hydroxy acid is brought even closer to the hydroxyl group (because the substituents on the double bond are *cis*), the reaction is even faster.*

---

* It should be added that isomerization (in alkaline solution) of the *cis*-hydroxy acid, derived by ring-opening of coumarin, to the *trans*-hydroxy acid makes lactone formation sterically impossible, and acidification yields the free phenolic acid (*trans-o*-hydroxycinnamic acid).

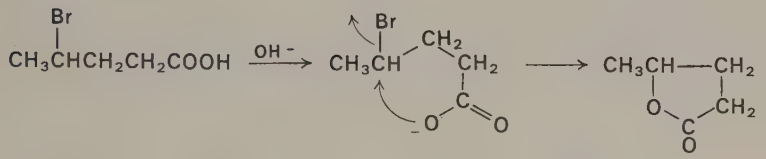
Lactone formation by *intramolecular* nucleophilic displacement of halogen by attack of the carboxylate anion is analogous to esterification by a similar *intermolecular* process:

Intermolecular

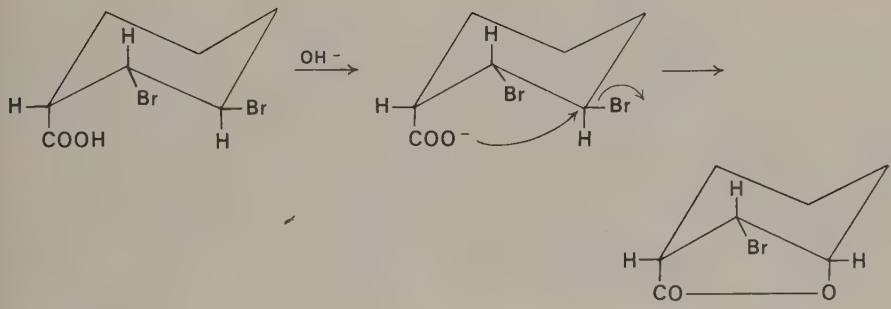


(41)

Intramolecular



(42)



(43)

Note that in this reaction, as in other nucleophilic displacement reactions of the S_N2 type, inversion of configuration occurs at the carbon atom from which the halogen is displaced.

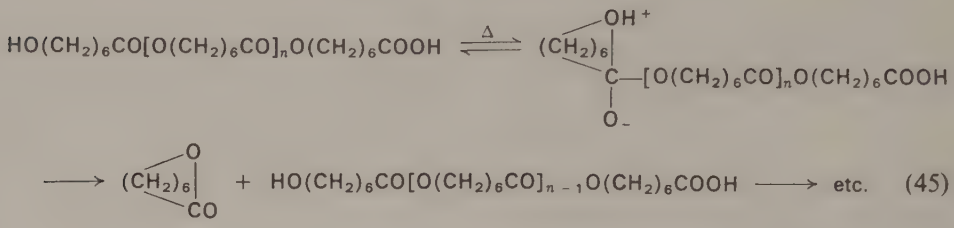
27-10 Macrocyclic lactones

Attempted acid-catalyzed cyclization of 7-hydroxyheptanoic acid, with a view to preparing the 8-membered cyclic lactone, does not succeed; instead, an intermolecular esterification gives the polymeric ester:

$$HO(CH_2)_6COOH \longrightarrow HO(CH_2)_6COO(CH_2)_6CO[O(CH_2)_6CO]_nO(CH_2)_6COOH \quad (44)$$

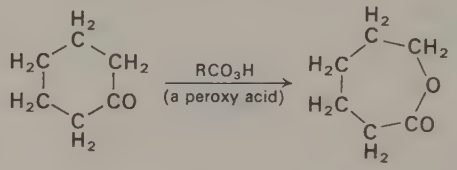
If, however, this linear polymeric ester is heated under reduced pressure at a temperature above the boiling point of the monomeric lactone, *intramolecular ester interchange* occurs slowly; the cyclic lactone formed in the equilibrium interchange

reaction volatilizes from the reaction mixture and can be recovered as a distillate of the pure 8-membered cyclic lactone:



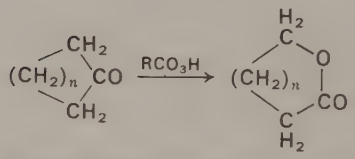
(45)

The most useful method of preparing macrocyclic lactones is by way of the intramolecular oxidative ring expansion known as the *Baeyer-Villiger* reaction. This reaction, shown here in summary form, is discussed in detail in Section 34-7 and should be referred to there.



(46)

In general



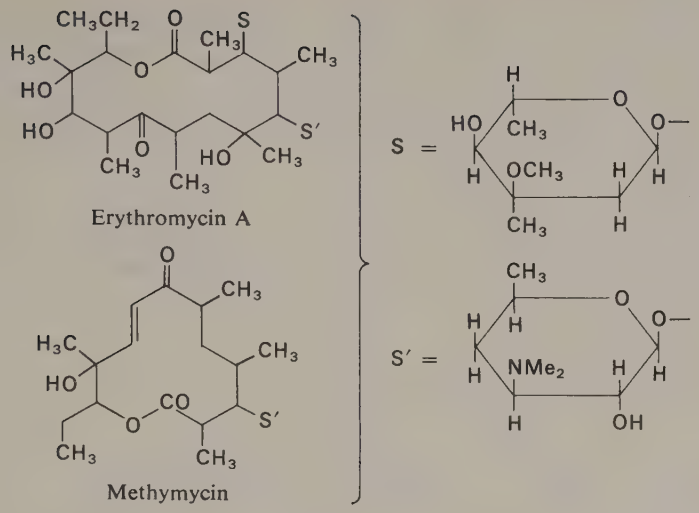
(47)

The Baeyer-Villiger synthesis of lactones

27-11 Macrolides

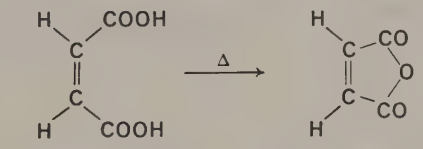
An important class of naturally occurring antibiotic compounds is composed of macrocyclic lactones of 12- to 17-membered rings. Two representative compounds are *erythromycin A* and *methymycin*. Certain of these lactones, known as *macrolides*, are clinically valuable antibiotic drugs; erythromycin is widely used in the therapy of infectious diseases of bacterial origin.

It is likely that the biological ring-closure reaction by which these large-ring compounds are formed is not the energetically improbable lactonization of the free open-chain hydroxy acid. Since these compounds are the metabolic products of living organisms (*Streptomyces*), and thus are synthesized under enzymatic catalysis, it is probable that one of the functions of the enzyme is to provide a specific binding site at which the hydroxyl and carboxyl groups are fixed in close proximity prior to the intramolecular esterification reaction.

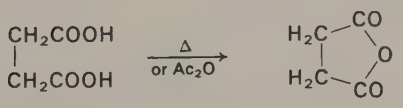


27-12 Cyclic acid anhydrides

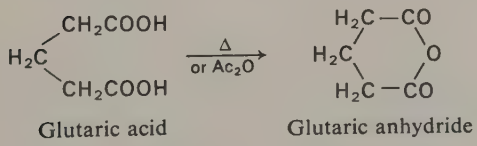
Dicarboxylic acids in which the two carboxyl groups are disposed in a 1,4 or 1,5 relationship are readily converted to the corresponding 5- or 6-membered cyclic anhydrides by heating or by treatment with acetyl chloride or acetic anhydride:



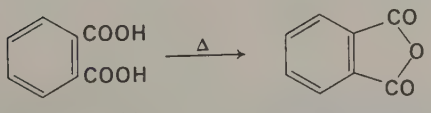
(48)



(49)



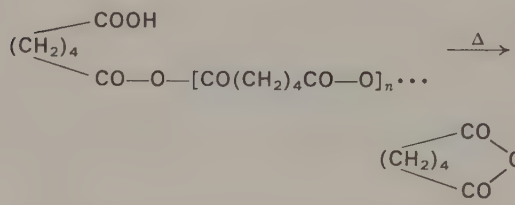
(50)



(51)

The cyclic anhydride of adipic acid is a seven-membered cyclic compound; it is not formed by the heating of adipic acid or by the reaction of adipic acid with acetic anhydride. Instead, a polymeric anhydride, $HOOC(CH_2)_4COO[CO(CH_2)_4COO]_n$-$CO(CH_2)_4COOH$, is formed. Higher dicarboxylic acids (pimelic, suberic, and so on) behave similarly.

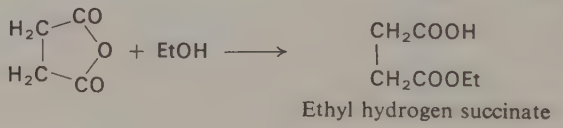
The polymeric linear anhydride can be converted into the monomeric cyclic anhydride by heating it under reduced pressure and allowing the monomer to distill; the process may be regarded as an anhydride-interchange reaction:



(52)

This conversion of the polymeric linear anhydride into the monomer is comparable to the conversion of a polymeric ester into a lactone (Section 27-10).

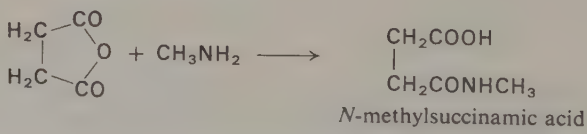
Cyclic anhydrides are useful intermediates in many synthetic procedures. They react with alcohols to yield mono-esters of the corresponding dicarboxylic acids:



Ethyl hydrogen succinate

(53)

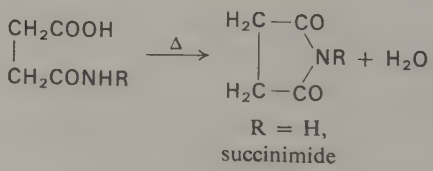
and with amines to form mono-amides:



N-methylsuccinamic acid

(54)

The mono-amides of ammonia and primary amines cyclize upon heating to yield cyclic imides:

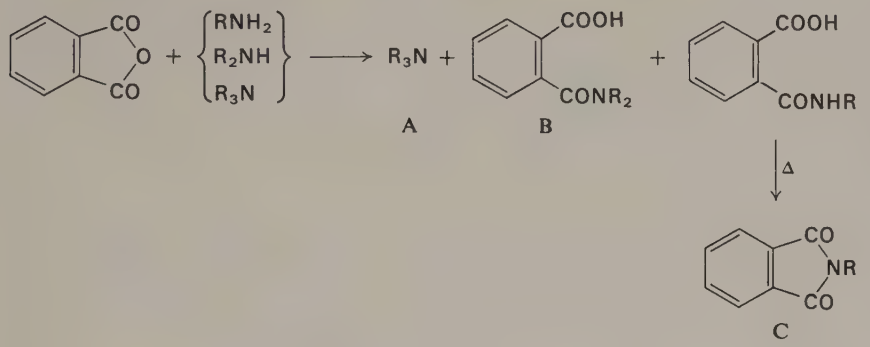


R = H, succinimide

(55)

These reactions of cyclic anhydrides with amines provide a useful method for characterizing and identifying amines, and for separating mixtures of primary,

secondary, and tertiary amines. Using phthalic anhydride as a typical reagent, the procedure is the following:*



(56)

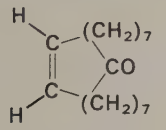
The tertiary amine (A) does not react with the anhydride and can be recovered by extraction with acid.

The secondary phthalamic acid (B) does not cyclize on heating and can be removed by extraction with alkali.

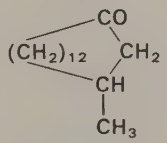
The *N*-substituted phthalimide (C) is a neutral compound, insoluble in both aqueous acid and alkali.

27-13 Naturally occurring macrocyclic compounds

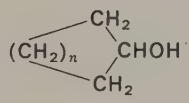
A number of large-ring ketones and lactones occur in natural sources. The macrocyclic ketones muscone and civetone are found in scent glands of the musk deer and the civet cat, respectively. These, along with a group of macrocyclic alcohols found in the scent glands of the muskrat and some allied compounds occurring in plants have the following structures:†



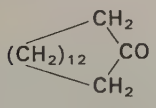
Civetone
(Civet cat)



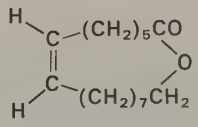
Muscone
(Musk deer)



n = 10, 12, 14, 16
(Muskrat)



From root of *Angelica* spp.



Ambrettolide
(Ambrette seed; *Hibiscus* spp.)

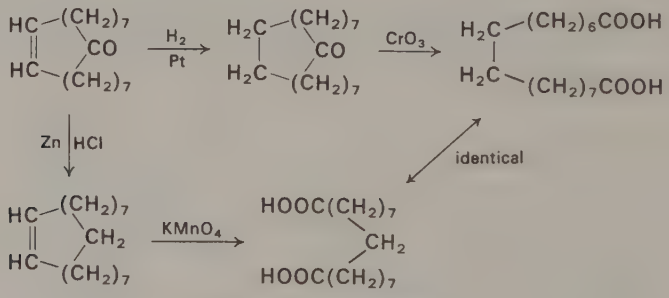
* In the practical application of this method the actual reagent used is 3-nitrophthalic anhydride, the derivatives of which are more readily separated and undergo the reactions described more readily.

† Note the ending "-olide" (macrolide, ambrettolide). This suffix is often used to denote the lactonic character of a compound.

All of these compounds, as well as many synthetic substances of similar structure, have characteristic musky odors. They are important articles of commerce, used in the perfume industry as bases for the compounding of perfumes, in which they serve to increase the diffusiveness, tenacity, and persistence of the scent. Because of the commercial importance of these compounds much study has been devoted to their chemistry. Indeed, the first fundamental studies in the formation and properties of large-ring compounds were motivated by the discovery that civetone and muscone were compounds of this class.

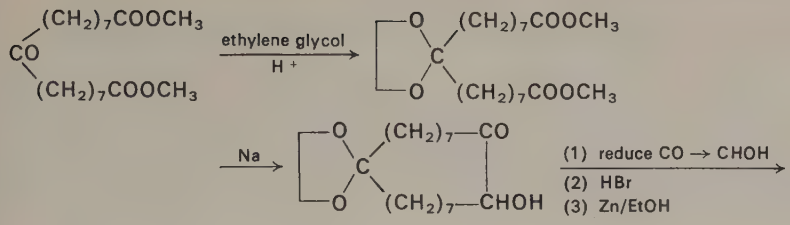
The original proof of the structures of these compounds depended upon degradative procedures, followed by total synthesis, which acquired special significance when it was discovered that structurally similar macrocyclic compounds (large-ring ketones) prepared by synthetic means also had musk-like odors and could be used instead of the more costly natural materials.

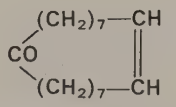
Civetone ($C_{17}H_{30}O$) was catalytically hydrogenated to dihydrocivetone ($C_{17}H_{32}O$), a saturated ketone. Chromic acid oxidation of dihydrocivetone gave a dicarboxylic acid, heptadecanedioic acid, while oxidation of civetone itself yielded no dicarboxylic acid larger than nonanedioic acid. Clemmensen reduction (Zn, HCl) of civetone converted —CO— into —CH_2—, giving the unsaturated hydrocarbon civetene. Oxidation of civetene with cleavage at the double bond also gave heptadecanedioic acid. These observations can all be accommodated by the structure shown for civetone:



Structure proof for civetone

The synthesis of civetone was accomplished by using the *acyloin condensation* (Equations (24) and (25), Section 27-3) to form the macrocyclic ring, with prior protection of the carbonyl group (which would otherwise react with the sodium used in the acyloin condensation step) by cyclic ketal formation (Eq. 58). Because of the flexibility of so large a ring, both *cis* and *trans* arrangements of the carbon-carbon double bond are possible. Both of these are known; the *cis* isomer is identical with natural civetone.



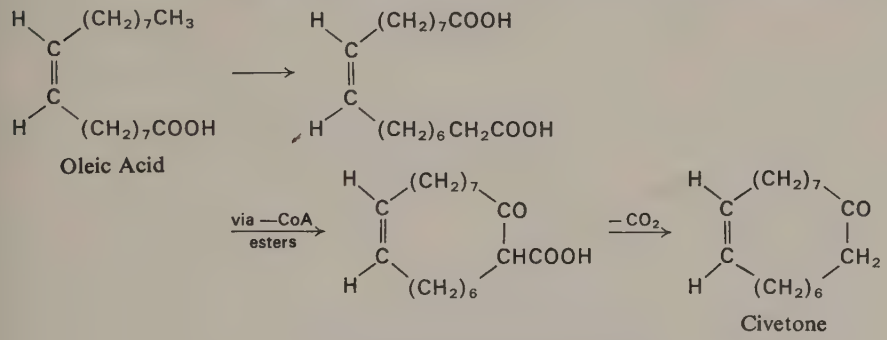


(58)

Mixture of *cis* civetone (natural) and *trans*-civetone

Synthesis of civetone

The unmistakable similarity between oleic acid (*cis*-9-octadecenoic acid) and the civetone molecule offers the compelling suggestion that civetone is biosynthesized from that acid. A suggested course for the biosynthesis is the following:



(59)

Suggested biosynthesis of civetone

Exercise 7

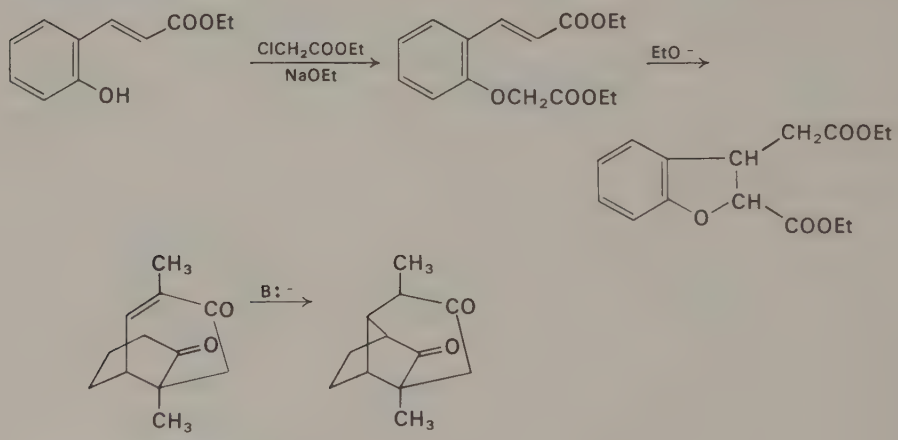
It has been suggested (but not established) that the biosynthesis of muscone starts with stearic acid, and involves (*a*) a terminal oxidation of $—CH_3$ to —COOH, followed by (*b*) two β-oxidations of the resulting 1,18-dicarboxylic acid. Complete a possible course of the biosynthesis of muscone, using these and any other necessary steps. Note that muscone is $C_{16}H_{30}O$; stearic acid is $C_{18}H_{36}O_2$.

27-14 Cyclization by intramolecular condensations of the aldol type

Intramolecular aldolization between carbonyl groups and active methylene groups has been discussed in Chapter 21. Further examples are found in sections to follow. The mechanistically related intramolecular Claisen condensations (Dieckmann reaction) are also dealt with elsewhere.

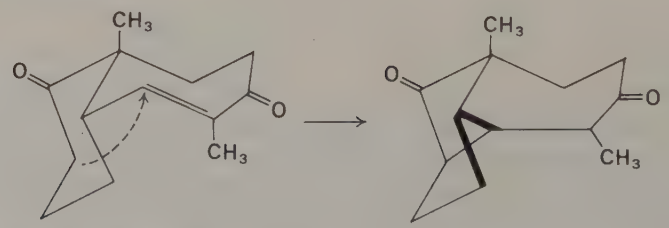
27-15 Ring formation by intramolecular Mannich and Michael reactions

Michael reactions. When the C=C—C=O grouping and an anionic carbon atom are present in the same molecule, and are suitably disposed, *intramolecular* (cyclic) Michael addition can be accomplished. The following two examples illustrate this reaction:



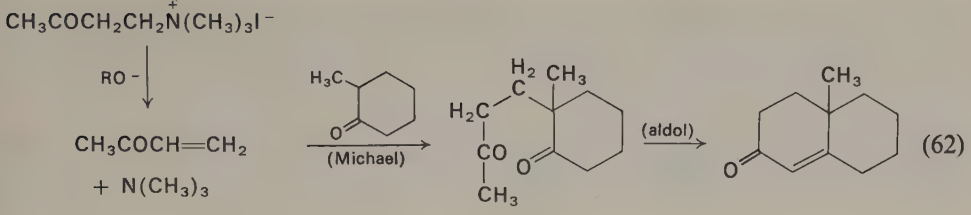
(60)

or, written in another way:



(61)

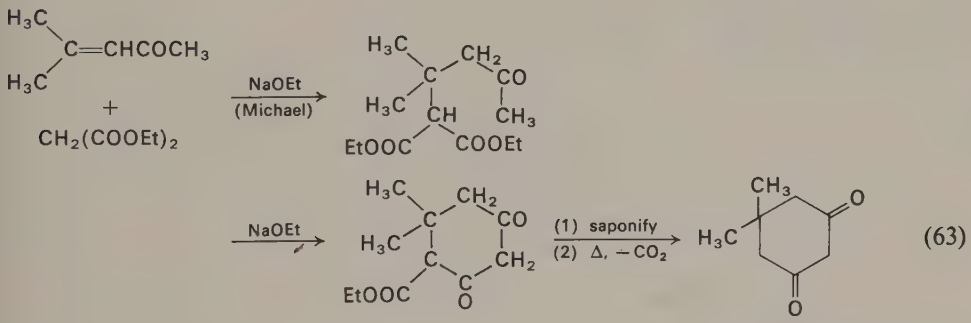
Michael addition reactions followed by ring closures provide a variety of synthetic routes to cyclic compounds. The Robinson-Mannich-base synthesis proceeds as follows:



(62)

The methyl vinyl ketone may be prepared and used separately, but its formation *in situ* by elimination of trimethylamine from the quaternary Mannich base gives better results.

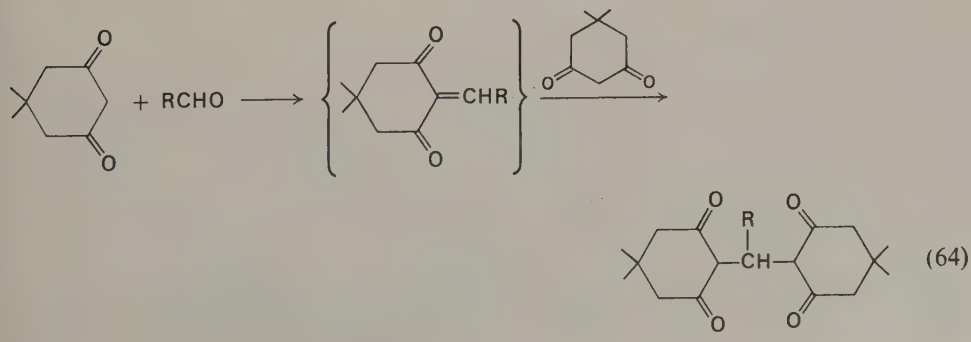
An acyclic Michael addition reaction followed by cyclization by an intramolecular ester condensation leads to a compound from which the useful reagent *dimedone* is prepared:



(63)

Dimedone

Dimedone is a valuable reagent for the preparation of crystalline derivatives of aldehydes. The dimedone derivative of formaldehyde is formed in quantitative yield, and thus the reaction affords a useful gravimetric method for the quantitative determination of formaldehyde.



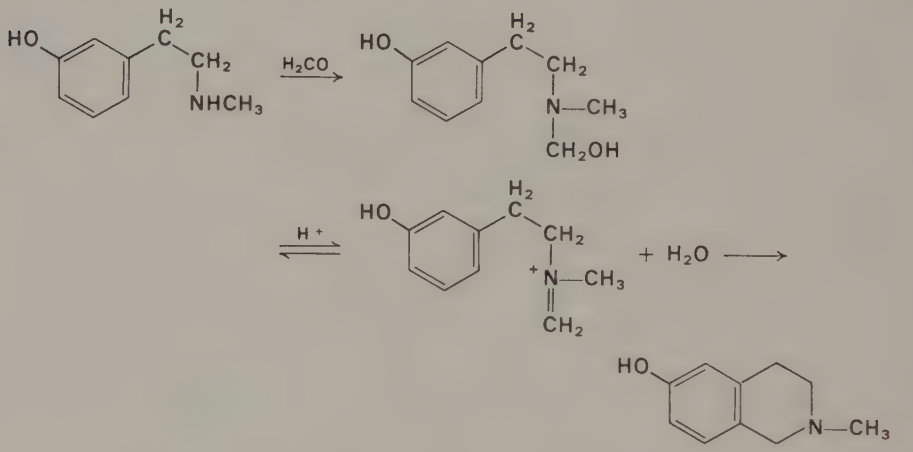
(64)

The reaction probably proceeds in two stages as shown: (1) the aldol condensation of the aldehyde with the active methylene group of dimedone, and (2) a Michael addition of a second molecule of dimedone.

Mannich reactions. The synthesis of cyclic compounds with the aid of the Mannich reaction can be accomplished in two ways:

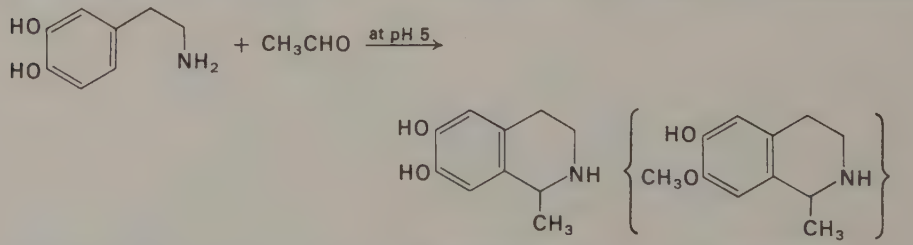
1. The ring closure reaction is itself the formation of the Mannich base (65)–(67).
2. A Mannich base is formed and undergoes cyclization as a second step (see the following section).

The first of these is most commonly encountered in reactions in which the carbanionic component is a phenol:



(65)

This cyclization procedure is of wide application, and proceeds satisfactorily with aldehydes other than formaldehyde itself, as well as with primary phenethylamines. It has been used as a synthetic route to a number of naturally occurring alkaloids of the tetrahydroisoquinoline group. An example is the synthesis of *O*-norsalsoline:



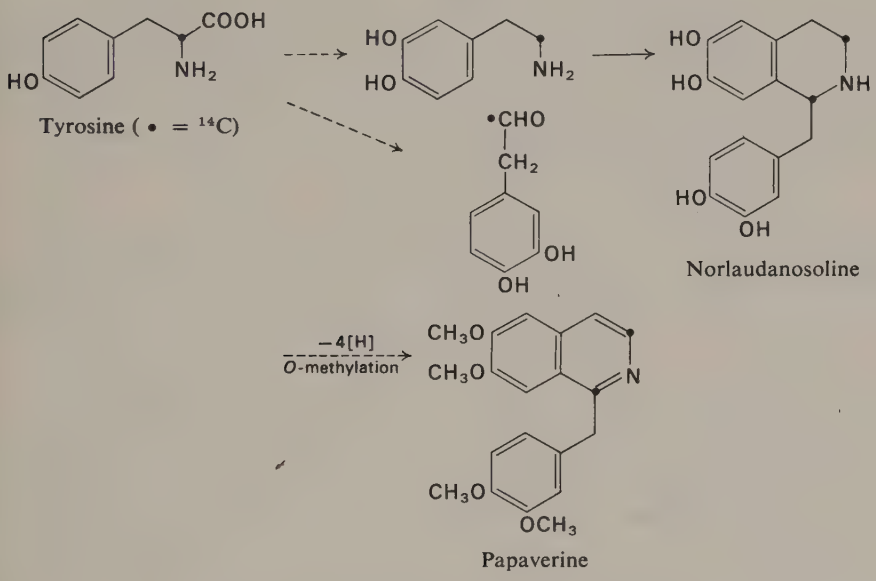
O-norsalsoline Salsoline

(66)

The success of this condensation under the mild conditions used (room temperature, pH 5) has caused it to be regarded as a laboratory model of the route by which

alkaloids of this class are synthesized in plants. It has been established by tracer experiments that the phenethylamine portion of natural isoquinoline alkaloids derives from the amino acids phenylalanine or tyrosine.

A somewhat more diverse and complex class of isoquinoline alkaloids, exemplified by one of the simplest, norlaudanosoline, also owe their origins in nature to Mannich reactions of this type. Experiments with isotopically labeled compounds indicate the following overall course of the natural synthesis:

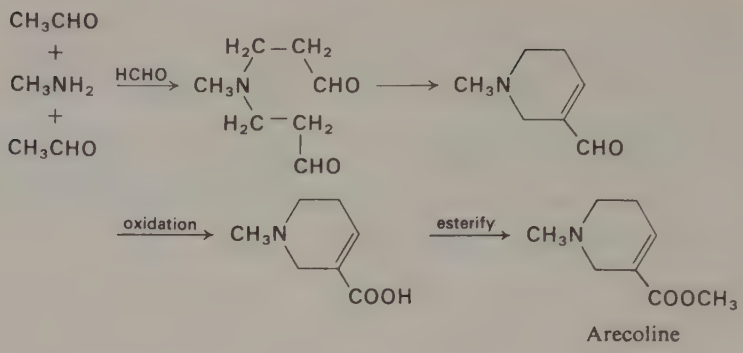


(67)

NOTE: The dashed arrows ---→ signify overall reactions occurring in the plant *Papaver somniferum*, the opium poppy, that are not relevant to the ring-closure reaction itself.

27-16 Aldol condensations in cyclization of Mannich bases

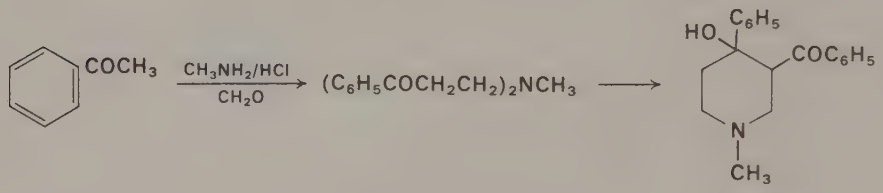
Many Mannich bases are ketones or aldehydes, and as such are capable of undergoing aldol condensations. A Mannich base derived from a primary amine H_2NR' and a ketone $RCOCH_3$ has the general structure $(RCOCH_2CH_2)_2NR'$. Intramolecular aldol condensations of compounds of this kind can lead to cyclic compounds, which, since the nitrogen atom is a part of the ring, are piperidine derivatives. The earliest of these was prepared by Mannich himself, and led to the synthesis of the alkaloid *arecoline*, the active principle of the betel nut (*Areca* species):



(68)

Arecoline

A reaction of the same kind is observed in the case of the Mannich base prepared from acetophenone, formaldehyde, and methylamine:



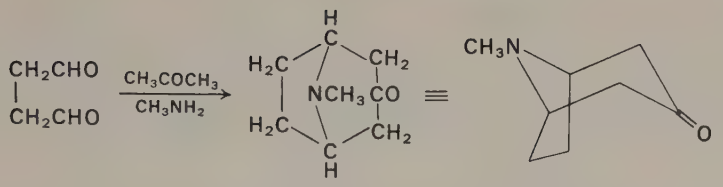
(69)

Exercise 8

When the cyclic aldol from $(C_6H_5COCH_2CH_2)_2NCH_3$ [in (69)] is dehydrated, the product is an unsaturated ketone that is *not* the α,β-unsaturated ketone. What is its structure and why is it formed instead of the α,β-unsaturated ketone?

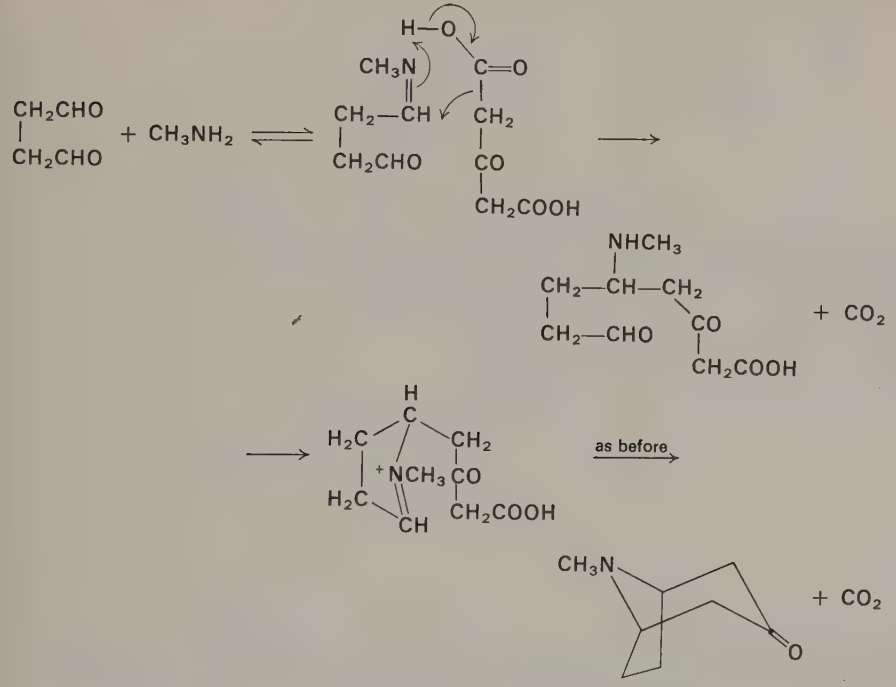
27-17 Bicyclic compounds by Mannich reactions

The base-catalyzed Mannich condensation of succinic dialdehyde, methylamine, and acetone results in the formation of the bicyclic Mannich base tropinone shown in Eq. (70). The same product is formed much more readily and under milder conditions (room temperature) if acetonedicarboxylic acid is used instead of acetone. At intermediate pH the condensation proceeds with concomitant loss of CO_2 to give the same product,



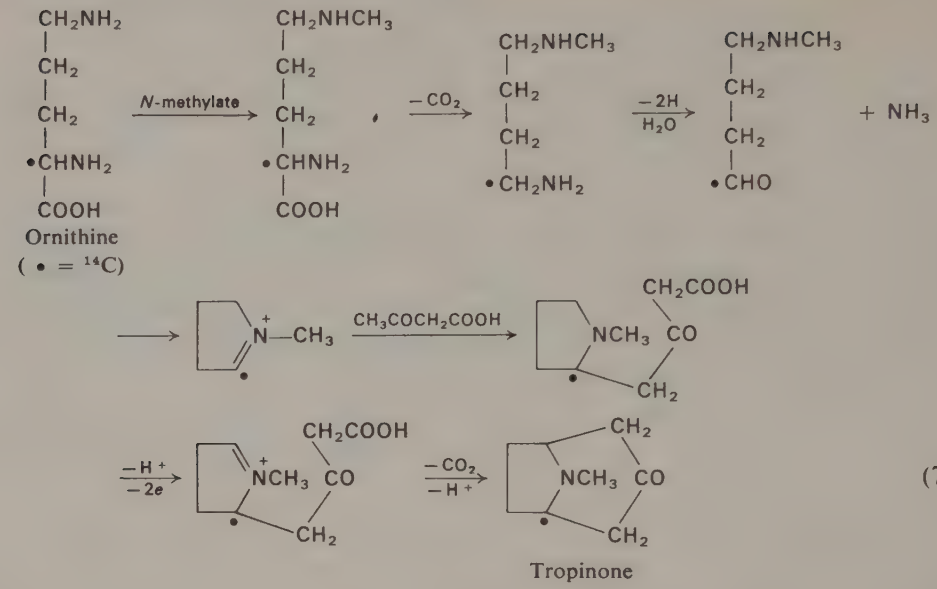
(70)

tropinone; at high pH (12–13) the product is tropinone dicarboxylic acid. It is evident that the —CH_2— group in HOOC—CH_2—CO— is a much more active methylene group than that in acetone, H—CH_2—CO—. The precise point in the condensation at which CO_2 is lost is not known with certainty, but it is probable that at intermediate pH the decarboxylation and condensation are concerted:



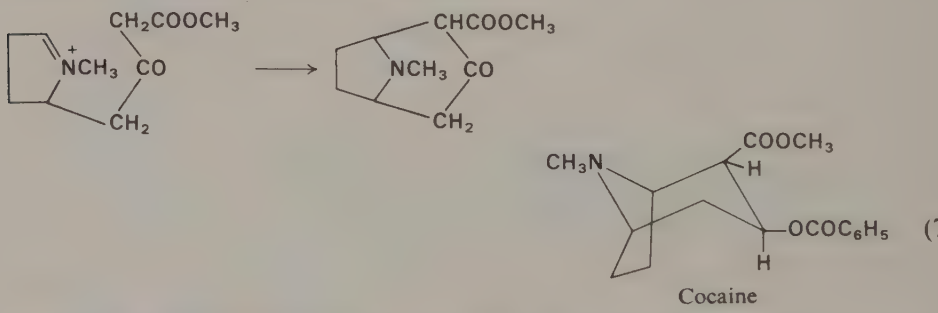
(71)

Tropinone is the ketone corresponding to tropine, the amino alcohol that, in esterified form, occurs in a number of important alkaloids, among them atropine (Section 16-2). The synthesis of tropinone shown above was once regarded as the *in vitro* model of the actual biosynthetic reaction. This concept gave rise to a general theory of alkaloid biosynthesis, to which the above synthesis of tropinone corresponds closely, although it differs in detail. The synthesis of the tropine ring system in a living plant can be formulated as follows; this scheme is supported by evidence from isotope-labeling experiments:



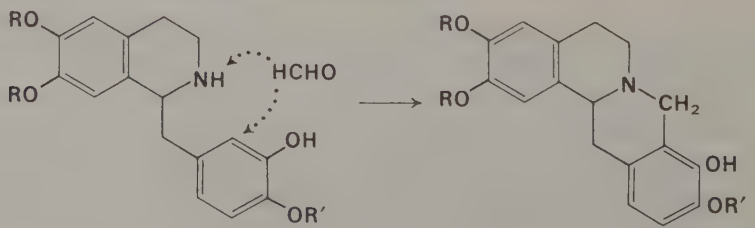
(72)

If the keto acid that participates in the final step of this sequence is present as the methyl ester, decarboxylation cannot occur and the ring system formed is that of cocaine, in which the $—COOCH_3$ is present:



(73)

A final example will illustrate yet another Mannich reaction used in the synthesis of the ring system of another class of alkaloids:



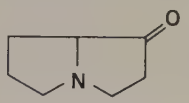
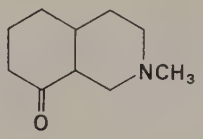
(74)

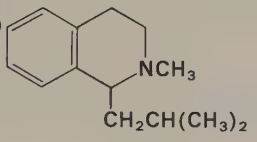
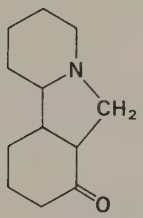
$R = CH_3$, $R' = OCH_2C_6H_5$

Dotted arrows indicate reaction centers for Mannich condensation.

Exercise 9

Each of the following compounds can be synthesized by reactions in which a Mannich condensation is the final step. In each case, write the equation for this last reaction (assume you have the necessary precursor).

(*a*) $(CH_3)_2NCH_2C{\equiv}CCH_3$ (*b*)  (*c*) 

(*d*)  (*e*) 

27-18 Cyclization by carbon alkylation

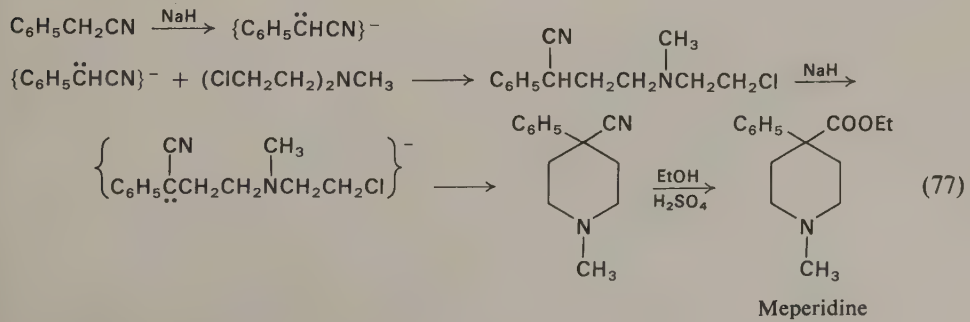
Carbon alkylation by the reaction of a carbanion with an alkyl halide has been described in the section on syntheses with acetoacetic ester and malonic ester. The use of this reaction for the formation of cyclic compounds has been illustrated there (Section 24-10).

Alkylation of carbanions derived by the removal of α hydrogen atoms activated by the cyano group proceeds according to the general reaction

$$RCH_2CN \underset{}{\overset{B:^-}{\rightleftharpoons}} \{R\ddot{C}HCN\}^- + B{:}H \qquad (75)$$

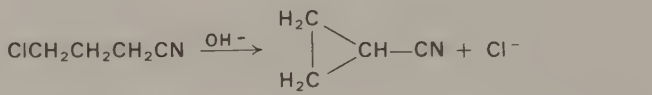
$$\{R\ddot{C}HCN\}^- + R'X \longrightarrow \underset{R'}{\overset{|}{R}}CHCN + X^- \qquad (76)$$

One example of a cyclization reaction of this kind is the first step in the synthesis of the important analgesic drug Demerol (meperidine); this is a di-alkylation reaction:

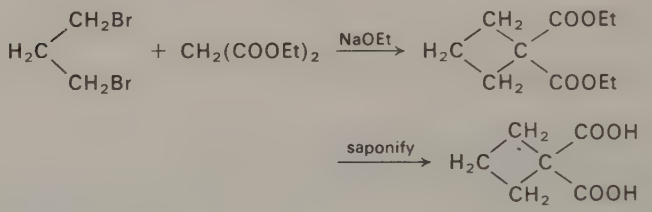


(77)

It will be noted that in cyclic carbon-alkylation reactions the carbon-carbon bond formation is substantially irreversible, for ring-opening to return to the reactants would require the unlikely attack by the poorly nucleophilic halide ion, with heterolytic cleavage of the C—C bond. Because of this irreversibility, cyclic carbon alkylation reactions leading to 3- and 4-membered rings can be accomplished in satisfactory yields. For example, cyclopropanecarboxylic acid can be obtained in about 75% yield by base-catalyzed cyclization of γ-chlorobutyronitrile followed by hydrolysis of the intermediate cyclopropyl cyanide. Cyclobutane-1,1-dicarboxylic acid, from the cyclic dialkylation of malonic ester with 1,3-dibromopropane, can be prepared in yields of about 25%.



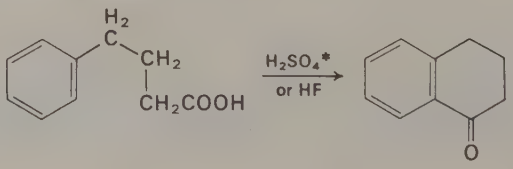
(78)



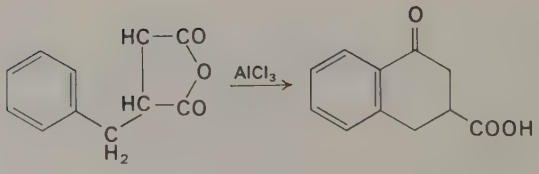
(79)

27-19 Cyclization by electrophilic aromatic substitution

The acylation of aromatic nuclei by the Friedel-Crafts and related reactions (Chapter 28) can be used to prepare cyclic ketones possessing 5- and 6-membered (and, less satisfactorily, 7-membered) rings:

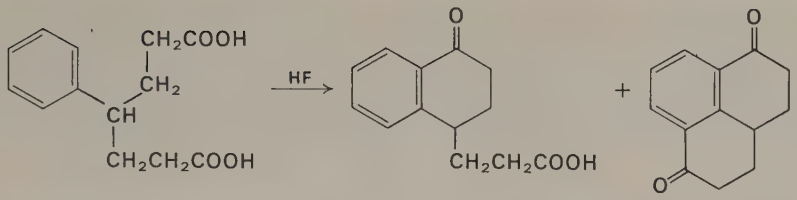


(80)



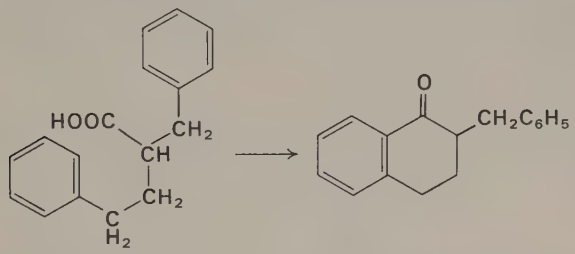
(81)

* Or via the acid chloride and $AlCl_3$.

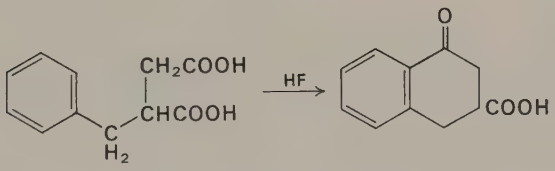


(82)

Experiments have shown that if a ring closure of this kind can lead to either a 5-membered or a 6-membered ring, the latter is preferred:

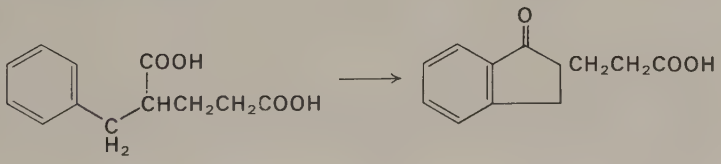


(no hydrindone) (83)



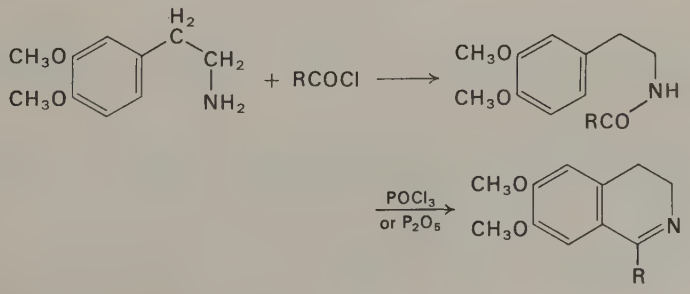
(84)

However, when the alternatives are a 5-membered and a 7-membered ring ketone, none of the latter is formed:



(85)

Heterocyclic ring closures related to cyclizations of the Friedel-Crafts type include the Mannich reaction and the *Bischler-Napieralski reaction*, of which the following is an example:



(86)

When R is 3,4-dimethoxybenzyl, the final product shown in the equation is 3,4-dihydropapaverine. This is readily dehydrogenated by heating with palladium-charcoal to yield *papaverine*, an important alkaloid of plants of the poppy family. Papaverine (hydrochloride) is used clinically as a smooth-muscle relaxant.

Exercise 10

Formulate a reasonable course for the Bischler-Napieralski reaction, using $POCl_3$ as the reagent and regarding the ring-closure step as an electrophilic aromatic substitution reaction.

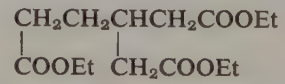
Problems

1. Write the structures of (*a*) 1,3-cyclohexadiene, (*b*) *trans*-1,3-dimethylcyclobutane, (*c*) cyclononane, (*d*) 1,3,5,7-cyclooctatetraene, (*e*) dioxane, (*f*) dioxadiene, (*g*) bicyclohexyl, (*h*) 3-bromocyclohexene, and (*i*) *cis*-cyclopropanedicarboxylic acid.

2. Using examples not described in the text, show the formation of a cyclic compound by the use of each of the following: (*a*) an aldol condensation, (*b*) the debromination of a 1,2-dibromo compound with zinc, (*c*) an ester (Claisen) condensation, (*d*) a malonic ester synthesis, (*e*) an acetoacetic ester synthesis, (*f*) lactonization of a bromo acid, (*g*) a pinacol reduction.

3. Draw conformational structures for the most stable forms of (*a*) chlorocyclohexane, (*b*) *trans*-1,4-dimethylcyclohexane, (*c*) *trans*-decalin, and (*d*) *cis*-1,3-dibromocyclohexane.

4. What product or products would you expect from the Dieckmann ring closure of the following?



5. Treatment of $CH_2{=}CHCH_2CH_2COOH$ with aqueous mineral acid causes it to isomerize to a neutral compound. Formulate the reaction, showing the intermediate stages.

6. When *optically active* cyclopentane-1,2-dicarboxylic acid is transformed by strong heating into its anhydride, the latter is *optically inactive*. Formulate the reaction and account for the stereochemical result.

7. Write the structures of the dimedone derivatives of (*a*) acetaldehyde, (*b*) isobutyraldehyde, and (*c*) methanal.

8. The product of the Michael addition of nitroethane to ethyl acrylate is a diester (A) of the composition $C_{12}H_{21}NO_6$. When this compound is reduced (catalytically) and the product heated, there is formed a neutral compound (B), $C_8H_{11}NO_2$. Reduction of B with lithium aluminum hydride gives C, $C_8H_{15}N$. Compound C is a tertiary amine and contains no carbon-carbon unsaturation. Formulate this series of reactions.

9. Devise a practical synthesis of the lactone of 7-hydroxyheptanoic acid, starting from cyclohexanone. NOTE: The first step is the ring enlargement of cyclohexanone to cycloheptanone. See Section 20-5.

28

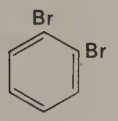
Substitution products of benzene. The electrophilic aromatic substitution reaction

This chapter and the one following deal with the electrophilic aromatic substitution reaction, of central importance in organic chemistry. The subject is divided into two chapters to make it possible to direct separate emphasis to the three principal aspects of the reaction: (1) the mechanistic interpretation of the reaction itself, (2) the effect of substituents upon the rate of the reaction, and (3) the factors that affect the position at which the incoming substituent enters the ring.

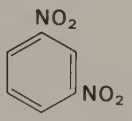
The electrophilic aromatic substitution reaction affords a means of synthesizing an almost limitless variety of organic compounds. As will be seen in chapters to follow, substituents introduced by direct nitration, acylation, halogenation, and so on can be modified further: nitro groups to amino groups, acyl compounds into carboxylic acids, and so on. The variety of the substituents that can be introduced by direct substitution is shown in Table 28-1, at the end of this chapter. A study of this table with an understanding of the mechanism of the fundamental reaction will make clear how wide a diversity of substitution reactions can be considered expressions of one central principle.

28-1 Terminology and nomenclature

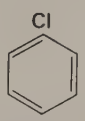
Disubstituted benzenes are usually named with the prefixes *ortho* (*o*), meta (*m*), and *para* (*p*) for the 1,2-, 1,3-, and 1,4-disubstituted compounds, respectively. For example:



o-dibromobenzene

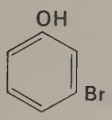


m-dinitrobenzene

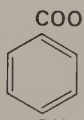


p-dichlorobenzene

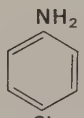
When the name is derived from that of a compound known by a common, or trivial, name, the same prefixes are used:



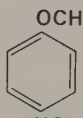
m-bromophenol



p-hydroxybenzoic acid

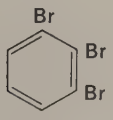


p-chloroaniline

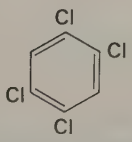


p-nitroanisole

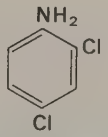
The prefixes *o*, *m*, and *p* are not used for tri- and poly-substituted benzenes. In these cases the substituents are numbered; and when the compound is a derivative of one bearing a common name, the number 1 is given to the substituent that characterizes the parent compound:



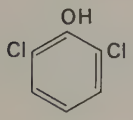
1,2,3-tribromobenzene



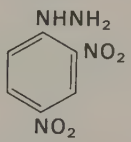
1,2,4,5-tetrachlorobenzene



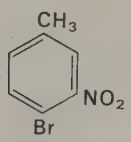
2,4-dichloroaniline



2,6-dichlorophenol



2,4-dinitrophenylhydrazine



4-bromo-3-nitrotoluene

Further discussion of the naming of aromatic compounds will be found in Appendix A. Most of the compounds found in the text will be named, and the student can best gain facility in naming by observing closely how a name attached to a formula corresponds to the appurtenant structure.

28-2 Orientation in the benzene ring

The word "orientation" refers to the relative positions of the substituents on the benzene ring. When a second substituent is introduced into a benzene ring, the directive influence of the first substituent upon the position that will be occupied by the incoming group is termed its *orienting* effect. Thus, we speak of groups as being *meta*-orienting, *para*-orienting, or *ortho*-orienting; or, more commonly, *meta*-directing, and so on.

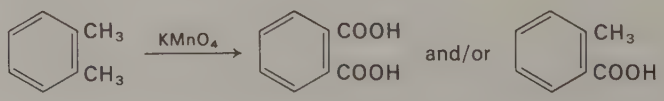
In the latter part of the nineteenth century, before many organic compounds were known, orientation of new polysubstituted benzene derivatives was established by what is called an *absolute* method. Consider the three dibromobenzenes: 1,2-, 1,3-, and 1,4-. Suppose these are converted by bromination into tribromobenzenes. It is evident that the 1,2-dibromobenzene will yield two, the 1,3-dibromobenzene three, and the 1,4-dibromobenzene only one tribromobenzene. The success of this procedure depends, of course, upon the isolation and separation of *all* of the tribromo compounds that are formed. It can now be seen that from the results of these experiments it is possible to do two things: (1) to identify which of the starting dibromobenzenes is 1,2-, which is 1,3-, and which is 1,4-dibromobenzene; and (2) to establish the orientation of the three tribromobenzenes.

Exercise 1

Call the three dibromobenzenes A, B, and C. A gives three tribromobenzenes, D, E, and F; B gives D and E; and C gives only D. Write the structures of A, B, C, D, E, and F.

With the growing number of known benzene derivatives the necessity for the often arduous establishment of absolute orientation disappeared, and new compounds could be characterized by *relative* methods, in which the unknown was related to a compound of known orientation that was already established.

Suppose we have on hand the three dimethylbenzenes, *o*-, *m*-, and *p*-xylene, and that we know the identity of each. If *o*-xylene is oxidized with potassium permanganate it will yield, depending upon the vigor with which the oxidation is carried out, either *o*-methylbenzoic acid, benzene-*o*-dicarboxylic acid (phthalic acid), or a mixture of the two:

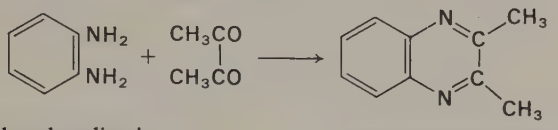


(1)

These two acids are now of known orientation. That phthalic acid is indeed the *ortho*-dicarboxylic acid can be confirmed by the fact that upon heating it readily loses

water and is converted into the anhydride. Similar manipulations in which one substituent on a benzene ring is transformed into another (by various methods to be encountered in forthcoming discussions) permit establishment of the orientation of benzene derivatives of countless kinds.

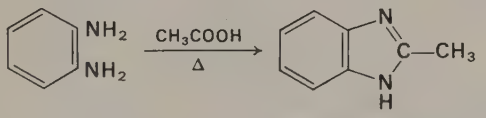
The distinction between an *ortho*-disubstituted compound and its *meta* and *para* isomers can often be made by using reactions that involve ring formation. For example, of the three diaminobenzenes, only the *ortho* isomer will react with a 1,2-diketone to yield the cyclic compound known as a quinoxaline:



(2)

o-phenylenediamine 2,3-dimethylquinoxaline

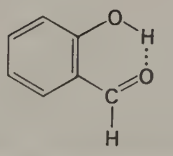
and with carboxylic acids to yield benzimidazoles:



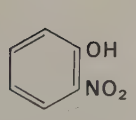
(3)

2-methylbenzimidazole

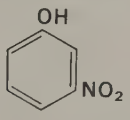
The steam-volatility of *o*-nitrophenol, salicylaldehyde, and *o*-hydroxyacetophenone is the consequence of intramolecular hydrogen-bond formation in these compounds. The corresponding *m*- and *p*-substituted compounds are not steam-volatile.



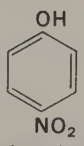
Hydrogen bonding in salicylaldehyde



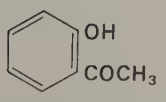
o-nitrophenol



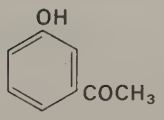
m-nitrophenol



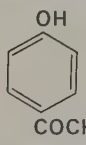
p-nitrophenol



o-hydroxyacetophenone



m-hydroxyacetophenone



p-hydroxyacetophenone

Steam-volatile Not steam-volatile

28-3 Substitution reactions

Although the term "substitution" can be used to describe any reaction in which one group is replaced by another, it is usual to limit the meaning of the term to the replacement of hydrogen.

Typical substitution reactions are halogenation, nitration, acylation, and alkylation, in which a hydrogen atom is replaced by a halogen atom, a nitro group, an acyl group, or an alkyl group.

Aliphatic substitution reactions, the replacement of hydrogen atoms of alkanes and cycloalkanes, are not generally useful in laboratory practice, although some industrial applications of them, which depend upon the availability of abundant and inexpensive starting materials, have practical importance.

Most substitution reactions of paraffin hydrocarbons proceed by free radical processes, the activation energy of which is supplied by heat or light. In the case of chlorination the initial step is the dissociation of the chlorine molecule into the atoms:

$$Cl_2 + \text{heat or light energy} \longrightarrow 2Cl\cdot \tag{4}$$

The highly reactive atomic chlorine attacks the hydrocarbon

$$\begin{aligned} Cl\cdot + HR &\longrightarrow HCl + R\cdot \\ R\cdot + Cl_2 &\longrightarrow RCl + Cl\cdot \end{aligned} \tag{5}$$

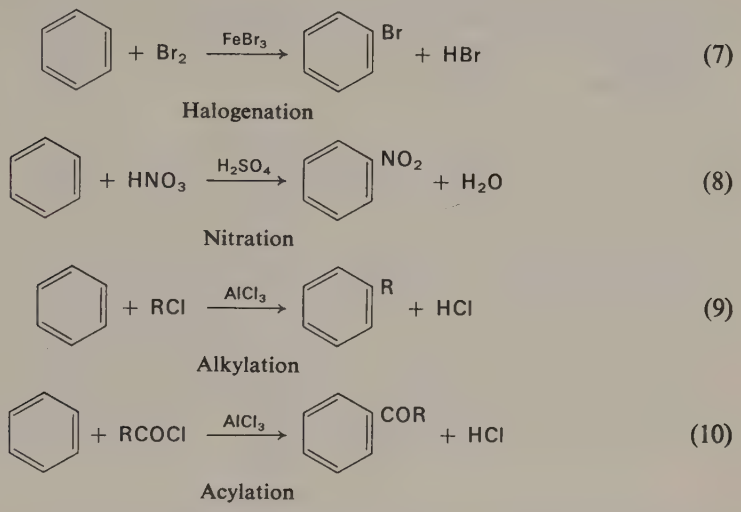
to yield the chloroalkane and a new chlorine atom, which can continue the process. This is a "chain reaction," and unless the free radicals (R·) or chlorine atoms are destroyed by some other process, a relatively few initial dissociations can lead to a great many substitution reactions. But because of the highly reactive nature of the chlorine atoms and other "free radicals," they show little discrimination in their attack upon a paraffin hydrocarbon, in which the individual CH_3 or CH_2 groups are nearly alike in character. Thus, reactions of this kind are apt to give rise to mixtures of monosubstituted and polysubstituted products. Halogenation of methane is practicable because the products, methyl chloride, dichloromethane, chloroform, and carbon tetrachloride, can easily be separated and isomerism is not possible.

Nitration of paraffin hydrocarbon is a commercial process; it takes place at high temperatures (vapor phase) and leads to mixtures of nitroparaffins, some of which arise by fission of carbon-carbon bonds:

$$CH_3CH_2CH_3 \xrightarrow[400^\circ]{HNO_3} CH_3CH_2CH_2NO_2 + (CH_3)_2CHNO_2 + CH_3CH_2NO_2 + CH_3NO_2 \tag{6}$$

Aromatic substitution reactions, however, take place by a quite different mechanism, and proceed under mild and controllable conditions to yield either monosubstituted products or polysubstituted products of predictable orientation.

Four characteristic aromatic substitution reactions will be described in detail in this chapter:



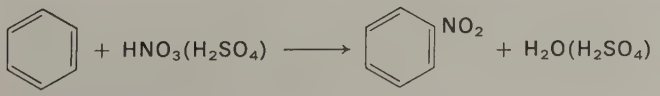
Many other reactions, mechanistically closely allied to these, are known and will be dealt with briefly; a summary is given in Section 28-6.

It should be noted that in each of (7)–(10) there is present, besides the reagent from which the substituent is derived, an additional reagent ($FeBr_3$, H_2SO_4, $AlCl_3$). This reagent is a strong mineral acid or a Lewis acid, and will be seen to play an essential catalytic role in the substitution reaction.

Nitration, halogenation, and so on are *electrophilic substitution reactions*; all of them take place through attack upon the aromatic ring by an electron-deficient species or a positively charged ionic species. It is important to recognize the reciprocal nature of the relationship between the reactants: the electrophilic substitution reaction can as well be regarded as a nucleophilic attack of the aromatic ring upon the electron-seeking reagent.

28-4 Nitration of aromatic compounds

Before we consider the nitration of a substituted benzene, let us examine the nitration of benzene itself:



This reaction proceeds readily when a mixture of concentrated nitric and sulfuric acids is used, but very slowly when nitric acid is used alone. Sulfuric acid alone, under the conditions of this reaction, has no effect upon benzene; consequently, its role in the nitration reaction is that of a catalyst—it converts nitric acid into a form that is capable of reacting with benzene.

Sulfuric acid is a strong acid, and reacts with nitric acid in the acid-base equilibrium

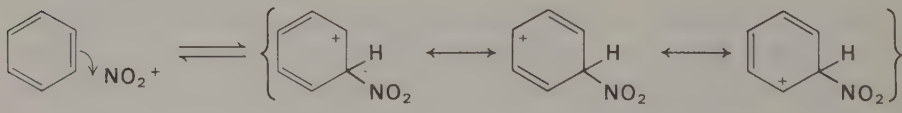
$$H_2SO_4 + HONO_2 \rightleftharpoons H_2\overset{+}{O}NO_2 + HSO_4^-$$

Freezing-point measurements show that this expression is incomplete and must be expanded as follows:

$$\begin{array}{ccc} H_2SO_4 + HONO_2 & \rightleftharpoons & H_2\overset{+}{O}NO_2 + HSO_4^- \\ & & \Big\downarrow\Big\uparrow \\ H_3\overset{+}{O} + HSO_4^- & \overset{H_2SO_4}{\rightleftharpoons} & H_2O + NO_2^+ \end{array}$$

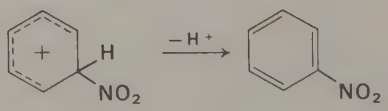
The presence of the nitronium ion (NO_2^+) in sulfuric-nitric acid ("nitration") mixtures has been established by spectroscopic studies (Raman spectra). The existence of the nitronium ion is independently confirmed in other ways: for example, crystalline nitronium salts (nitronium perchlorate, $NO_2^+ClO_4^-$; nitronium nitrate, $NO_2^+NO_3^-$) have been prepared as pure substances.

The NO_2^+ ion formed in this reaction is a powerful electrophile. It is, of course, a Lewis acid, and can accept an electron pair from the benzene ring in a step that is conveniently formulated as



(12)

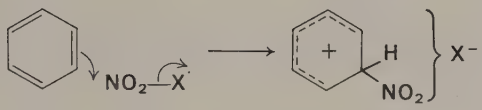
The loss of a proton to some proton-acceptor in the solution (for example, HSO_4^-, HNO_3) leads to the reconstitution of the aromatic nucleus and thus to the restoration of the stability inherent in the aromatic structure:



(13)

We shall see that the presence of certain substituents can increase the reactivity of the ring in the nitration reaction; in such cases much milder conditions are sufficient for the substitution. The range of effective nitrating agents runs from aqueous nitric

acid to solutions of fuming nitric acid in fuming sulfuric acid. Under these various conditions the attacking reagent may be either a nitronium ion or a nitronium-ion carrier, which we can formulate as NO_2—X. The more readily X can be displaced from NO_2—X by the nucleophilic attack of the ring, the better the nitrating ability of the reagent. Thus, for nitronium-ion carriers we can write the more general nitration reaction as



(14)

The species NO_2—OH, NO_2OCOR, NO_2—ONO_2, $NO_2OH_2^+$, and NO_2^+ (that is, NO_2X where X = OH, RCOO, NO_3, and ^+H_2O) are all nitrating agents capable of supplying NO_2^+ to a nucleophilic molecule.

The attack of NO_2^+ upon the benzene ring resembles in its initial stage certain reactions of nitric-sulfuric acid mixtures with olefins. Ethylene, for example, reacts as follows:

$$CH_2{=}CH_2 \xrightarrow[H_2SO_4]{HNO_3} \begin{matrix} CH_2NO_2 \\ | \\ CH_2ONO_2 \end{matrix} \qquad (15)$$

The initial complex, $(CH_2CH_2NO_2)^+$, yields the addition product by reacting with nitric acid, rather than losing a proton, as in the case of benzene. In the nitration of benzene, the reconstitution of the aromatic nucleus by loss of a proton represents an energetic advantage for the substitution reaction.

The rate-determining step in the nitration of benzene is the formation of an intermediate complex in which NO_2^+ has formed a bond with a carbon atom of the benzene ring, with the use of two of the six π electrons of the ring. The subsequent loss of a proton from the intermediate leads to nitrobenzene. There is evidence to suggest that the reaction starts by the formation of a complex (called a π complex) in which there is a weak association between the electron-deficient reagent and the π-electron system of the ring. The formation of the species shown as the resonance hybrid in Equations (12), (13), and (14) follows this initial complex formation. An energy diagram for the general case in which an electrophilic reagent X^+ attacks benzene, with the formation of C_6H_5X, is shown in Figure 28-1.

Among the experimental observations supporting the view that the breaking of the C—H bond is not the rate-determining step in nitration is the fact that when monotritiated benzene (C_6H_5T) is nitrated, the ratio of the products $C_6H_4TNO_2$ to $C_6H_5NO_2$ is 5:1. It is known from other studies that the rate of breaking a C—T bond is much slower than that of a C—H bond. Consequently, were the C—T bond-breaking step rate-determining, the relative amount of replacement of T by NO_2 should be much less than the statistical (and observed) one-fifth of the total.

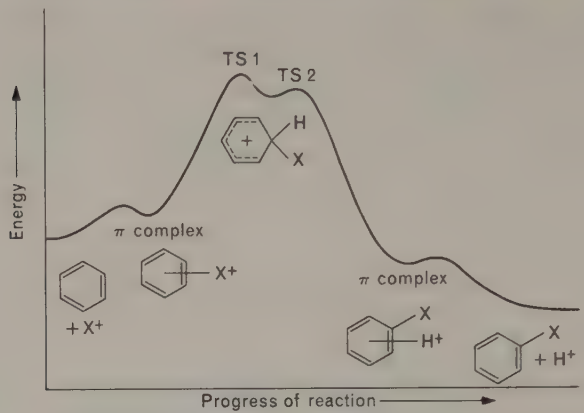
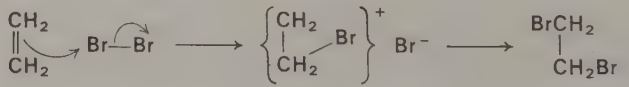


Figure 28-1
Energy profile for the aromatic substitution
$C_6H_6 + X^+ \rightarrow C_6H_5X + H^+$

In Figure 28-1, the energy of activation (or, approximately, the energy of the intermediate $C_6H_6X^+$) determines the rate of the overall reaction. *Any structural influence*—for example, of a substituent on the ring—*that stabilizes this intermediate (lowers its energy) will increase the rate of substitution relative to that of benzene.* This will be considered in detail in a later section.

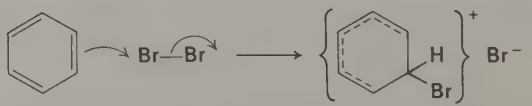
28-5 Other electrophilic substitution reactions

Halogenation. We may preface our consideration of the reaction between bromine and benzene by recalling the reaction between bromine and an olefin. The addition of bromine to ethylene, for example, is a stepwise process of which the first step can be described equivalently as either an electrophilic attack of bromine upon ethylene or a nucleophilic attack of ethylene upon bromine:



(16)

The first stage in the bromination of benzene proceeds in a parallel manner:



(17)

Now benzene itself (as distinguished from certain substituted benzenes) reacts very slowly with bromine, but in the presence of a suitable catalyst the reaction proceeds

readily. Catalysts effective in promoting the reaction are Lewis acids such as $FeBr_3$ and $AlBr_3$. The role of the Lewis acid is to develop positive character in one of the atoms of the halogen molecule

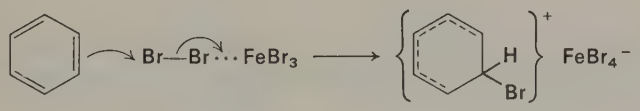
$$Br—Br + FeBr_3 \rightleftharpoons \{Br^+\}FeBr_4^- \tag{18}$$

and thus to increase the *electrophilic* character of the halogen. The symbol Br^+ is shown in braces because it is not possible to specify the degree to which *free* Br^+ is present; but apparently between the states of the completely covalent bromine molecule and the completely ionized molecule there must be states that can be formulated as

$$\overset{\delta+}{Br}\cdots\overset{\delta-}{Br}\cdots FeBr_3$$

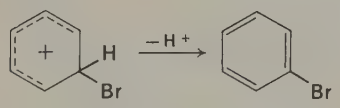
with varying degrees of electrophilic character in one of the bromine atoms.

Thus, we may expand the equation showing the catalytic effect of $FeBr_3$ upon aromatic bromination:



(19)

The remaining step in the overall reaction, as in nitration, is the loss of the proton and the restoration of the aromatic structure:



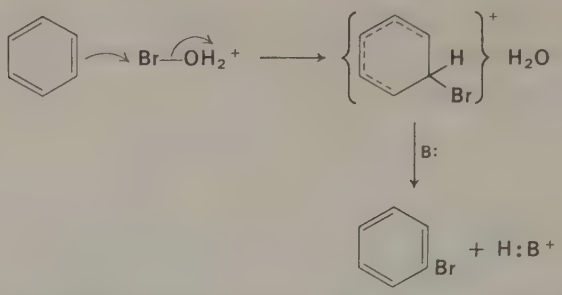
(20)

The difference between halogen addition to an olefin and halogen substitution into the aromatic ring is thus seen to reside chiefly in the fate of the positively charged fragment formed in the first stage of the reaction. Specifically, the difference lies chiefly in the tendency of the aromatic system to reconstitute itself.

Other sources of Br^+ can also be brominating agents. It has been observed that hypobromous acid, HOBr, is not itself an effective brominating agent; but in an acidic medium, the protonation of HOBr

$$HOBr + HA \rightleftharpoons \overset{+}{H_2O}Br + A^- \tag{21}$$

leads to the very active brominating agent $\overset{+}{H_2O}Br$. This may be regarded as a "bromonium-ion carrier," just as $\overset{+}{H_2O}NO_2$ is a nitronium-ion carrier, and it reacts as follows:

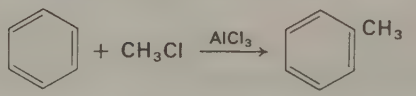


(22)

Other effective brominating reagents consist of mixtures of bromine with salts of silver or mercury; in these reagents the formation of silver or mercury halides provides the active (electrophilic) reactant Br^+.

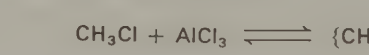
It is to be emphasized again that the bromination reaction is a *nucleophilic attack of the ring upon the bromine-carrying reagent*, as well as the *electrophilic attack of the latter upon the ring*. Thus, if the ring contains substituents that increase its nucleophilic properties (that is, increase its electron-supplying ability), the less powerfully electrophilic will the reagent need to be.

Alkylation. The reaction of an alkyl halide with benzene in the presence of a Lewis acid (typically, aluminum chloride), is known as the *Friedel-Crafts reaction*. A typical electrophilic substitution reaction, it can be expressed in its simplest form as



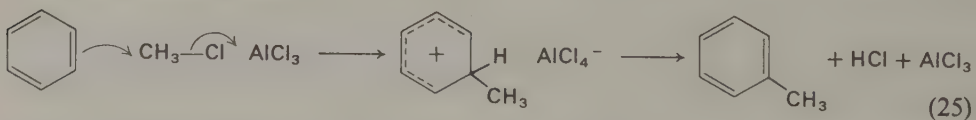
(23)

The function of the aluminum chloride is to supply the electron-deficient attacking species—in this case, the fragment CH_3^+:



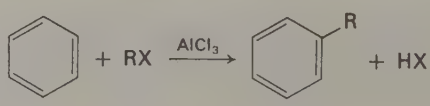
(24)

Again, the braces indicate that the exact degree to which a free methyl-carbonium ion exists in the solution cannot be specified. The substitution reaction can now be rewritten in greater detail:



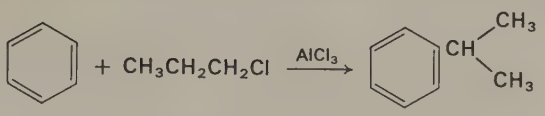
(25)

In the Friedel-Crafts alkylation reaction a considerable variation in the nature of the alkyl group is possible. However, the general equation that can be written

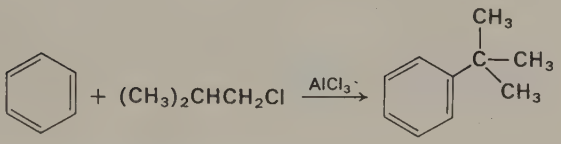


(26)

is not always correct in detail, for *rearrangement of the alkyl group is sometimes observed*:

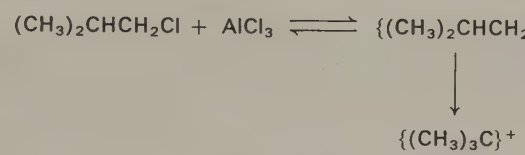


(27)



(28)

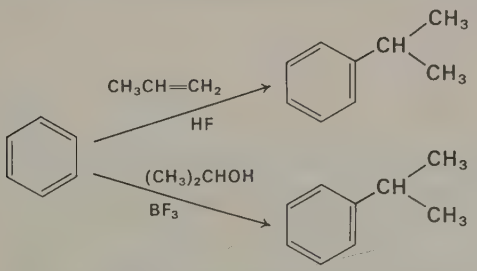
This rearrangement is in complete accord with our picture of the nature of the reaction. If the alkyl halide is converted into a complex in which the alkyl group is dissociated to form a carbonium ion, for example,



(29)

we can anticipate the rearrangement of primary to secondary or tertiary carbonium ions, and secondary to tertiary, after which the rearranged alkyl group will engage in the substitution step. Thus, the preparation of *n*-alkyl-benzenes by the Friedel-Crafts reaction is not practicable (except for ethylbenzene): the reaction yields mixtures of isomers, rearrangement products derived from the *n*-alkyl halide.

Since the necessary requirement for the alkylation is not the alkyl halide itself but the alkyl carbonium ion to which it gives rise, it may be expected that alkylation of benzene would be brought about by other reagents that can generate alkyl carbonium ions. Since olefins, alcohols, ethers, and esters can, in the presence of acids, give rise to carbonium ions (or charged complexes that serve as carbonium-ion donors), these reagents should serve as alkylating agents. This is indeed the case; for example,

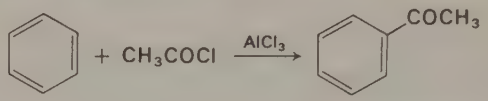


(30)

The Friedel-Crafts reaction is not generally practicable for the preparation of monoalkyl benzene derivatives. Besides the rearrangements that occur when complex alkyl halides are used, the presence of alkyl substituents on the aromatic ring increases

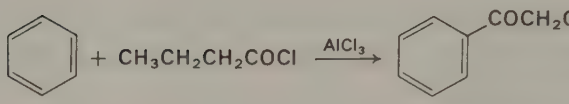
its nucleophilicity, so that polyalkylation is a frequent result. The preparation of monoalkylbenzenes and benzene derivatives is carried out in other ways, which will be described later.

Acylation. The use of an acyl halide in place of an alkyl halide in the Friedel-Crafts reaction leads to the formation of a ketone:



(31)

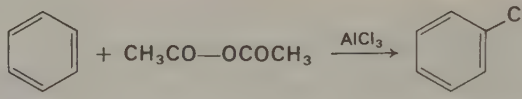
Acetophenone



(32)

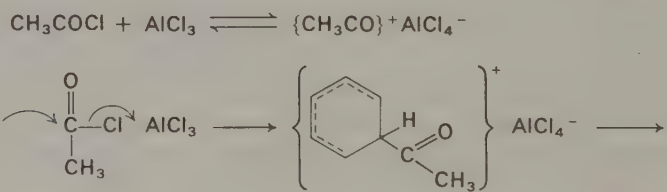
n-butyrophenone

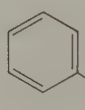
Acid anhydrides can be used in place of acyl halides, the —OCOR group undergoing displacement:



(33)

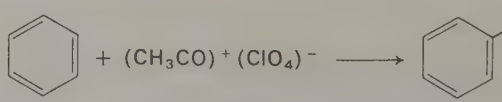
The course of these reactions is again an electrophilic attack by an electron-deficient fragment, in this case the "acylium" ion formed by a mechanism similar to the one that leads to a carbonium ion in the analogous alkylation reaction:





+ HCl + $AlCl_3$ (34)

In confirmation of the conclusion that the attacking species is an acylium ion, it is found that acetyl perchlorate, $(CH_3CO)^+(ClO_4)^-$, is a very effective acetylating reagent:



(35)

Again, the true reactant (CH_3CO^+) can be generated in more than one way.

The acylation reaction, in contrast to alkylation, is of general usefulness in synthesis.

Exercise 2

Write the reactions for the acylation of benzene with (*a*) propionyl chloride, (*b*) isobutyryl chloride, and (*c*) bromoacetyl bromide.

Exercise 3

Can you suggest what product would be formed by the action of aluminum chloride on β-phenylpropionyl chloride?

A revealing insight into the nature of the Friedel-Crafts acylation reaction is found in the reactions of pivaloyl (trimethylacetyl) chloride with benzene, with toluene, and with anisole. The nucleophilicity of anisole is greater than that of toluene, and that of toluene greater than that of benzene. Hence, the reactivity of these three compounds in electrophilic substitution reactions is anisole ≫ toluene > benzene.

The reaction of benzene with pivaloyl chloride and aluminum chloride yields not trimethylacetophenone, but *t*-butylbenzene. This can be accounted for by the great stability of the *t*-butyl carbonium ion, which can be formed from the intermediate acylium ion by loss of carbon monoxide:

$$(CH_3)_3CCOCl + AlCl_3 \longrightarrow ((CH_3)_3C\overset{+}{C}O)AlCl_4^- \longrightarrow (CH_3)_3C^+AlCl_4^- + CO \qquad (36)$$

The *t*-butyl carbonium ion then attacks the benzene ring to give *t*-butylbenzene.

Toluene gives some *p*-*t*-butyltoluene and some of the expected ketone; but anisole gives only *p*-methoxypivalophenone.

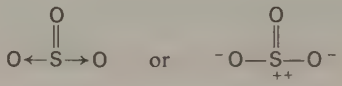
The explanation of these results is that the rates of the two reactions (*a*) and (*b*) in the following equation

$$\begin{array}{ccc} ArH + ((CH_3)_3C\overset{+}{C}O)AlCl_4^- & \xrightarrow{(a)} & ArCOC(CH_3)_3 \\ \Big\downarrow (b) & & \\ CO + ((CH_3)_3C^+)AlCl_4^- & \xrightarrow{ArH} & Ar{-}C(CH_3)_3 \end{array} \qquad (37)$$

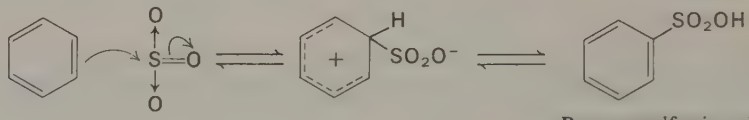
are such that with a highly nucleophilic ArH, reaction (*a*) takes place with such rapidity that decomposition according to path (*b*) does not occur. In the case of toluene, which is of intermediate reactivity, reactions (*a*) and (*b*) proceed at comparable rates and both products are formed; and benzene, which is the least nucleophilic of the

three, reacts slowly by path (*a*), permitting path (*b*) to dominate the course of the overall reaction.

Sulfonation. Sulfur trioxide is a powerful Lewis acid, and it reacts with aromatic hydrocarbons to form sulfonic acids. The structure of SO_3 can be most simply represented as follows:



The sulfur atom, its electron density greatly diminished by the two electronegative oxygen atoms attached by semipolar bonds, is strongly electron-demanding, and attacks the aromatic ring in the manner already discussed:



Benzenesulfonic acid (38)

Aromatic sulfonic acids are useful in several ways. The sulfonyl chlorides, for example *p*-toluenesulfonyl chloride, prepared by the reaction of sulfonic acids with phosphorus halides, are valuable reagents; they react with alcohols and amines to form *O*- and *N*-sulfonyl derivatives. The use of *O*-sulfonyl derivatives in displacement reactions, in which the $—OSO_2R$ group is the displaced group, has been alluded to a number of times in earlier chapters.*

Miscellaneous. As we shall see in later chapters, there are a great many electrophilic substitution reactions, mechanistically allied to those just discussed, that are limited to special types of aromatic nuclei. This is because electrophilic character (that is, degree of electrophilicity) can vary over a wide range, and not all electrophilic reagents can attack all aromatic rings. The reciprocal relationship between the nucleophilic character of the aromatic compound and the electrophilicity of the reagent suggests that weakly nucleophilic aromatic nuclei will be attacked only by powerful electrophiles.

The degree of nucleophilicity of an aromatic ring is governed by its substituents. The discussion so far has been based upon the reactions of benzene itself; but benzene derivatives, in which one hydrogen has been replaced by some other group, vary widely in the ease with which they undergo electrophilic attack. The next chapter will deal with the effect of a substituent already present upon the introduction of a second substituent.

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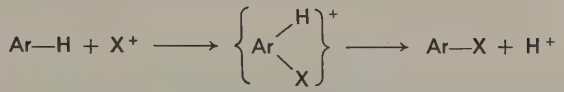
* *p*-Toluenesulfonyl chloride is so commonly used that it is usually referred to by the abbreviated name "tosyl chloride," which is represented by the symbol TosCl.

28-6 Summary of principal electrophilic aromatic substitution reactions

The electrophilic species in the general expression



$$\text{Ar—H} + \text{X}^+ \longrightarrow \left\{ \text{Ar}\begin{matrix}\diagup \text{H} \\ \diagdown \text{X}\end{matrix} \right\}^+ \longrightarrow \text{Ar—X} + \text{H}^+ \qquad (39)$$

can vary widely in structure and in degree of electrophilicity. The reactions chosen for detailed discussion in this chapter are only a few of many that proceed by the same fundamental mechanism. Table 28-1 is a succinct tabulation of the principal electrophilic reagents; most of these will be encountered in chapters to follow, as participants

Table 28-1
Principal aromatic electrophilic substitution reagents

Reagent	*Electrophile* (X^+)
HNO_3/H_2SO_4	NO_2^+
SO_3	SO_3
$HOSO_2Cl$	$HOSO_2^+ \cdots Cl^-$
$Br_2(FeBr_3)$	$Br^+ \cdots FeBr_4^-$
$RCl/AlCl_3$	$R^+ \cdots AlCl_4^-$
$RCOCl/AlCl_3$	$R\overset{+}{C}O \cdots AlCl_4^-$
RCOOH/HA*	$R\overset{+}{C}O \cdots OH_2$
$RCH{=}CH_2/HA$	$R\overset{+}{C}HCH_3$
ROH/HA	$R^+ \cdots OH_2$
ArN_2^+	$ArN{=}N^+$
$R_2NH/CH_2O/HA$	$R_2N{-}\overset{+}{C}H_2$
RCHO/HA	$R\overset{+}{C}HOH$
CO_2	CO_2
$Hg(OAc)_2$	$\overset{+}{Hg}{-}OAc \cdots OAc^-$
$RCN/ZnCl_2/HCl$	$R\overset{+}{C}{=}NH$
$CO/HCl/AlCl_3$	$H\overset{+}{C}{=}O$
HA	$H^+ \cdots A^-$
$HCHO/HCl/ZnCl_2$	$H_2\overset{+}{C}{-}OH$

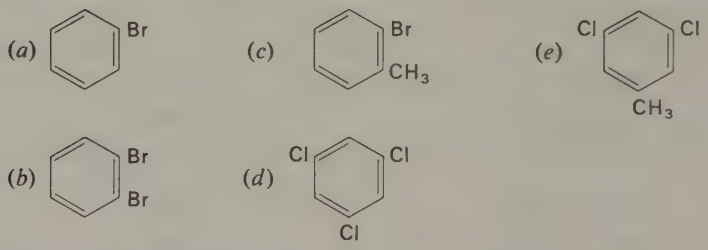
* The symbol HA represents a mineral acid, usually H_2SO_4, HCl, H_3PO_4, or HF, in most cases as the concentrated reagent.

in "name" reactions such as the Hoesch reaction, the Bischler-Napieralski reaction, and in the chloromethylation reaction, the diazonium coupling reaction, and so on. The tabulation is provided at this time so that the student will be prepared to recognize the essential mechanistic unity of these seemingly diverse reactions as they appear in the discussion.

It should be borne in mind that not all of the reactions in which the reagents of Table 28-1 take part can be realized with all aromatic compounds, for these reactions depend upon both the degree of electrophilicity of the reagent and the nucleophilicity of the aromatic nucleus.

Problems

1. Show all the possible mononitration products of each of the following:



2. Write the structures of all of the possible tetramethylbenzenes. How many bromotetramethylbenzenes can exist?

3. How many dibromocyclooctatetraenes can exist? Write their structural formulas.

4. Suppose the following reaction could be carried out on each of the three known trimethylbenzenes.

$$C_6H_3(CH_3)_3 \xrightarrow{\text{oxidize}} C_6H_3(CH_3)_2COOH \xrightarrow{\text{decarboxylate}} C_6H_4(CH_3)_2$$

Describe how this sequence of reactions could be used to determine the orientation of the methyl groups in the three trimethylbenzenes (an "absolute" method).

5. One of the three bromo-*m*-xylenes was treated with methyl iodide and metallic sodium to form a trimethylbenzene. The same trimethylbenzene was formed when *p*-xylene was brominated and the resulting bromo-*p*-xylene subjected to the Wurtz-Fittig reaction (Section 30-11) with methyl iodide and sodium. What was the structure of the original bromo-*m*-xylene?

6. How could you distinguish experimentally between *p*-xylene (1,4-dimethylbenzene) and ethylbenzene, using as the only experimental procedure the introduction of a nitro group by direct nitration?

7. Write the equations for the nitration, bromination, Friedel-Crafts acetylation, and sulfonation of (*a*) 1,4-dimethylbenzene (*p*-xylene) and (*b*) 1-methyl-4-ethylbenzene (*p*-ethyltoluene).

8. What alkylbenzene (consider only monoalkylation) would you expect to be formed by the Friedel-Crafts alkylation of benzene with aluminum chloride and (*a*) ethyl chloride, (*b*) *n*-butyl chloride, (*c*) *t*-butyl chloride, (*d*) allyl chloride, (*e*) 2-methylpropene, and (*f*) 2-butene.

29

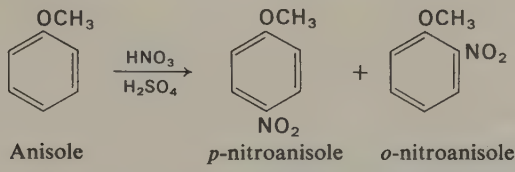
The effect of substituents upon the electrophilic aromatic substitution reaction

This chapter continues the study of the electrophilic aromatic substitution reaction by describing how the rate of the reaction and the position of entry of a substituent are governed by substituents already present on the aromatic ring. By appropriate manipulation of the conditions of the synthesis—the nature of the starting materials and of the electrophilic reagents—nearly any number and arrangement of substituents can be obtained.

29-1 The nitration of anisole and nitrobenzene

A substituent already present on the benzene ring affects the attack of an electrophilic reagent in two ways: (*a*) it affects the ease of substitution (the rate of the reaction) relative to benzene itself; and (*b*) it determines the position that is taken by the entering substituent. We can examine this question by an analysis of the nitration of two typical monosubstituted benzenes, *anisole* and *nitrobenzene*.

The experimental observations can be summarized as follows: (*a*) Anisole is nitrated faster and under much milder conditions than are required for the nitration of benzene. The product is largely *p*-nitroanisole, along with some *o*-nitroanisole. No appreciable amount of the *meta* isomer is obtained.



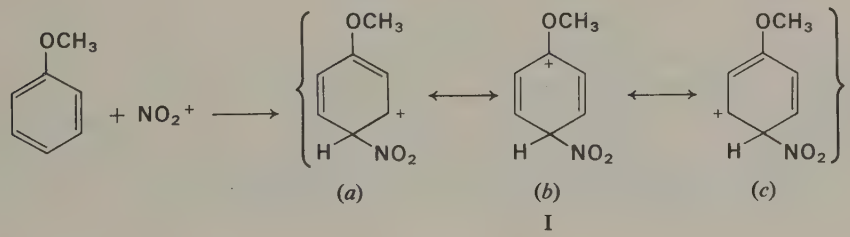
(1)

We conclude that the methoxyl group is an *ortho-para directing* group, and *activates* the ring toward electrophilic attack. (*b*) Nitrobenzene is nitrated with difficulty; mixtures of fuming nitric acid and sulfuric acid are used at an elevated temperature. The product is almost exclusively *m*-dinitrobenzene. We conclude that the nitro group is *meta-directing* and *deactivating*.

Since the electrophilic reagent (for simplicity this will be regarded as the nitronium ion, NO_2^+) attacks anisole at the *para* position,* it is clear that the transition state for *para* attack must be more stable than that for *meta* attack. Moreover, since the nitration of anisole is faster than that of benzene, the transition state for the nitration of anisole is at a lower energy than that for the nitration of benzene.

29-2 The nitration of anisole: Rate of reaction

Applying the mechanism for aromatic electrophilic substitution discussed in Chapter 28 to the attack of NO_2^+ upon anisole, we formulate the reaction as follows:†



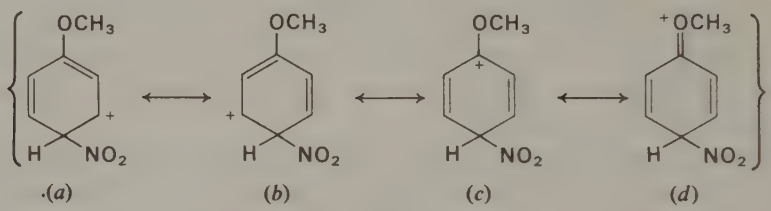
(2)

* It will become clear as we proceed that the mechanistic arguments for *para* substitution can be applied to *ortho* substitution as well; thus *para* substitution will be taken as the model in this discussion.

† The resonance hybrid I in the braces does not represent the true transition state, but its use here is justified because the resonance stabilization shown by this intermediate is also to be found in the actual transition state. Thus the energy-lowering factors in the activated complex of the reactants can be examined in this nearly equivalent stage.

An examination of I now discloses that another important contribution to the state of this system should be added: that supplied by the oxygen atom, with its unshared electron pairs. Examining I(*b*) more closely, we see that the positive charge on the carbon atom holding the methoxyl group can be transferred to oxygen by the formal change

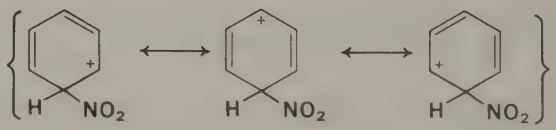
Thus, the resonance hybrid I is incomplete as written above; it is actually II, in which a *fourth contributing structure*, II(*d*), has been added:



(*a*) (*b*) (*c*) (*d*)

II

Let us now recall the course of the nitration of benzene, and examine the system at the stage represented by I; in this case the same three contributing structures make up the hybrid



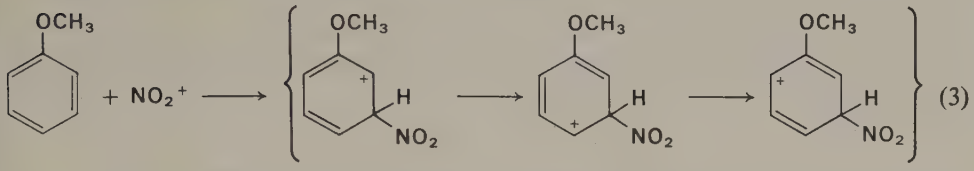
but *here there can be no fourth form corresponding to II(d) involved in the resonance.*

If we make the simplifying assumption that the energy differences between reactants and products do not differ by a large amount in these two reactions, the one factor that is quite different in the two cases is the resonance stabilization of the transition state. Since that through which anisole and NO_2^+ pass is more highly stabilized (that is, has a greater number of important contributing structures) than that passed through by benzene and NO_2^+, the nitration of anisole is much faster than the nitration of benzene.

29-3 The nitration of anisole: Position of substitution

We can examine the question of the *position* of electrophilic attack upon anisole by comparing the *para* substitution shown in (2) with attack at the *meta* position.

Meta attack by NO_2^+ is formulated as follows:

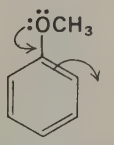


It can be seen from the formal structure of the contributing forms in the transition state of reaction (3) that there is none in which the positive charge is adjacent to the methoxyl group, and thus that there is no important contributing structure in which $\rangle C{=}\overset{+}{O}CH_3$ participates. Thus, while the methoxyl group supports attack at the *para* position, it does not contribute to charge delocalization in *meta* attack. Consequently, the lower energy transition state for *para* attack greatly favors the route leading to *p*-nitroanisole.

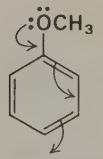
Exercise 1

Show the course of *ortho* attack of NO_2^+ upon anisole and the participation of the methoxyl group in charge delocalization of the transition state.

A simplified picture of the role of the methoxyl group in electrophilic substitution into anisole—one in which the foregoing analysis is implicit—is the following expression:



Electron availability at *ortho* position

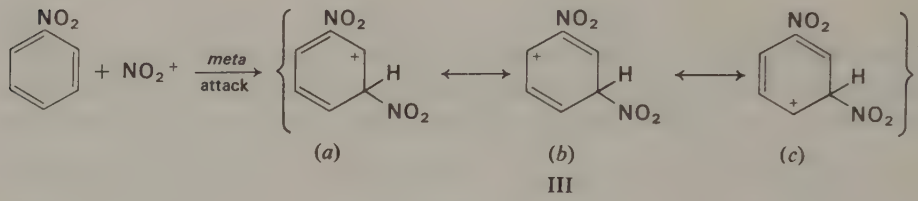


Electron availability at *para* position

It will be recalled that electrophilic aromatic substitution can be described as either *electrophilic attack upon the ring* by the electron-seeking reagent or as *nucleophilic attack by the ring* upon the reagent. The foregoing picture shows how the methoxyl group increases the nucleophilic character of the *ortho* and *para* positions, *supports the demand* made by the electrophilic reagent, and makes electrons available at the specific positions at which substitution takes place.

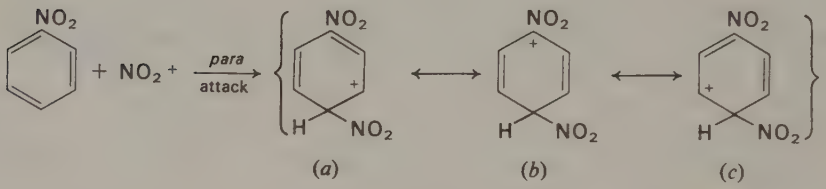
29-4 The nitration of nitrobenzene

The analysis of the nitration of anisole can now be applied to the nitration of nitrobenzene. The consequences of *meta* attack and *para* attack are described in the following equations:



(4)

III



(5)

IV

Now it is apparent that the nitro group, with no nonbonding electrons on nitrogen, cannot act as the methoxyl group does in supplying electrons *to* the ring. Indeed, the formal charges in the N—O semipolar bond of the nitro group confer upon the nitrogen atom a large degree of positive character, and consequently form IV(*b*)

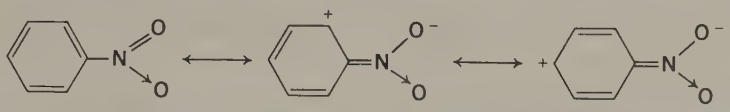
IV(*b*)

can be dismissed as a significant stabilizing contribution to the transition state for *para* attack. It may be concluded from this analysis that for *meta* attack (4) there are three principal structures contributing to the resonance hybrid, and for *para* attack (5) only two. Thus the reaction will proceed through the more stabilized, lower-energy activation state and lead to *meta* substitution.

29-5 Deactivation of the ring by the nitro group

The slowness of the nitration of nitrobenzene is the consequence of the reluctance of the ring to supply electrons to the attacking electrophile, NO_2^+. Indeed, the forms

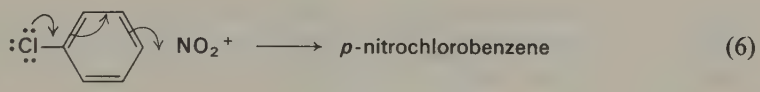
contributing to the structure of nitrobenzene show not only that the ring is electron-deficient, but also that the deficiency is greatest at the *ortho* and *para* positions:



Therefore, no reinforcement of electron supply can be made at any position of the ring, and consequently the electron-demanding NO_2^+ group is nowhere aided in its attack, although it finds electrons more available at the *meta* position than at the *ortho* and *para* positions. Thus, the nitro group is deactivating and *meta*-directing.

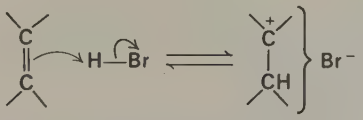
29-6 Inductive and resonance effects in aromatic electrophilic substitution

The nitration of chlorobenzene results in *ortho-para* substitution; yet chlorobenzene is less reactive than benzene. Thus, chlorine is *ortho-para*-orienting but *deactivating*, in contrast to the methoxyl group, which is *ortho-para*-orienting but strongly activating. The effect of the chlorine is to reduce electron availability to the attacking electrophile; but when electron availability is called into play by the reagent, it occurs at the *ortho* and *para* positions:



(6)

It will be recalled that the addition of a halogen acid to an olefin is initiated by electrophilic attack upon the carbon-carbon double bond:



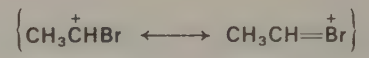
(7)

Markovnikov's rule, which describes the direction of such an addition to an unsymmetrical olefin, *is an expression of an orientation effect.* This is more clearly demonstrated by the addition of HBr to vinyl bromide, the product of which is 1,1-dibromoethane:

$$CH_2{=}CHBr + HBr \longrightarrow CH_3CHBr_2 \qquad (8)$$

Vinyl bromide reacts a great deal more slowly in this reaction than does propylene, but both vinyl bromide and propylene add HBr in accordance with Markovnikov's rule. *The inductive effect of bromine reduces electron availability* to the attacking

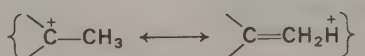
electrophile; but the ability of bromine to participate in charge delocalization of the intermediate ion

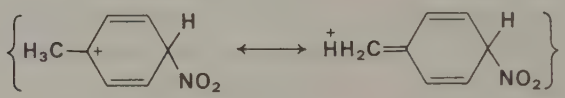


allows bromine to have the same kind of *orienting effect* as the methyl group.

We might predict that since propylene undergoes HBr addition at a faster rate than ethylene, toluene should undergo electrophilic substitution at a faster rate than benzene. This is indeed correct. Moreover, the methyl group in toluene is *ortho-para*-orienting.

The ability of the methyl group to participate in stabilizing the transition state for *para* substitution and the ability of the methyl group to stabilize an adjacent carbonium carbon atom can be seen to be expressions of the same property:





The inductive effect of the halogen atom withdraws electrons from the ring; the inductive effect of the methyl group is in the opposite direction.

All of the substituents that we shall discuss affect both *electron supply* and the *positions of electron availability* in the aromatic ring to which they are attached. A discussion of the role they play in electrophilic substitution reactions is facilitated by a terminology that permits a concise and convenient description of the way in which substituents affect electron availability to an electrophilic reagent. Two useful terms are the *resonance* (R) *effect* and the *inductive* (I) *effect*.

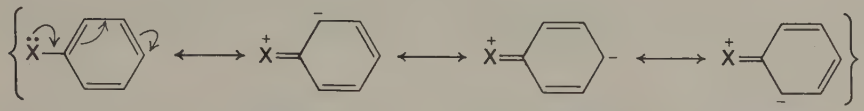
29-7 The resonance (R) effect

The resonance effect* of a substituent may be such as to provide electrons to the ring (+R effect) or to withdraw electrons from the ring (−R effect).

---

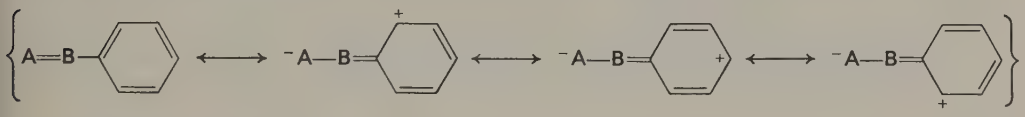
* The term resonance effect is now preferred for what used to be called the *tautomeric* (T) effect. The latter term was used before the concept of resonance and the distinction between resonance and tautomerism were well established. Since the R effect describes the way in which a substituent participates in the stabilization of the transition state for substitution, and because we can describe this state by writing the structures that contribute to this resonance hybrid, the term resonance effect is an appropriate one. Some organic chemists, particularly in Great Britain, use still another designation, and speak of *mesomeric* (M) effects. A discussion of the subtle differences that may exist in the interpretation of these terms is beyond the scope of our treatment, and we can regard them as equivalent.

The +R effect is shown by atoms or groups whose unshared pairs of electrons can participate in contributions of the following kind:



Thus, a +R substituent *supplies* electrons to the ring at the *ortho* and *para* positions. Three +R substituents have already been discussed: $—OCH_3$, $—CH_3$, and —Cl. Others of this group are: $—NR_2$, —NHCOR, —OH, $—O^-$, Br, I, F, —SR, —OR, and —OCOR. *All of these groups or atoms possess one or more unshared electron pairs on the atom adjacent to the ring* (with the exception of the alkyl group, which has been discussed). They are *ortho-para*-directing and, except for halogen, activating.

The −R effect is shown by atoms or groups for which forms such as the following bring about a *withdrawal* of electrons from the *ortho* and *para* positions:



The nitro group is a typical −R group, others being —COOH, —COOR, —COR, CHO, and CN. In these examples, the generalized group A=B— in the above expression is represented by O=N— in the nitro group, O=C(|)— in the carbonyl substituents, and N≡C— in the cyano group.

Exercise 2

Rewrite the general expressions shown above in specific terms of each of the substituent +R and −R groups and atoms mentioned.

It is to be noted that none of the −R groups shown has an unshared pair of electrons on the atom adjacent to the ring. Thus, *they cannot furnish electrons to the ring* when called upon to do so by the attack of an electrophilic reagent. These groups are typically deactivating, *meta*-orienting substituents.

29-8 The inductive (I) effect

The inductive effect of a substituent is the result of charge dissymmetry in the bond that joins it to the ring. Inductive effects are designated as −I or +I, depending upon

whether the result is the reduction (−I) or reinforcement (+I) of electron density in the ring.

The intensity and direction of inductive effects may be inferred from two experimental criteria: the strength of carboxylic acids, and the direction and magnitude of dipole moments.

In a series of carboxylic acids RCOOH differing only in the nature of R, differences in pK_a values can be correlated with differences in the inductive effects of substituents in the group R attached to the carboxyl group. Consider acetic and chloroacetic acids. These have markedly different pK_a values:

$H—CH_2COOH$	$\overleftarrow{Cl—CH_2COOH}$
$pK_a = 4.75$	$pK_a = 2.80$

The withdrawal of electrons in the Cl—C bond by the −I effect of chlorine (indicated by the arrow in the above formula) results in decreased electron density at the —OH group and a consequently readier release of the proton. Propionic acid, on the other hand, is a weaker acid than acetic acid. This indicates that the methyl group has an effect opposite from that of chlorine; that is, a +I effect:

$\overrightarrow{CH_3—CH_2COOH}$	$H—CH_2COOH$
$pK_a = 4.90$	$pK_a = 4.75$

Measurement of the strengths (pK_a values) of substituted acetic acids (Table 29-1) is a means of comparing the inductive effects of substituent groups.

Two properties of the inductive effect are noteworthy: (1) The inductive effect diminishes rapidly as the substituent is moved farther from the carboxyl group. This can be seen from the example of the three chlorobutyric acids given earlier (Table

Table 29-1
Inductive effects of substituent groups of some substituted acetic acids

Acid	pK_a	I *effect of substituent*
HCH_2COOH	4.75	H = reference point
CH_3CH_2COOH	4.90	+I
CH_3OCH_2COOH	4.30	−I
ICH_2COOH	3.0	−I
$BrCH_2COOH$	2.9	−I
$ClCH_2COOH$	2.8	−I
$HOOCCH_2COOH$	2.8 (pK_1)	−I
$(CH_3)_3\overset{+}{N}CH_2COOH$	1.8	−I

Table 29-2
Dipole moments of some substituted methanes

Compound	*Dipole moment* (D)
$CH_3—H$	0.00
CH_3NH_2	1.32
CH_3OH	1.69
CH_3F	1.81
CH_3Cl	1.83
CH_3Br	1.79

23-2). (2) The inductive effect does not involve contributions from additional valence-bond structures in which electron pairs occupy available orbitals of different atoms. This is most strikingly shown by $(CH_3)_3\overset{+}{N}—CH_2COOH$, in which the nitrogen atom possesses a complete octet and cannot accommodate additional electrons.

The dipole moments of organic compounds provide other evidence for inductive effects of substituents. The dipole moment is a manifestation of electrical dissymmetry in a bond and is determined by measurement of the tendency for a molecule to orient itself in an electrostatic field. If the molecule is symmetrical, as are ethane, benzene, and carbon tetrachloride, there is no dipole moment. Replacement of one of the hydrogens of methane by hydroxyl, halogen, or amino, as in the compounds in Table 29-2, results in charge dissymmetry and the creation of a dipole moment. It will be noticed that the increasing nuclear charge as we progress along the first row from nitrogen to halogen is reflected in an increasing dipole moment.

Compounds in which structures that involve charge separation make significant contributions to the resonance hybrid, as in carbonyl compounds, show enhanced dipole moments. For example, propionaldehyde and butyraldehyde have dipole moments of 2.73 D and 2.72 D, respectively.

Trimethylamine oxide, $(CH_3)_3\overset{+}{N}—O^-$, in which there is a formal unit charge separation in the N—O bond, has the large dipole moment of 5.0 D.

29-9 Dipole moments of substituted benzenes

The *direction* of the inductive effect ($-$I or $+$I) can be determined from the dipole moments of molecules in which two groups are present in the *para* positions of the benzene ring. The nitro group, the inductive effect of which can with confidence be designated as $-$I, can be used as a reference. If we compare the dipole moments of

Table 29-3
Dipole moments of some benzene derivatives

Compound	*Dipole moment* (D)
benzene	0.00
p-xylene	0.00
p-dichlorobenzene	0.00
chlorobenzene	1.55
toluene	0.40
p-chlorotoluene	1.90
nitrobenzene	3.95
p-chloronitrobenzene	2.50
aniline	1.53
p-nitroaniline	6.10
anisole	1.16
phenyl acetate (acetoxybenzene)	1.52

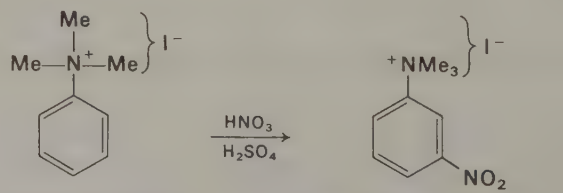
toluene, nitrobenzene, and *p*-nitrotoluene, we find that they are 0.40 D, 3.95 D, and 4.40 D. Clearly the methyl group has an effect opposite to that of the nitro group, and thus is a +I group. Dipole moments of other benzene derivatives are shown in Table 29-3.

Exercise 3

Account for the fact that the dipole moment of *p*-nitroaniline (6.10) is greater than the sum of the dipole moments of aniline and nitrobenzene.

29-10 Inductive effects on orientation

The powerful inductive effect of a positively charged atom attached directly to the benzene ring results in *meta* orientation and deactivation:

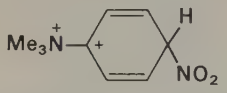


Trimethylanilinium iodide

Nearly exclusive (>90%) *meta* orientation

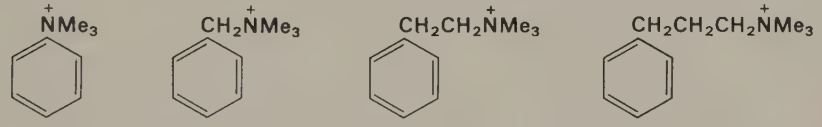
(9)

In terms of the transition-state theory of the effects of substituents on aromatic substitution, it can be seen that the improbability of effective contributions such as



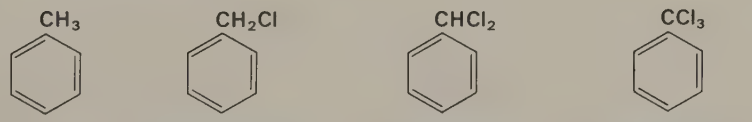
which would be involved in *para* attack, leads to *meta* substitution and deactivation.

If the positively charged atom is not attached directly to the ring, as in the following series of compounds, the relative amount of *meta* substitution falls off with increasing distance between the ring and the positively charged center; it can be seen that the effect drops off as the $-NMe_3^+$ group moves farther from the ring:



% *meta* nitration	95	88	19	5

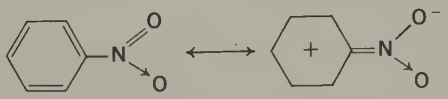
Increasing the number of $-I$ groups adjacent to the ring causes a predictable increase in the amount of *meta* substitution:



	Toluene	Benzyl chloride	Benzal chloride	Benzotrichloride
% *meta* nitration	4	14	34	64

29-11 Steric inhibition of resonance

Structural contributions to a resonance-stabilized transition state may have important steric consequences in electrophilic aromatic substitution. For instance, in the resonance contributions of the nitro group



A B

in structure B the oxygen atoms, the nitrogen atom, and the carbon atoms of the ring are all in the same plane. If substituents are present in the 2,6-positions, this coplanarity is inhibited and the deactivating effect of the nitro group is diminished.

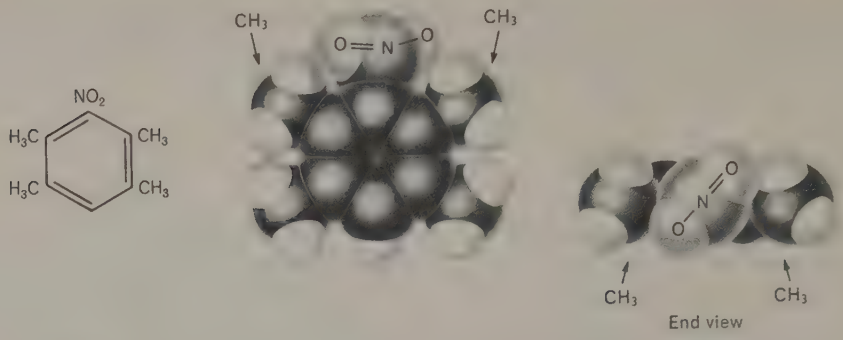
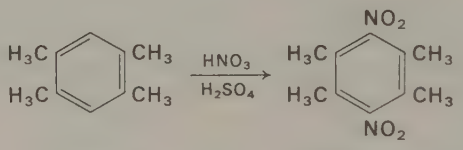


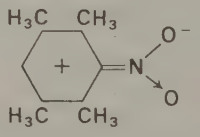
Figure 29-1
Molecular model of nitrodurene. The end view shows steric interference of *ortho* methyl groups with effective participation of the nitro group in resonance with the ring.

This is demonstrated by the nitration of durene (1,2,4,5-tetramethylbenzene). Durene is nitrated readily to yield the 1,4-dinitro compound:



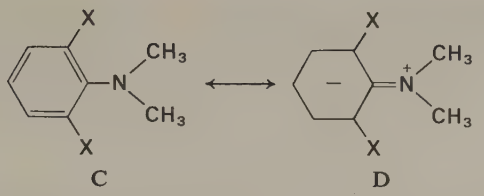
Durene Dinitrodurene (10)

This indicates that in the mononitro derivative the structure



does not contribute effectively to deactivation of the ring because the two *ortho* methyl groups prevent (that is, raise the energy requirement for) the bringing of the oxygen atoms of the nitro group into coplanarity with the ring. This is illustrated by the drawing of Figure 29-1.

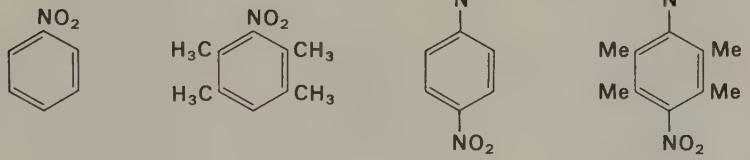
Steric inhibition of resonance can also account for a diminution in activating effects. For example, the strongly activating dimethylamino grouping is responsible for the high reactivity of *N*,*N*-dimethylaniline in electrophilic substitution. The nucleophilic contribution of the $—NMe_2$ group is associated with the resonance contribution shown in structure D, in which the methyl groups are coplanar with the ring:



C D

When the substituents X are hydrogen, form D can make its full contribution. When the groups X are bulky, the resonance contribution of forms D is inhibited. As would be expected, 2,6,*N*,*N*-tetramethylaniline is far less reactive toward electrophilic reagents than is dimethylaniline itself.

Dipole-moment data are also revealing:



3.95 D | 3.39 D (CH_3NO_2 = 3.10 D) | 6.87 D | 4.11 D

Exercise 4

Interpret the above dipole moments in terms of the foregoing discussion of the steric inhibition of resonance.

29-12 Summary of orienting effects in monosubstituted benzene derivatives

In Table 29-4 are gathered data on the orienting effects of a number of commonly encountered substituents. A close examination of these data, in the light of the preceding discussion, will afford further insight into the effects of orienting influences.

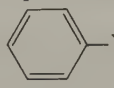
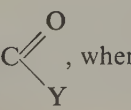
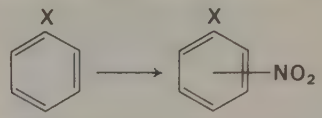
It is instructive to notice the relationship between the effects of atoms or groups Y on (*a*) electrophilic attack upon the ring of  and (*b*) nucleophilic attack upon the carbonyl carbon atom of  , where Y is Cl, H, CH_3, NH_2, and O^-. It will

Table 29-4
Orientation by substituents in aromatic nitration*



X	% *meta*	% *ortho-para*†
$\overset{+}{N}Me_3$	95	—
$\overset{+}{As}Me_3$	98	—
NO_2	93	7/0
COOH	82	17/1
CN	80	20
CHO	79	21
SO_3H	72	21/7
CCl_3	64	7/29
$COCH_3$	55	45/0
CH_2Cl	12	41/47
OH	—	55/45
$NHCOCH_3$	—	19/79
NH_2	—	100
Cl	—	30/70
Br	—	38/62
I	—	41/59
F	—	12/88
CH_3	4	59/37
OCH_3	—	100
C_6H_5	—	100
CH_2COOH	—	100
CH_2CN	—	100
$CH{=}CHCOOH$	—	100
$C{\equiv}CCOOR$	8	92

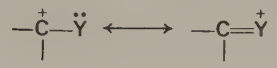
* These values are not to be regarded as absolute, since they are gathered from various sources and are subject to some variations of conditions, isolation, and separation procedures. They do, however, offer a basis for comparison by placing the various substituents in their proper categories.

† Where the *ortho-para* ratio is known it is given as a fraction (e.g., for $—CCl_3$ it is 7/29). The total (*ortho* + *para*) for this example is 36%. Single figures give total *ortho* + *para*.

be recognized that reactivity in electrophilic attack upon Ar—Y is inversely correlated with reactivity in nucleophilic attack upon RCOY.

The explanation is clear upon consideration of the mechanisms of these two types of reaction. Electrophilic attack upon Ar—Y is aided by electron release from Y. Nucleophilic attack upon RCOY is slowed by electron release from Y.

We have already seen that the more effective *activating* groups Y in Ar—Y are those that are the more effective in stabilizing an adjacent carbonium ion:



The following tabulation summarizes these observations:

In R—C(=O)—Y, *rate of nucleophilic attack on* C=O	Y	*In* Ar—Y, *rate of electrophilic attack on ring*
fastest ↑	Cl	slowest ↓
	H	
	CH_3	
	OCH_3	
	NH_2	
slowest	O^-	fastest

Exercise 5

Arrange the following groups in the order of their effect as substituents Y upon the susceptibility of Ar—Y to electrophilic attack: (*a*) —$OCOCH_3$, (*b*) —$NHCOCH_3$, (*c*) —$N(COCH_3)_2$, (*d*) —$COCH_3$, (*e*) —NO_2.

29-13 Other orienting influences

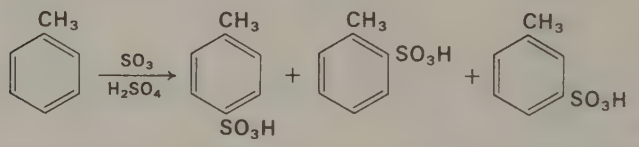
Although the distinction between *ortho-para* and *meta* orientation is usually quite clear, it will be noticed from the figures given in Table 29-4 that the ratio of *ortho* to *para* substitution does not appear to follow any pattern. There are a number of subtle influences upon the *ortho*/*para* ratio; these cannot be coordinated in a general concept that permits accurate predictions of this ratio. One of these is a steric effect. A bulky *o-p*-orienting substituent offers steric interference to the introduction of a group in a position *ortho* to it; in the same way, if the entering substituent is bulky, it finds the unhindered attack upon the *para* position more favorable. An examination of the data in Table 29-5 will show that a bulky substituent (for example, Br) or a bulky entering group (for example, Br, SO_3H) favor a larger ratio of *para* to *ortho* substitution.

Table 29-5
Effect of nature of substituent and of entering group upon the *ortho-para* ratio

Substance	*Orienting substituent*	*Ortho/para ratio by group introduced*			
		Cl	NO_2	Br	SO_3H
toluene	CH_3	—	56/41	40/60	32/62
chlorobenzene	Cl	39/55	30/70	11/87	0/100
bromobenzene	Br	45/53	38/62	13/85	0/100
phenol	OH	50/50	40/60	10/90	—

Temperature is also a factor, but its effect is seldom predictable on *a priori* grounds. Table 29-6 shows the effect of temperature in the sulfonation of toluene at 0° and at 100°.

Table 29-6
Effect of temperature on sulfonation of toluene



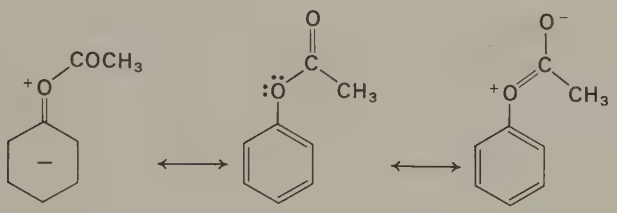
Temp.	*para*	*ortho*	*meta*
0°C	52.5%	45%	2.5%
100°C	73%	17%	10%

The effect of temperature upon the *ortho/para* ratio in sulfonation can be explained by the reversibility of the sulfonation reaction, and the fact that the *para* isomer is the most stable. Since the methyl group is *ortho-para*-directing, the initial substitution takes place predominantly at the two *ortho* positions and the *para* position. At the higher temperature, the establishment of the equilibrium leads to the predominance of the more stable *para* isomer, with the observed shift in the *ortho/para* ratio.

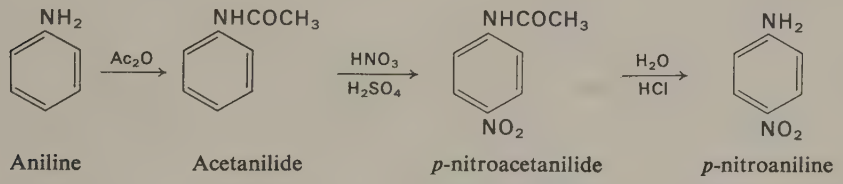
29-14 Alteration of orienting and activating effects of substituents by "protecting" hydroxyl and amino groups

The anionic oxygen atom, as in the phenoxide anion, is a powerfully activating substituent by virtue of its possession of three pairs of unshared (nonbonding) electrons.

The hydroxyl group is also strongly activating: bromination of phenol leads rapidly to 2,4,6-tribromophenol. The mobility of the electrons on oxygen can be sharply reduced by acylation. Although the —$OCOCH_3$ group is still activating and *ortho-para*-directing, it is much less so than the free hydroxyl group. Both the —OH group and the —$OCOCH_3$ group have two pairs of nonbonding electrons on oxygen, but those in the acetoxy group are influenced by an "opposing resonance" that reduces their availability to the ring and thus reduces their activating effect:



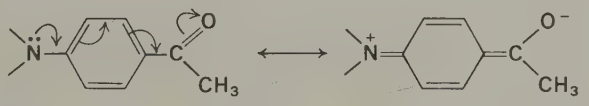
Aniline, like phenol, is very reactive in electrophilic substitution. The amino group can be "deactivated" by acylation; and acetanilide, in contrast to aniline, can be smoothly and controllably nitrated or brominated to *p*-nitro- and *p*-bromoacetanilide, subsequent hydrolysis of which provides the corresponding *p*-substituted anilines:



(11)

Aniline — Acetanilide — *p*-nitroacetanilide — *p*-nitroaniline

Infrared and ultraviolet absorption spectra provide further evidence for the decrease in electron availability of hydroxyl and amino groups upon acylation. For example, the C=O stretching frequency in *p*-aminoacetophenone is found to be 1677 cm^{-1}, while that of *p*-acetaminoacetophenone is at 1686 cm^{-1}. It is clear from these data that the carbonyl group in the amino compound has a greater degree of single-bond character than that in the acetylated compound. This shows that contributions of the following kind are of greater importance in the free amine than in the acetyl derivative:

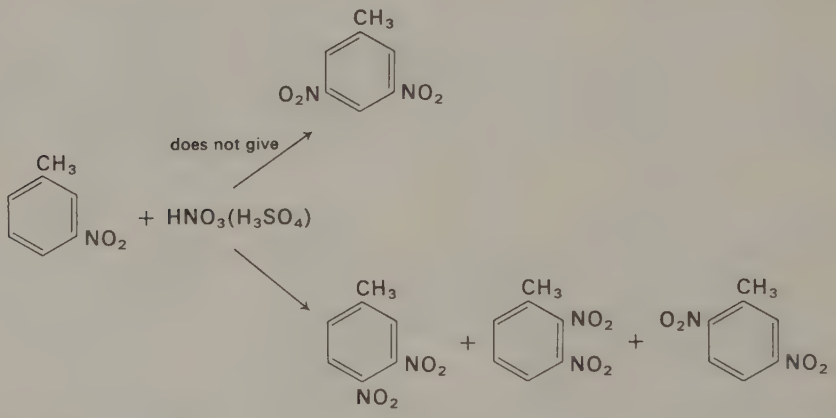


The shift in the UV maximum of *p*-hydroxyacetophenone from 276 nm to 325 nm upon the addition of alkali also shows the effect of increasing electron availability by the change of —OH to —O^-.

These deactivating procedures are of great value in synthetic manipulations in aromatic compounds. The alternation of $—NH_2$ to $—NHCOCH_3$ by *N*-acetylation preserves the orienting effect but reduces the activating effect to a degree that permits electrophilic substitution to be carried out successfully. Later hydrolysis [as in (10)] regenerates the free amino group.

29-15 Competitive orienting effects of two substituents

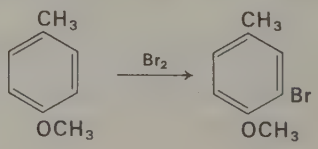
The nitration of *p*-nitrotoluene gives 2,4-dinitrotoluene. Since the second nitro group enters *meta* to the first and *ortho* to the *ortho-para*-directing methyl group, it is not possible to decide from this result alone whether the orienting influence at work is that of the methyl or of the nitro group. If *m*-nitrotoluene is nitrated, the products are a mixture of 3,4-, 2,5-, and 2,3-dinitrotoluenes. None of the products is 3,5-dinitrotoluene, indicating that the controlling directive influence is that of the methyl group:



(12)

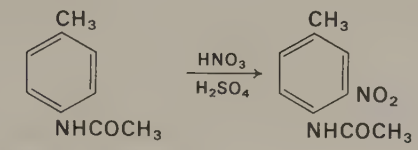
When a *meta*-directing substituent and an *ortho-para*-directing substituent both are present, the controlling directive influence will be that of the *ortho-para*-directing group. Since the *ortho-para*-directing group can *actively aid the reaction by supplying electrons upon the demand* of the attacking electrophile, whereas the *meta*-directing group deactivates by decreasing electron availability, the predominant effect of the former can be understood.

When two *ortho-para*-directing groups are present in a ring, the controlling directing power will be exerted by the group that is the more capable of responding to the electron demand made by the substituting reagent:



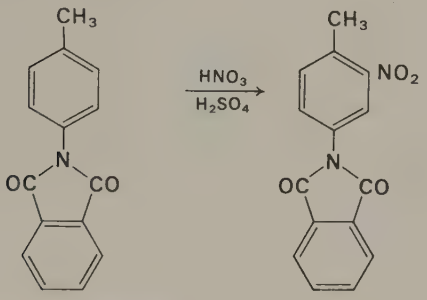
Predominant product (13)

In aceto-*p*-toluidide the substitution occurs *ortho* to the acetamino group; but when the activating power of the nitrogen is further diminished by diacylation, the methyl group dominates:



(14)

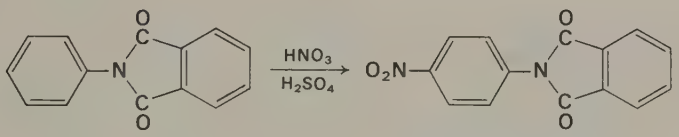
Aceto-*p*-toluidide



(15)

N-*p*-tolylphthalimide

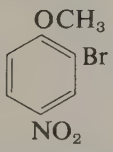
But that the diacylated amino group is still an *ortho-para*-directing group and not a *meta*-directing group is shown by



(16)

N-*p*-nitrophenylphthalimide

29-16 Applications to synthesis

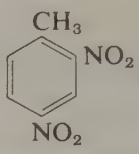
1. Suppose we wish to prepare 

from anisole. There are two alternatives:

(1) bromination, followed by nitration; and (2) nitration, followed by bromination. The second of these is preferable, for the following reasons. Bromination of anisole would be expected to give largely *p*-bromoanisole, and relatively little *o*-bromoanisole. Suppose, nevertheless, that one were to separate the *o*-bromoanisole and subject it to nitration. Now further complications arise. It will be seen that with two *ortho-para*-directing groups (OCH_3 and Br) in the molecule, the nitro group can enter at any of several positions. Thus, even if 2-bromo-4-nitroanisole (the desired compound) were

the predominant product, as it would be, problems of separation and purification would have to be dealt with.

The other alternative is preferable because the predominant product of nitration of anisole is *p*-nitroanisole. Bromination of this gives *only* the desired 2-bromo-4-nitroanisole.

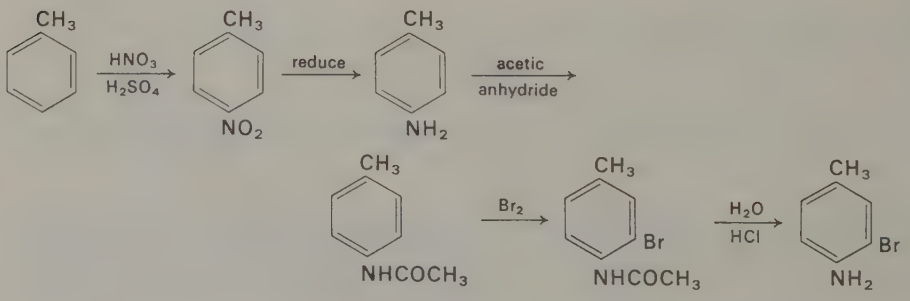
2. Suppose it is desired to prepare  from benzene. Here the choice is

clear, because if the first step were the dinitration of benzene it would be impossible to introduce the methyl group into this compound at the desired position. Indeed, because of the great deactivation caused by two nitro groups, the Friedel-Crafts alkylation reaction does not proceed at all. *Even nitrobenzene, with only a single nitro group to deactivate the ring, is not reactive in the Friedel-Crafts alkylation reaction.*

Thus, the desired compound could be prepared from benzene only by the route: benzene → toluene → 2,4-dinitrotoluene.

It should be added that the preparation of toluene from benzene by the Friedel-Crafts alkylation reaction is not satisfactory from a practical standpoint because polyalkylation, with the formation of polymethylbenzenes, would occur.

3. To prepare 3-bromo-4-aminotoluene it would be impracticable to use aniline as the starting compound because the introduction of a methyl group into aniline by the Friedel-Crafts reaction would not be successful; nor would bromination of aniline or acetanilide give a practical yield of the *ortho*-bromo derivative. The use of toluene as the starting material, however, would be practicable, for the mononitration of toluene gives the readily separable *o*- and *p*-nitrotoluenes. Reduction of the nitro group, acetylation of the amine, bromination, and deacetylation leads to the desired compound:

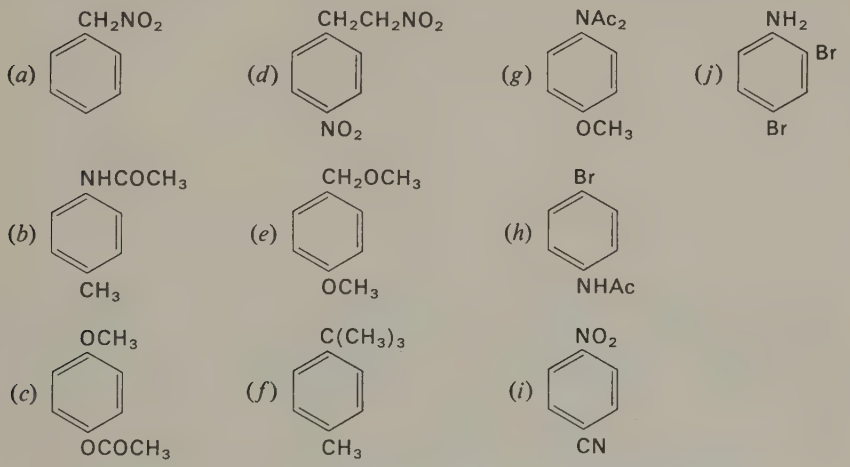


(17)

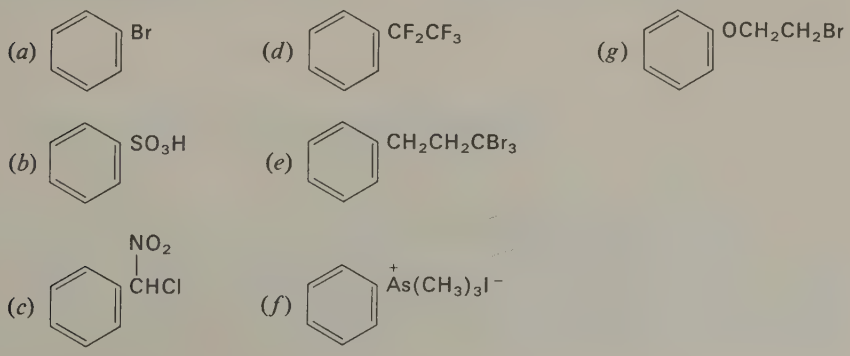
The organic chemist has at his disposal many monosubstituted and disubstituted benzene derivatives, available from commercial sources. *p*-Toluidine is an important industrial chemical, and in actual practice it would be used as the primary starting material in a laboratory synthesis of the bromotoluidine.

Problems

1. Show by the use of appropriate symbols the manner in which the resonance effect of the following substituents (on a benzene ring) would operate: (*a*) —OCH_3, (*b*) —NMe_2, (*c*) —Br, (*d*) —CHO, (*e*) —$NHCOCH_3$, (*f*) —COOEt, (*g*) —NO.
2. Explain why the dipole moment of nitrodurene is only about 0.56 D lower than that of nitrobenzene, whereas *p*-nitrodimethylaniline and 1-nitro-4-dimethylaminodurene differ by 2.76 D.
3. With reference to your discussion in Exercise 2, why are the dipole moments of bromobenzene and bromodurene nearly the same?
4. Each of the following compounds gives largely only a single monosubstitution product upon nitration. Write the structure of the *mono*-nitro derivative of each.

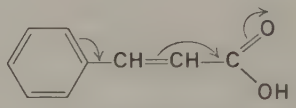


5. Which of the following compounds would undergo predominantly *meta* electrophilic substitution?



6. Formulate a practical synthesis for each of the following compounds:
   (*a*) *p*-bromonitrobenzene, from benzene
   (*b*) 2-bromo-4-nitrotoluene, from toluene
   (*c*) *m*-bromonitrobenzene, from benzene
   (*d*) *p*-bromoacetophenone, from benzene
   (*e*) 3-bromo-4-aminotoluene, from *p*-toluidine.

7. For electrophilic substitution into cinnamic acid we can represent a $-R$ effect by the following symbols:



Why, then, does cinnamic acid undergo *ortho-para* substitution?

30

Aromatic halogen compounds. Nucleophilic aromatic substitution

Aromatic compounds containing halogen atoms attached to a benzene ring differ greatly from alkyl halides in their chemical behavior. In this chapter are described the nature of aromatic halides, their mechanisms of reaction, and their applications to synthesis. Special attention is devoted to the replacement of aromatic halogen by nucleophilic reagents, a reaction that differs markedly from the nucleophilic substitution reactions of aliphatic halides. The behavior of aromatic halogen compounds in such reactions will be seen to depend upon structural factors that stabilize (lower the energy level of) the transition states and intermediates through which the reactions proceed.

30-1 Preparation of aromatic halogen compounds

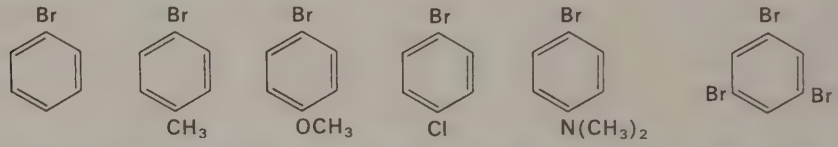
The methods employed for the preparation of alkyl halides are not generally applicable to the preparation of aryl halides. Although alcohols react with hydrogen halides, phosphorus halides, and thionyl chloride to yield the corresponding halides, most phenols cannot be converted into aryl halides with these reagents. Di- and trinitrophenols react with PCl_5 and PBr_5 to yield the corresponding di- and trinitro

halogenated benzenes, but these preparative methods are not generally useful. One of the most widely applicable synthetic methods, besides direct halogenation, for the preparation of chloro-, bromo-, and iodo-derivatives of benzene and substituted benzenes is a reaction (the Sandmeyer reaction) that will be the subject of Chapter 32.

30-2 Reactivity of aryl halides

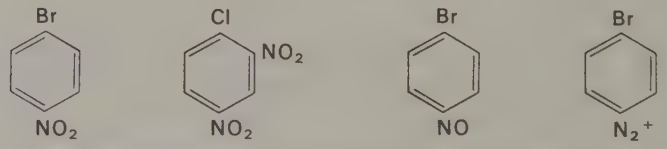
Aromatic compounds that contain halogen bound to the aromatic ring can be placed into two general classes:

1. Those, like chlorobenzene, the bromotoluenes and -xylenes, and others in which there are present either halogen alone or halogen and substituents that are electron-releasing (+R), that are characterized by inertness of the halogen atom to displacement by nucleophilic reagents:



Not reactive toward nucleophilic reagents; halogen not displaced by OH^-, NH_3, CN^-, $:CH(COOEt)_2^-$, and comparable nucleophiles under usual conditions of ionic displacement reactions.

2. Those, like *p*-bromonitrobenzene, 2,4-dinitrochlorobenzene, and others in which the halogen atom is *ortho* or *para* to a strongly electron-withdrawing, *meta*-directing substituent (−R), that undergo displacement of the halogen by nucleophilic reagents:



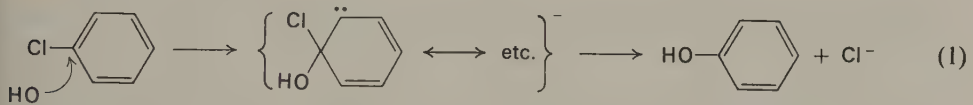
Reactive toward nucleophilic reagents; halogen displaced by nucleophilic attack of OH^-, OR^-, NH_3, and comparable nucleophiles under usual conditions of ionic displacement reactions.

30-3 The hydrolysis of chlorobenzene

Chlorobenzene is inert to the action of hot aqueous sodium hydroxide. Nevertheless, phenol is produced in an industrial process by the hydrolysis of chlorobenzene; the reaction is carried out under drastic conditions (elevated temperature and pressure) that are in marked contrast to those that suffice for the hydrolysis of alkyl halides.

Thus, chlorobenzene can be "hydrolyzed" to phenol but the reaction does not appear to be a nucleophilic displacement reaction of the S_N1 or S_N2 type. For one thing, a (S_N2) rear-side attack of a nucleophile (for example, OH^-) upon the carbon atom holding the halogen is sterically impossible; because the carbon-chlorine bond is a shorter, stronger bond than that in an alkyl halide, and, moreover, a $C_6H_5^+$ species has no stabilizing features, the S_N1 route is also highly unlikely.

Another kind of attack that the hydroxide ion might make upon chlorobenzene is pictured as follows:



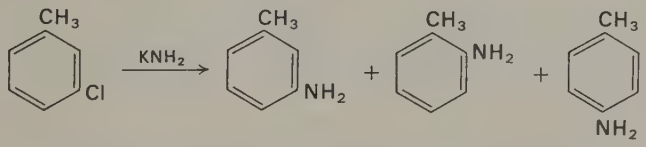
(1)

A reaction of this kind appears to be mechanistically acceptable but energetically disadvantageous, with a high activation energy. Under the conditions of the industrial preparation of phenol by the hydrolysis of chlorobenzene, the high temperature used may permit this route to be followed at an acceptable rate.

There is another possible course, described in the following section, that may be the route followed when chlorobenzene reacts with alkali at elevated temperatures.

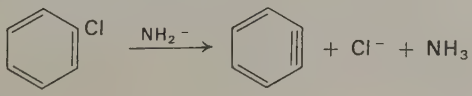
30-4 The "benzyne" intermediate in replacement of halogen from aromatic halides

Certain aromatic halides react with strong bases such as alkali-metal amides in liquid ammonia to yield substituted anilines. The remarkable feature of these reactions is that the entering $-NH_2$ group does not always occupy the position of the halogen in the original compound. Mixtures are often obtained:



(2)

Studies of this reaction have led to the conclusion that it proceeds by way of elimination of the elements of hydrogen halide, with the formation of a highly reactive intermediate (which is not isolated) that is most simply formulated as containing a triple bond. This intermediate is called a "benzyne." The reaction of chlorobenzene with potassium amide is formulated as follows:

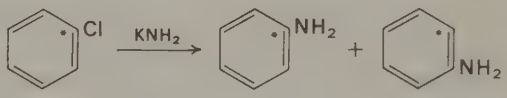


(3)

The intermediate benzyne or "dehydrobenzene" could contain a true triple bond only with extreme distortion of the bond angles. An alternative symbol for benzyne is the following; it is a more realistic representation although it is somewhat noncommittal in respect to the details of orbital hybridization:

The tendency for the reconstitution of the stable sp^2/π-orbital structure of the normal benzenoid nucleus is such that the benzyne intermediate reacts at once with ammonia to yield aniline.

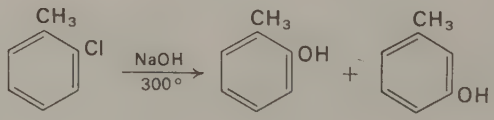
That aniline is produced by the addition of ammonia in both possible ways has been demonstrated by using radioactive (^{14}C) chlorobenzene:



(* = ^{14}C) (4)

By degradation of the aniline formed, it was found that one-half of the radioactivity was in the carbon holding the amino group, the other half in the position *ortho* to this. The formation of all three toluidines from the reaction of *m*-chlorobenzene with potassium amide [equation (2)] is, of course, entirely in accord with this interpretation of the reaction.

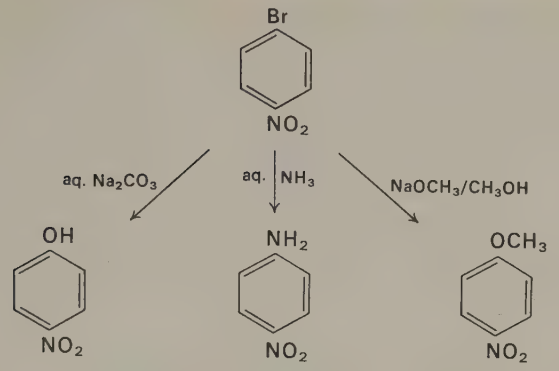
The reaction of *o*-chlorotoluene with sodium hydroxide at a high temperature yields both *o*-cresol and *m*-cresol. This is evidence that a benzyne is intermediate in this case as well:



(5)

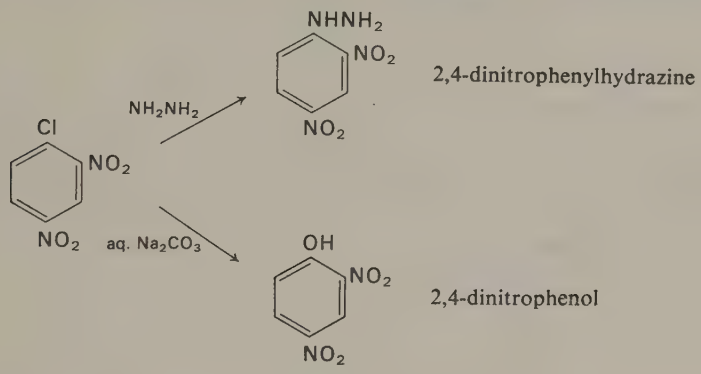
30-5 Nucleophilic displacement of halogen from *p*-nitrobromobenzene

When the halogen on the aromatic ring is *ortho* or *para* to a nitro group, replacement of the halogen by nucleophilic attack proceeds with ease and without the "rearrangements" that occur in replacements by the benzyne mechanism. In the case of *p*-nitrobromobenzene itself, the following reactions are observed to occur at moderate temperatures:



(6)

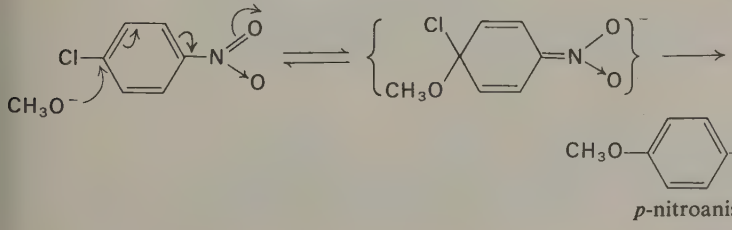
The presence of two or three nitro groups *ortho* and *para* to the halogen atom encourages a high degree of reactivity in such nucleophilic displacement reactions. Such compounds as 2,4-dinitrochlorobenzene, 2,4,6-trinitrobromobenzene, and 2,4,6-trinitrochlorobenzene undergo ready displacement of the halogen atom:



(7)

In 2,4,6-trinitrochlorobenzene the reactivity of the halogen atom in reactions of this kind is so great that the compound bears the trivial name "picryl chloride," a name that suggests an order of reactivity comparable to that of an acid halide.

The exceptional reactivity toward nucleophilic replacement of a halogen atom activated by an *ortho* or *para* nitro group can be accounted for in the following way. Attack of the nucleophile (for example, CH_3O^-) is facilitated by the ability of the nitro group to accommodate the negative charge provided by the attacking anion:

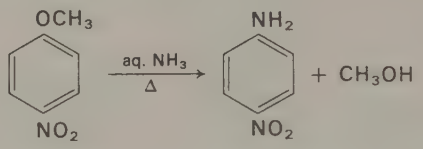


(8)

The resonance contribution of the nitro group to the delocalization of the negative charge stabilizes the transition state and lowers the activation energy. When two or three nitro groups can participate in such delocalization, the transition state is correspondingly stabilized to a greater degree and the reaction is much faster. The completion of the reaction, with expulsion of the halide ion and retention of the methoxyl group, reflects the weakly nucleophilic character of the halide ion compared with the alkoxide ion. It is a corollary that attack of bromide ion on *p*-nitroanisole would not be expected to yield *p*-nitrobromobenzene with displacement of methoxide.

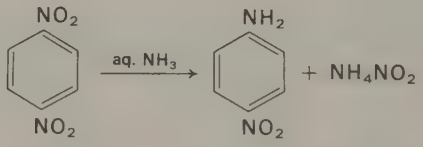
It is now clear why chlorobenzene reacts so slowly with such nucleophiles as hydroxide ion and methoxide ion, for no comparable stabilization by delocalization of the negative charge is possible. With sufficiently strong bases such as the amide ion the reaction takes the alternative course through the benzyne intermediate.

Nucleophilic displacement of groups other than halogen can also take place when activating nitro groups are present. *p*-Nitroaniline can be prepared by the reaction of *p*-nitroanisole with ammonia at 200°C:



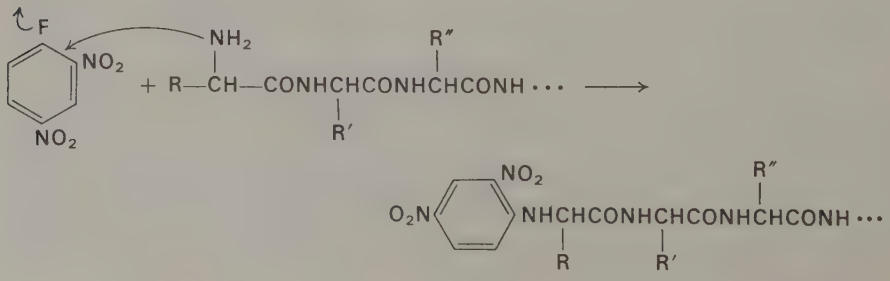
(9)

The replacement of a nitro group (which is eliminated as the nitrite ion, NO_2^-) is accomplished similarly:



(10)

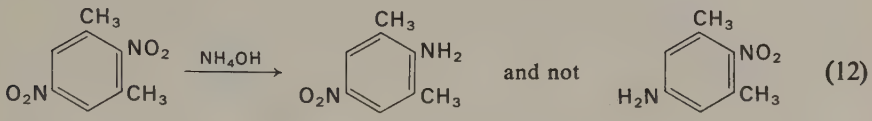
An interesting and important practical application of the nucleophilic aromatic displacement reaction is the use of 2,4-dinitrofluorobenzene in the structure determination of polypeptides (discussed further in Chapter 37). The replacement of fluorine by a free amino group occurs under mild conditions, giving a dinitrophenyl derivative of the polypeptide:



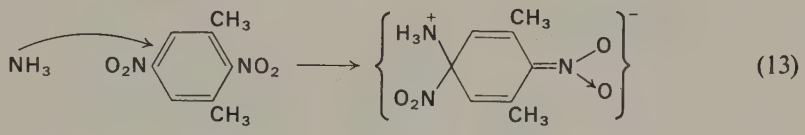
(11)

30-6 Steric inhibition in aromatic nucleophilic displacement

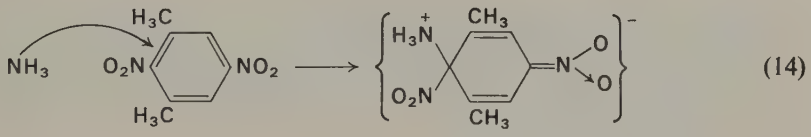
The nucleophilic replacement of a nitro group of 1,3-dimethyl-2,5-dinitrobenzene provides another example of the steric inhibition of resonance:



The ability of the 2 nitro group to engage in resonance stabilization of the intermediate



is inhibited by the *ortho* methyl groups (Figure 30-1); but attack in the other position, leading to



is not inhibited in this way (here the $\overset{+}{N}H_3$ and NO_2 groups in the 2 position are not coplanar with the ring, since in this intermediate stage the 2 carbon atom is tetrahedral).

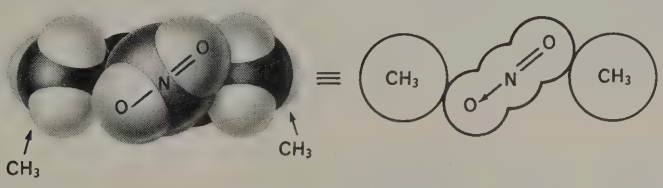


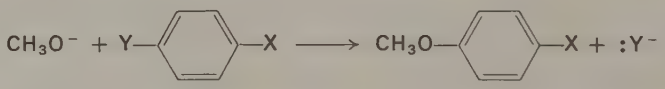
Figure 30-1
Model showing how *ortho* methyl groups interfere with the ability of a nitro group to become coplanar with the aromatic ring.

Table 30-1
Replaceability of groups Y and activating effect of groups X in nucleophilic aromatic substitution

Y	X
F (most readily replaced)	N_2^+ (most activating)
NO_2	NO
I, Cl, Br	NO_2
OR	SO_2CH_3
SO_2R	NMe_3^+
NR_2	

30-7 Relative activity of groups in aromatic nucleophilic substitution

Table 30-1 lists the common groups (X) activating the aromatic ring to nucleophilic attack, and those (Y) capable of being replaced by the nucleophile. For attack by CH_3O^- (as a typical nucleophile) in the reaction



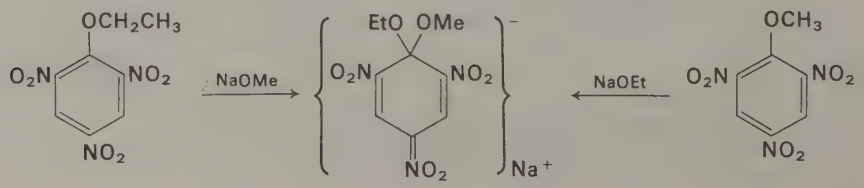
(15)

the tabulation shows the rank of replaceability of Y and the activating effect of X.

It should be noted that $-NMe_3^+$, a strongly deactivating and *meta*-directing group in electrophilic substitution, is not correspondingly activating in nucleophilic substitution. Why is this so?

30-8 Experimental support for the mechanistic interpretation of aromatic nucleophilic substitution

The validity of the mechanism for nucleophilic substitution discussed above is supported by some cases in which the intermediate addition compound can be isolated: for example, the same compound is formed by the reaction of sodium methoxide with 2,4,6-trinitrophenetole and by the reaction of sodium ethoxide with 2,4,6-trinitroanisole:



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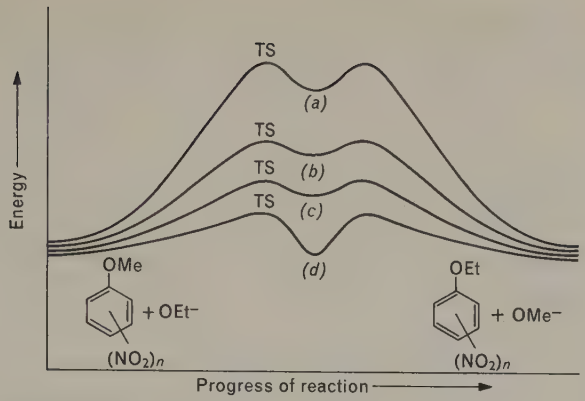


Figure 30-2
Energy profiles for the nucleophilic displacement reaction in ethanol:

$$MeO—Ar(NO_2)_n + EtO^- \rightarrow EtO—Ar(NO_2)_n + MeO^-$$

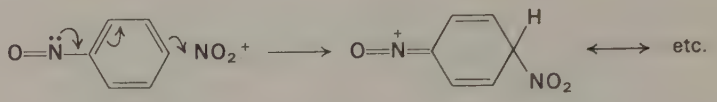
(*a*) $n = 0$ (anisole); (*b*) $n = 1$ (*p*-nitroanisole); (*c*) $n = 2$ (2,4-dinitroanisole); (*d*) $n = 3$ (2,4,6-trinitroanisole).

We can now summarize in a representative energy diagram the nucleophilic aromatic substitution reaction for the four typical substitution patterns that have been discussed. Figure 30-2 shows energy profiles for the reaction of anisole, *p*-nitroanisole, 2,4-dinitroanisole, and 2,4,6-trinitroanisole with the ethoxide ion. Anisole, in which there is no nitro group to stabilize the intermediate anionic complex, reacts so slowly as to appear not to react at all; the activation energy for formation of the unstabilized intermediate is high. With increasing substitution of nitro groups in the *ortho* and *para* positions there is increasing opportunity for charge delocalization in the transition state, with lowering of the activation energy and increasing stability of the intermediate; and in the trinitro compound, the intermediate is a stable compound that can be isolated. In these diagrams the simplifying assumption is made that the energies of the initial and final systems are equal; since the two substituents involved in the replacement are the ethoxyl and methoxyl groups, this is probably nearly correct.

30-9 The nitroso group as a substituent

The nitroso (—$\ddot{N}$=O) group orients *ortho-para* in electrophilic substitution, and also activates *ortho* and *para* halogen to nucleophilic substitution. For this reason, it offers a most interesting example of the operation of resonance effects in these two types of aromatic substitution.

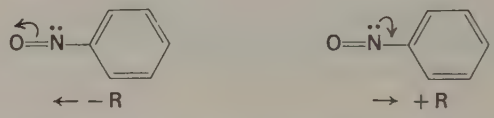
The *ortho-para*-directing power of the nitroso group depends upon its ability to *furnish* the unshared electron pair on nitrogen to the ring upon *demand* of the electrophilic reagent:



Exercise 1

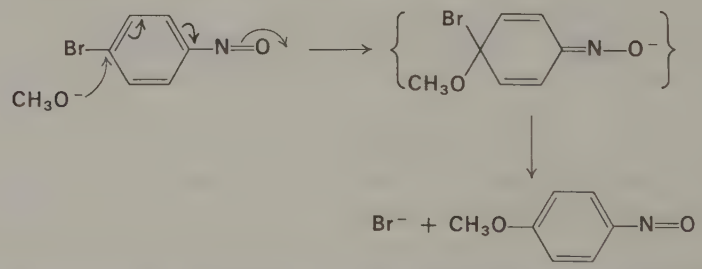
Complete this formulation to the final substitution product.

Although the resonance effect of the nitroso group can be conceived of as operating in either direction



it is only the latter of these (+R) that is called upon by electrophilic attack.

However, when the attack is nucleophilic, the ability of the nitroso group to *accommodate* the electron pair is called into play:



(17)

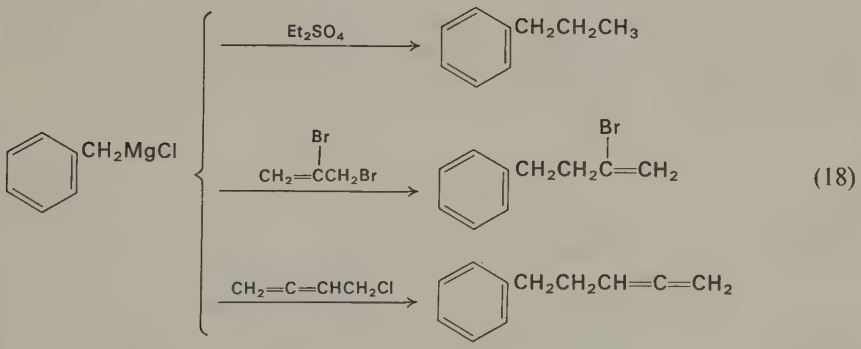
It is apparent that an appreciation of the mechanisms of the reactions involved allows an understanding of the behavior of the nitroso group, which acts in two ways that may appear superficially to be mutually exclusive. The nitroso group is thus acting quite normally in its ability to activate the *ortho-para* positions to *both* electrophilic and nucleophilic attack.

30-10 Other properties of aromatic halogen compounds

The formation of Grignard reagents and lithium derivatives of aryl halides such as bromobenzene, iodotoluenes, and bromonaphthalene proceeds with ease and with

satisfactory yields of the organometallic reagents. This property of aryl halides suits them to a wide variety of synthetic applications. What has been said in earlier chapters about the uses of Grignard reagents applies to arylmagnesium halides, of which phenylmagnesium bromide may be regarded as typical.

Compounds containing halogen in an aromatic side-chain are not properly considered "aromatic halogen compounds"; they behave in general like alkyl halides. The usual displacement reactions of alkyl-bound halogens proceed in the expected way. Benzyl halides are exceptional only in their greater degree of reactivity. Benzyl chloride, bromide, and iodide are rapidly hydrolyzed by alkali; they react with ammonia to yield benzylamine, and with alkali cyanides to give phenylacetonitrile (benzyl cyanide). Benzylmagnesium chloride is readily prepared in good yield. A reaction of benzylmagnesium chloride that is not typical of Grignard reagents in general is its reaction with alkyl sulfates and sulfonates and with allylic halides. Some examples of this are shown in the following equations. It will be seen that this provides a synthetic route to alkylated benzenes:



(18)

Exercise 2

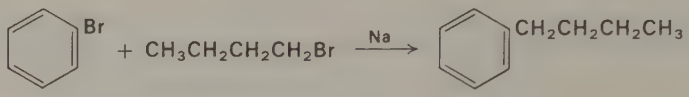
In the reaction of benzylmagnesium chloride with 2,3-dibromo-1-propene, why does the reaction proceed as shown rather than by replacement of the bromine atom at carbon atom 2?

30-11 The Wurtz-Fittig reaction

The reaction of alkyl halides with metallic sodium to give hydrocarbons formed by coupling of the two alkyl groups is known as the *Wurtz reaction*:

$$2CH_3CH_2CH_2CH_2Br + 2Na \rightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3 + 2NaBr$$

Aryl halides do not undergo this coupling reaction; but when an aryl halide and an alkyl halide are allowed to react with metallic sodium, the alkylbenzene is formed:

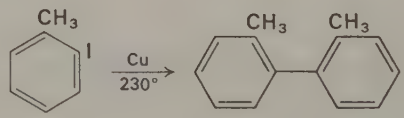


(19)

This reaction is known as the *Wurtz-Fittig reaction*, and is a useful method for the preparation of some alkylbenzenes. The course of both reactions is by way of intermediate sodium derivatives, the alkylsodium and the arylsodium. The Wurtz reaction involves nucleophilic displacement of halogen from the alkyl halide by attack of the alkyl anion provided by $R:^{-}Na^{+}$. Since the aryl halide is not susceptible to the nucleophilic displacement of the halogen, the aryl anion cannot react with it to form a biaryl; but the aryl anion can effect a displacement by attack upon the alkyl halide, and the alkylbenzene is produced in satisfactory yield. The reaction, which is practicable only with primary alkyl halides, yields products in which the alkyl group has not undergone rearrangement, for displacement by the S_N2 mechanism results in attachment of the aryl group at the carbon atom from which the halogen is displaced.

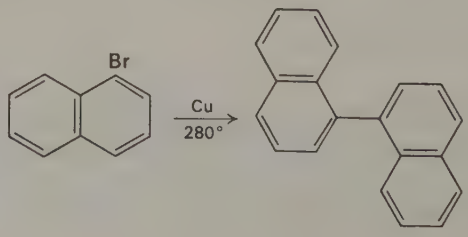
30-12 The Ullmann reaction

The coupling of aromatic nuclei by the reaction of iodo- or bromobenzenes with copper (or sometimes silver) powder is known as the *Ullmann reaction*. *o*-Iodotoluene yields 2,2′-dimethylbiphenyl:



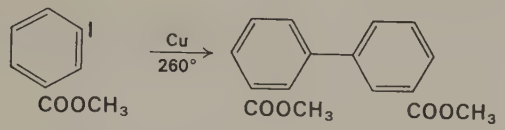
(20)

and 1-bromonaphthalene yields 1,1′-binaphthyl:



(21)

Complex substituted biphenyl derivatives can be prepared by this method; in many cases the yield is not high but there is no more satisfactory method:



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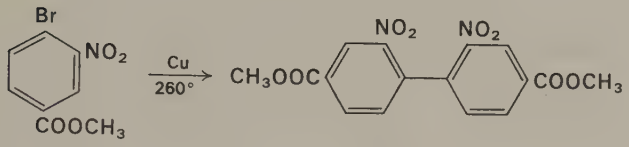
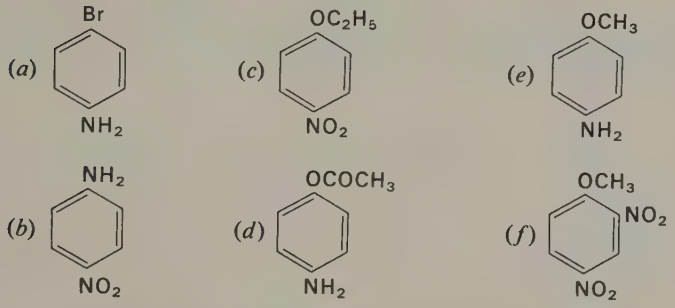


(23)

The preparation of biphenyl derivatives capable of existence in optically active forms is accomplished by the Ullmann reaction. The product of the coupling reaction is, of course, the racemic biphenyl, which is then resolved by usual methods into the enantiomeric forms (Chapter 6).

Problems

1. With a monosubstituted benzene as the starting material, show how the following compounds can be prepared.

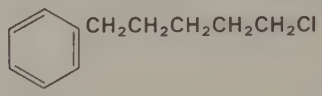


2. Write the reaction between 2,4-dinitrofluorobenzene and (*a*) α-aminopropionic acid, (*b*) aminoacetamide, (*c*) benzylamine, (*d*) aqueous alkali.

3. Complete the following equations, using structural formulas.
   (*a*) 1,3-dimethyl-2,5-dinitrobenzene + methylamine →
   (*b*) 2,3-dinitrotoluene + sodium methoxide →
   (*c*) *p*-dinitrobenzene + hydrazine →
   (*d*) *p*-nitrosonitrobenzene + ammonia →
   (*e*) 3,4-dibromonitrobenzene + aniline →

4. Why is benzyl chloride more reactive in displacement reactions (with nucleophilic reagents) than *n*-heptyl chloride? Would *p*-methoxybenzyl chloride show even greater, or less, reactivity? Why?

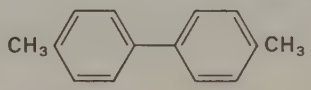
5. Ethyl benzenesulfonate can be used in place of diethyl sulfate in the alkylation of a Grignard reagent. Suggest a method for the preparation of

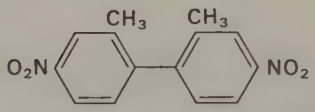


if 4-chloro-1-butanol and benzenesulfonyl chloride are available.

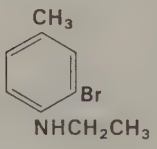
6. Devise practical ways of carrying out the following transformations:
   (*a*) benzene → benzylamine
   (*b*) toluene → phenylacetic acid
   (*c*) toluene → benzene-1,4-dicarboxylic acid
   (*d*) benzene → triphenylcarbinol
   (*e*) bromobenzene → *p*-xylene

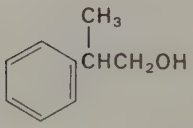
7. Show how the following compounds could be prepared from toluene:

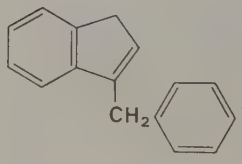
(*a*) 

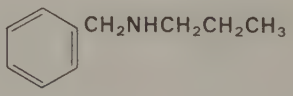
(*b*) 

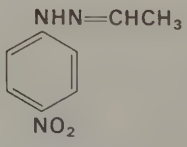
8. Starting with benzene or toluene, and any necessary aliphatic and inorganic reagents, and using reactions that have been described up to this point in the text, devise practical syntheses for the following compounds:

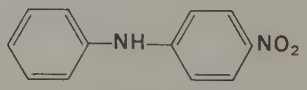
(*a*) 

(*b*) 

(*c*) 

(*d*) 

(*e*) 

(*f*) 

31

Aromatic nitro and nitroso compounds

The nitration of aromatic compounds has been one of the most carefully studied electrophilic aromatic substitution reactions; from these numerous investigations has come much of our understanding of the mechanism of the aromatic substitution reaction.

The properties and practical value of the nitro compounds also deserve special mention, for they are a class of substances with unique uses and valuable applications to chemical synthesis.

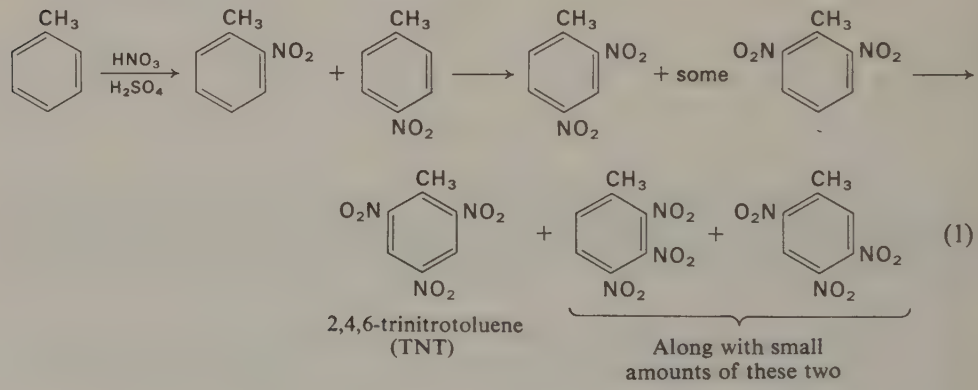
The presence of the nitro group on the aromatic ring often confers upon a compound a tendency toward ready crystallization and a melting point within a useful range. For this reason many reagents used to prepare derivatives are nitro compounds: 2,4-dinitrophenylhydrazine, 3,5-dinitrobenzoyl chloride, and so on. Polynitro compounds form characteristic well-crystallizable charge-transfer complexes that are useful in the isolation, purification, and characterization of polycyclic aromatic compounds.

This chapter describes these and other practical values of nitro compounds, and also serves as an introduction to their use in organic syntheses by way of the amines into which they are easily converted by reduction. The latter subject will be discussed further in the chapters immediately following.

31-1 Preparation of aromatic nitro compounds

Aromatic amines and nitro compounds form a large class of compounds of inestimable importance in organic chemistry. Nitro compounds have many direct uses of their own, but their chief importance is in their ready formation by direct nitration of benzene derivatives and the ease with which they can be reduced to substituted anilines and other aromatic amines. The coal-tar dye industry is based principally upon the aromatic amines, and is so called because the hydrocarbons found in coal tar are converted into the many final products through nitration and reduction to aromatic amines. The great technical importance of these compounds is due largely to the abundance of low-cost starting materials (among them benzene, toluene, xylenes, phenols, naphthalene) and to the ease with which these raw materials can be converted into an enormous array of dyes, pharmaceuticals, vitamins, polymers, and other products indispensable to the convenience, pleasure, and well-being of mankind.

Aromatic nitro compounds are usually prepared by direct nitration. Because of the *meta*-directing effect of the nitro group, di- and trinitration usually lead to compounds in which the nitro groups are 1,3 and 1,3,5 to one another:

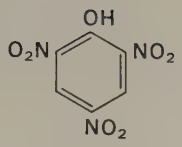


(1)

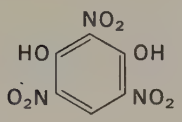
1,3,5-Trinitrobenzene (TNB) cannot be prepared practically by direct nitration of benzene. It can be prepared by decarboxylation of the acid that is formed from 2,4,6-trinitrotoluene by oxidation.

Phenols, which are very reactive in electrophilic substitution, are nitrated with ease, and dilute (aqueous) nitric acid converts phenol into a mixture of *o*- and *p*-nitrophenols. These compounds are readily separated by steam distillation, the success of this operation depending upon the fact that *o*-nitrophenol is volatile with steam, whereas *p*-nitrophenol is not.

Further nitration of partially nitrated phenol leads to the formation of *picric acid* (2,4,6-trinitrophenol). Another important trinitrophenol is *styphnic acid*, 2,4,6-trinitroresorcinol:

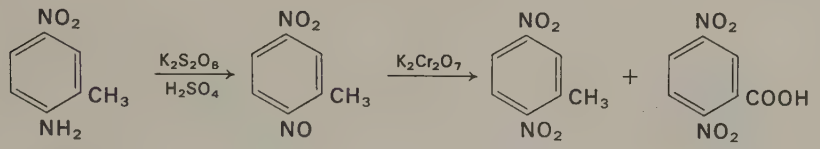


Picric acid



Styphnic acid

Nitro compounds can also be prepared by methods that do not involve direct nitration. A useful procedure is the oxidation of an aromatic amino group to a nitro group. For example, the preparation of 2,5-dinitrobenzoic acid is carried out by the following reactions; the nitroso compound is intermediate:

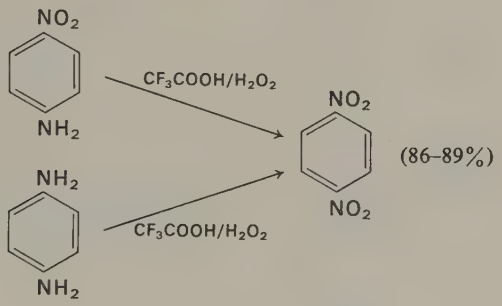


2-amino-5-nitrotoluene

2,5-dinitrobenzoic acid

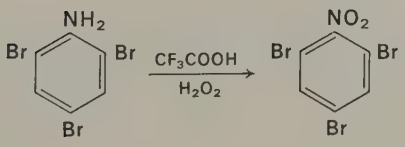
(2)

The direct oxidation of $—NH_2$ to $—NO_2$ can be accomplished by the use of peroxytrifluoroacetic acid ($F_3C{\cdot}CO_3H$):



(3)

(4)



(100%)

(5)

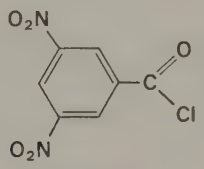
Exercise 1

Devise a synthesis for 3-bromo-4-nitrotoluene from *p*-toluidine.

The replacement of an amino group by a nitro group can also be accomplished by diazotization (Chapter 32) and treatment of the diazonium fluoborate with sodium nitrite and copper powder. *p*-Dinitrobenzene can be prepared from *p*-nitroaniline by this method.

31-2 Uses of aromatic nitro compounds

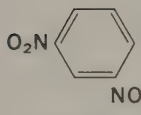
The tendency for compounds containing one or more nitro groups to form well-defined crystalline solids makes many nitro compounds useful in the preparation of derivatives for characterizing and identifying organic substances.



3,5-dinitrobenzoyl chloride

+ alcohols ⟶ alkyl 3,5-dinitrobenzoates (6)

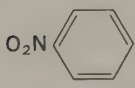
(Methyl 3,5-dinitrobenzoate, m.p. 107°C)



2,4-dinitrophenylhydrazine

+ aldehydes, ketones ⟶ 2,4-dinitrophenylhydrazones (7)

(Acetone 2,4-dinitrophenylhydrazone, m.p. 128°C)



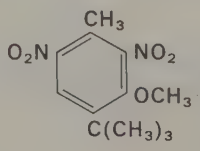
p-nitrobenzyl bromide

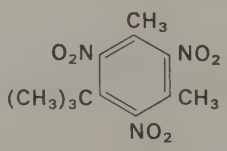
+ acids (As sodium salts) ⟶ *p*-nitrobenzyl esters (8)

(*p*-nitrobenzyl acetate, m.p. 78°C)

The nitration of aromatic hydrocarbons is useful for identification purposes, for di- and poly-nitro derivatives have relatively high melting points: *m*-dinitrobenzene melts at 90°C, 2,4-dinitrotoluene at 70°C, 2,4,6-trinitro-*m*-xylene at 182°C.

An application of nitro compounds that is of special interest is the use of 3-methoxy-2,6-dinitro-4-*t*-butyltoluene, 2,4,6-trinitro-1,3-dimethyl-5-*t*-butylbenzene, and several other related compounds in perfumery as "synthetic musks":





Exercise 2

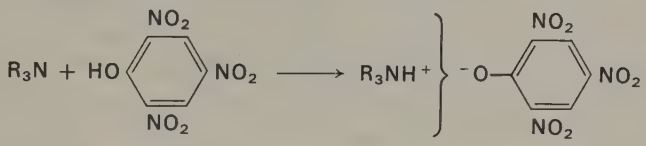
Suggest a synthesis of 2,4,6-trinitro-1,3-dimethyl-5-*t*-butylbenzene, starting from *m*-xylene.

The *n*-propyl ether of 2-amino-4-nitrophenol has the remarkable property of being 4,000 times sweeter than cane sugar.

Some nitro compounds are widely used explosives. TNT, 1,3,5-trinitrobenzene, picric acid, trinitroxylene, *N*,2,4,6-tetranitro-*N*-methylaniline are high explosives of great technical and military importance.

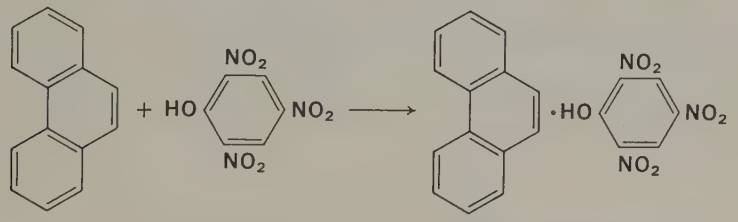
31-3 Picrates and styphnates. Complex formation with polynitro compounds

An important use of picric and styphnic acids in laboratory practice is in the preparation of the *picrates* and *styphnates* of amines. These compounds are salts; their value lies in the fact that they are usually nicely crystalline compounds and are useful for the isolation, purification, and identification of amines:



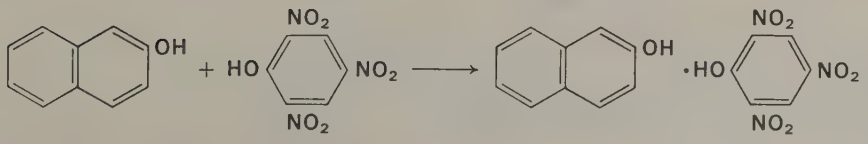
(9)

Crystalline "picrates" are also formed from the reaction of picric acid with polynuclear aromatic hydrocarbons and their derivatives. These are molecular complexes, not salts of the kind that are formed with amines. They possess definite compositions (usually one mole of picric acid per mole of hydrocarbon), and find use in the characterization of such compounds as naphthalene and phenanthrene derivatives and other polycyclic aromatic compounds:



(10)

Phenanthrene picrate



(11)

Picrates such as those of phenanthrene and naphthalene derivatives have a special usefulness in addition to their value as crystalline derivatives of definite and characteristic melting point: the picric acid that they contain can be titrated with standard alkali, so that an *equivalent weight* can be obtained for the complex. Since the molecular weight of picric acid is known, the equivalent (or molecular) weight of the hydrocarbon can be obtained.

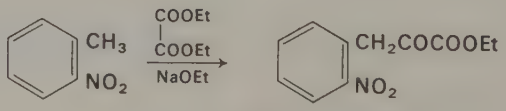
The ability of picric acid to form complexes of this kind does not depend upon the presence of the phenolic hydroxyl group, for trinitrobenzene forms similar complexes.

The exact nature of the complexes formed between hydrocarbons and polynitro compounds has been the subject of much discussion and speculation. The following experimental facts must be taken into consideration: the bonding energy between the two molecules in a complex is small, so that the complexes are easily dissociable; most of the complexes are deeply colored, many of them brilliantly so; and the formation of the complexes is facilitated both by an increasing number of nitro groups in the polynitro compound, and by increasing basicity in the hydrocarbon. Hexamethylbenzene forms a crystalline complex with 1,3,5-trinitrobenzene, but benzene and toluene do not. It appears that there is some charge-transfer between the two members of the complexing pair, not to an extent that constitutes covalent bonding, but to a greater extent than can be ascribed to simple electrostatic interaction between polarized molecules. Complexes of this kind, and others of related types that are formed between strongly electrophilic and strongly nucleophilic aromatic compounds, are usually referred to as *charge-transfer complexes* or *π complexes*.

31-4 Activation of the methyl group by the nitro group

The methyl group of *o*- and *p*-nitrotoluenes is an "active" methyl group with properties comparable to those of methyl groups activated by carbonyl and cyano groups in aliphatic compounds. This property of the methyl group is greatly enhanced in 2,4-dinitro- and 2,4,6-trinitrotoluene.

o-Nitrotoluene can be acylated with oxalic ester under the influence of alkali metal alkoxides:

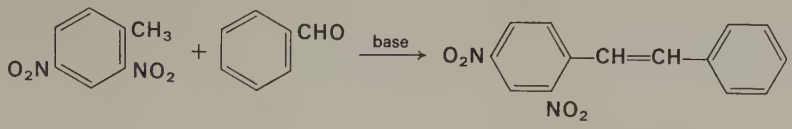


(12)

Ethyl *o*-nitrophenylpyruvate

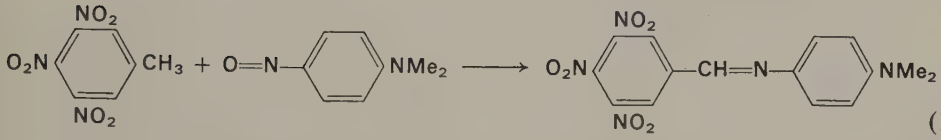
p-Nitrotoluene undergoes a similar reaction.

With the additional activation furnished by two or three nitro groups, the methyl group is capable of undergoing a condensation of the aldol type with aldehydes and aromatic nitroso compounds:



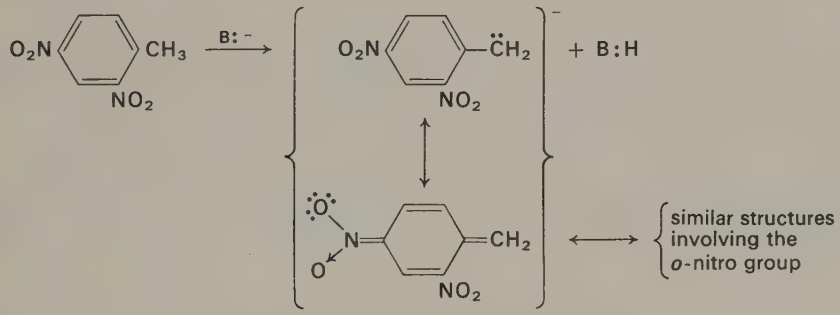
(13)

2,4-dinitrostilbene



(14)

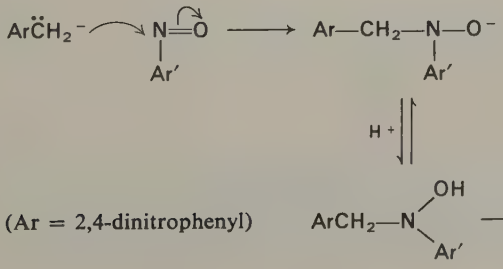
The enhancement of the acidity of the methyl group in the nitrotoluenes is related to the resonance stabilization of the anion that is formed by the removal of a proton:



Exercise 3

Write the structures involving the *o*-nitro group in the above anion.

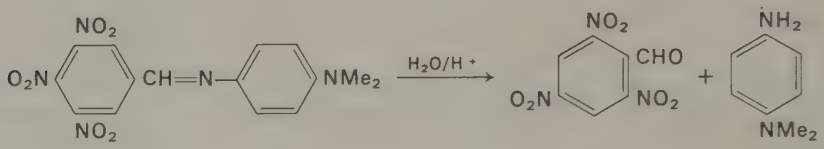
The condensation of 2,4-dinitrotoluene with a nitroso compound may be formulated:



(Ar = 2,4-dinitrophenyl) $\quad ArCH_2—N(OH)—Ar' \longrightarrow ArCH{=}NAr' + H_2O$ (15)

These condensations are clearly analogues of the related condensations of the aldol type.

The condensation product of 2,4,6-trinitrotoluene and *p*-nitrosodimethylaniline, shown earlier in this section, is a Schiff base. It is evident that it is the Schiff base that would be formed by the condensation of 2,4,6-trinitrobenzaldehyde and *p*-dimethylaminoaniline, and thus that it can be hydrolyzed to these compounds:

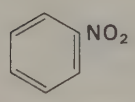


(16)

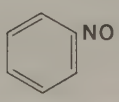
This is a convenient method of preparing 2,4,6-trinitro- or 2,4-dinitrobenzaldehyde.

31-5 Compounds formed by the reduction of nitro compounds

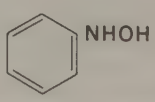
The nitro group represents the highest, the amino group the lowest, oxidation state of nitrogen attached to carbon. Between these extremes two others are known, as shown by the following benzene derivatives:



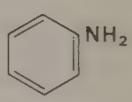
Nitrobenzene



Nitrosobenzene



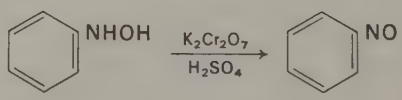
Phenylhydroxylamine



Aniline

31-6 Aromatic nitroso compounds

The reduction of nitrobenzene to nitrosobenzene cannot be carried out by generally practical means. Nitrosobenzene is best prepared by the oxidation of phenylhydroxylamine:

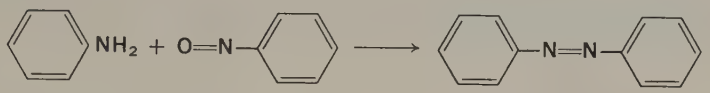


(17)

Nitrosobenzene has the interesting property of being a colorless crystalline solid but of melting to a green liquid and forming green solutions. The colorless solid is a dimeric form; the green liquid is a monomeric form. This is a property of the nitroso

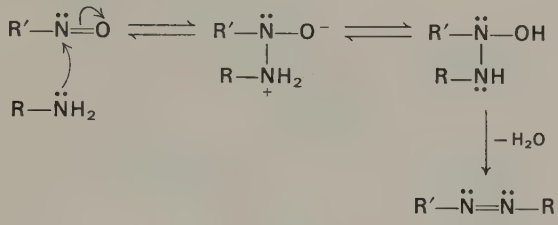
group, since the tertiary aliphatic nitroso compound Me_3CNO behaves similarly: it is colorless in the solid state, blue in the liquid state (melted).

Aromatic nitroso compounds undergo condensation reactions with primary amines and with active methylene compounds. The reaction of nitrosobenzene with aniline gives azobenzene:



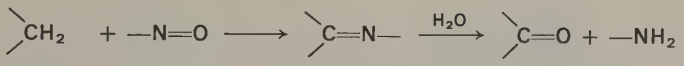
Azobenzene (18)

The capacity of the nitroso group to undergo addition reactions with amines can be represented by the partial equation



(19)

and is a manifestation of the same property that is shown in the reaction of nitroso compounds with active methylene compounds, exemplified by (14), (15), and the partial formulation



Active methylene (20)

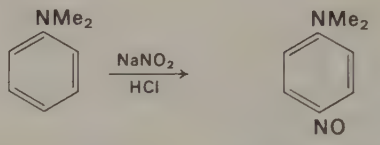
An inspection of (20) discloses that the overall result is an oxidation of the active methylene group to a carbonyl group, with concomitant reduction of —NO to $—NH_2$.

Exercise 4

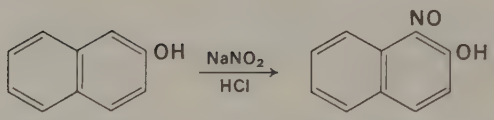
Account for the fact that hydrolysis of the  linkage gives  and $—NH_2$ rather than  and —NO.

31-7 Direct nitrosation of phenols and amines

The most commonly encountered nitroso compounds are those formed by the direct nitrosation of the aromatic nucleus. This reaction, an electrophilic substitution, requires a sufficiently activated aromatic ring and is useful chiefly with phenols and amines having free *o* and *p* positions. The reaction is carried out by acidifying a solution containing the phenol and sodium nitrite, or by adding sodium nitrite to a solution of the amine hydrochloride:

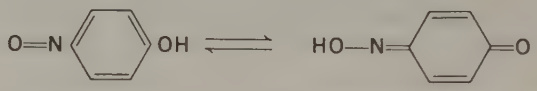


p-nitrosodimethylaniline (21)



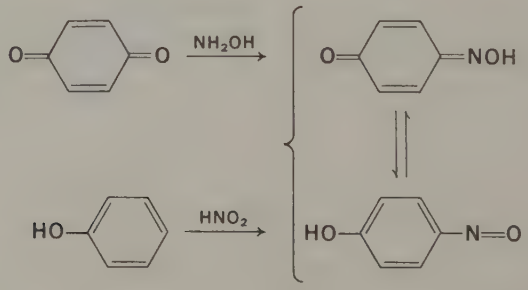
β-naphthol 1-nitroso-2-naphthol (22)

Nitrosophenols are of special interest because they exist as mixtures of the tautomeric forms:



p-nitrosophenol *p*-benzoquinone monoxime

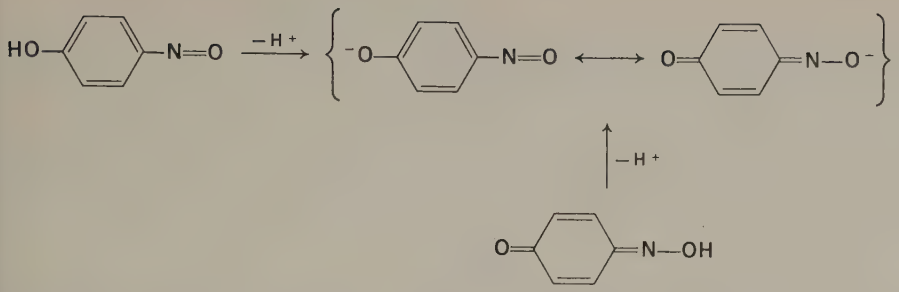
Indeed, the same compound is obtained by the nitrosation of phenol and by the reaction of hydroxylamine with *p*-benzoquinone:



(23)

(24)

The interconversion of the nitrosophenol and the quinone monoxime can be understood when it is recognized that the anion that would be formed by ionization of the proton from either of these is the hybrid ion:



(25)

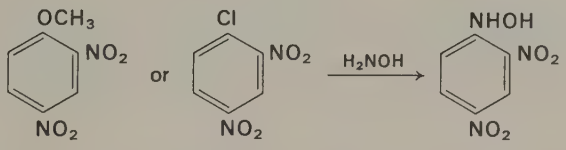
Recapture of a proton by this ion gives the equilibrium mixture of the two tautomers.

31-8 Arylhydroxylamines

Phenylhydroxylamine, the next-lower reduction state from nitrosobenzene, can be prepared by the reduction of nitrobenzene with zinc in a buffered medium (ammonium chloride solution). It is probable that nitrosobenzene is the first reduction product formed from nitrobenzene and is easily reduced further.

Since phenylhydroxylamine can be oxidized by an ammoniacal solution of silver nitrate (Tollens' reagent) to form a silver mirror (or black metallic silver), the reduction of nitro compounds to arylhydroxylamines, followed by testing with Tollens' reagent, is a useful *diagnostic test for the nitro group*.

Di- and trinitrophenylhydroxylamines can be prepared by treating the appropriate chloro or methoxy compounds with hydroxylamine; for example (see Section 30-5):

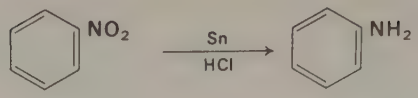


(26)

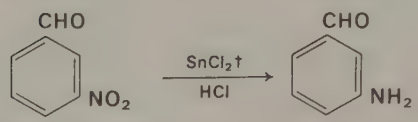
31-9 Amines

The most important reduction products of aromatic nitro compounds are the amines. These are produced by the action of most reducing agents on nitro compounds. Because of the great importance of the aromatic amines, many methods of carrying out these reductions have been discovered. The following equations describe a number of important technical and laboratory methods:*

* The procedures described in the equations are not mutually exclusive, with the exception of the last, which is a special method of reducing one nitro group of a pair. The examples given are those of specific preparations, in which the choice of the reducing agent was governed by the particular considerations of convenience, yield, and availability of the starting material.



(27)



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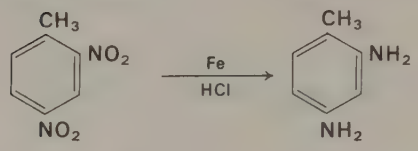

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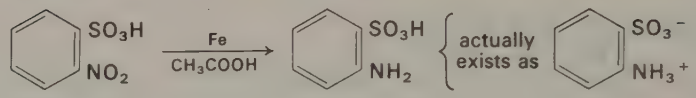

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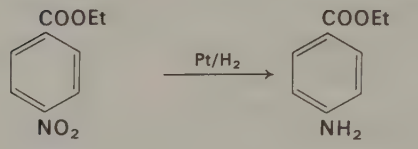

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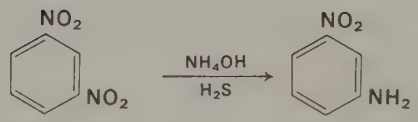


(32)

The industrial reduction of nitrobenzene is carried out on a large scale, and, as a matter of economy, an inexpensive reducing agent must be used. The reduction is carried out with iron (scrap and waste iron) in the presence of a small amount of HCl. The effective reagents are thus iron and water, the products aniline and oxides of iron.

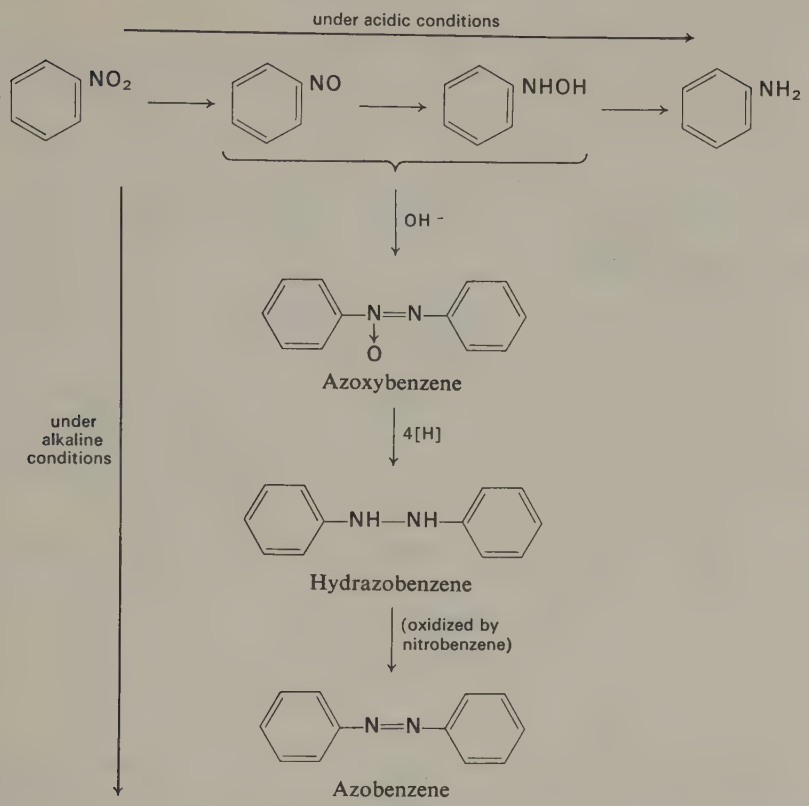
31-10 Reduction of nitro compounds under alkaline conditions

The reduction of nitrobenzene in an alkaline medium leads to various products. The intermediate reduction products (nitrosobenzene and phenylhydroxylamine), in the presence of alkali, engage in condensation reactions with one another, with nitrobenzene, and with aniline to form "bimolecular" reduction products containing two aromatic rings and two nitrogen atoms.

---

* The use of stannous chloride is often advantageous, since the theoretically required amount of reducing agent can be somewhat more easily used than when metallic tin is employed. When metallic tin is used in excess, the tin is oxidized chiefly to the stannous state, with the result that the extent to which the possible reducing power of the metal ($Sn \rightarrow 4e + Sn^{4+}$) is utilized may be uncertain and not subject to precise control.

The course of these reductions may be summarized as:



(33)

1. Azoxybenzene is the chief product of the reduction of nitrobenzene with an alkaline solution of glucose.

2. Hydrazobenzene is prepared by the reduction of nitrobenzene with zinc and alkali.

3. Azobenzene may be prepared by reduction of nitrobenzene with stannous chloride and alkali, but it is most conveniently prepared by the oxidation of hydrazobenzene with air. It can also be prepared by the reduction of azoxybenzene with iron in aqueous solution.

Problems

1. Write the equations for the mononitration of each of the following compounds. Show the predominant product only. (*a*) bromobenzene, (*b*) *p*-xylene, (*c*) *p*-nitrotoluene, (*d*) anisole, (*e*) acetanilide, (*f*) *o*-bromoacetanilide, (*g*) *m*-xylene,

(*h*) *p*-*tert*-butyltoluene, (*i*) benzoic acid, (*j*) *p*-toluic acid, (*k*) 1,2,3-trimethoxybenzene.

2. Show by equations how the following compounds can be prepared. Any monosubstituted benzene may be used as starting material. (*a*) *p*-nitroaniline, (*b*) 3,4-dinitrobromobenzene, (*c*) 2,5-dinitrotoluene, (*d*) 2,4-dinitroaniline.

3. Show the mechanistic details of the reaction between sodium propionate and *p*-bromobenzyl bromide.

4. Another reagent for the preparation of crystalline derivatives of carboxylic acids is *p*-bromophenacyl bromide. The derivatives are esters. Show by means of an equation how this reagent is used to prepare the derivative of acetic acid.

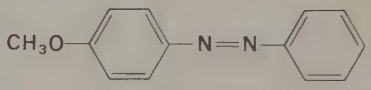
5. Write the equations that describe the preparation of 2,4-dinitrobenzaldehyde, with toluene and *N*,*N*-dimethylaniline as the organic starting materials.

6. Suggest a method by which mesoxalic acid (as the diethyl ester) could be prepared from diethyl malonate: $CH_2(COOEt)_2 \rightarrow CO(COOEt)_2$.

7. Write the reaction showing the equilibrium between the tautomeric forms of 1-nitroso-2-naphthol (compare with *p*-nitrosophenol).

8. Read the entry "Explosives" in a good encyclopedia, and from it make a list of aromatic nitro compounds that are used as explosives.

9. How could *p*-methoxyazobenzene



be prepared, starting with benzene?

32

Reactions of amines with nitrous acid. Diazo compounds

The reactions of amines with nitrous acid have unique features, the chemistry of which requires special description. Moreover, the products of the reaction of primary aromatic amines with nitrous acid—diazonium salts—are compounds of great synthetic value. Aromatic diazonium salts are versatile reagents (often the only practical means) for introducing substituents into the aromatic ring.

Because most aromatic amines are derived from the corresponding nitro compounds (Chapter 31), which can be prepared in ways that lead to predictable orientation, the synthetic pathway [nitro compound → amine → diazonium salt → final products] provides a versatile means for the preparation of substituted benzene derivatives of many kinds.

The preparation and fate of aliphatic primary amines is here alluded to only briefly because it has been discussed earlier (Chapter 16). Other aspects of the chemistry of aromatic amines, in particular the enhanced nucleophilic reactivity of the aromatic ring, have been dealt with in other contexts in earlier chapters. One that is relevant to the present topic, the nuclear nitrosation of aromatic amines, is discussed further in this chapter. It will be recognized, however, that nuclear nitrosation is but another example of the electrophilic aromatic substitution reaction, and does not require extended comment.

32-1 Reactions of amines with nitrous acid

One of the most interesting and useful reactions of amines, both aromatic and aliphatic, is with nitrous acid. Reactions of this kind lead to various consequences, depending upon whether the amine is primary, secondary, or tertiary, aliphatic or aromatic. We shall examine each of these, and it will be seen that in every case *the initial stage of the reaction involves the nucleophilic attack of the amine upon the nitrous acid*; the subsequent events are governed by the structure of the amine. Certainly the most important of these reactions is between primary aromatic amines and nitrous acid, leading to the aromatic diazonium compounds. This reaction, called *diazotization*, applied to synthetic processes both in the laboratory and in the chemical industry, is capable of such a degree of versatility that we shall devote special attention to it. Certain aspects of the behavior of amines of other kinds are discussed in the following sections.

Nitrous acid can be described by the structure H—Ö—N̈=Ö:. It is, of course, a hydrogen acid; by removal of the proton it yields the nitrite ion, NO_2^-:

$$\left\{ :\ddot{O}—\ddot{N}=\ddot{O}: \longleftrightarrow :\ddot{O}=\ddot{N}—\ddot{O}: \right\}^-$$

Whereas the nitrite ion is a nucleophile, nitrous acid is typically electrophilic in character, attack by a nucleophilic reagent upon the nitrogen atom (2) resembling the first step in carbonyl addition reactions (1):

$$B:^- + \underset{|}{C}=O \rightleftharpoons B—\underset{|}{C}—O^- \qquad (1)$$

$$B:^- + \ddot{N}=O \rightleftharpoons B—\ddot{N}—O^- \qquad (2)$$

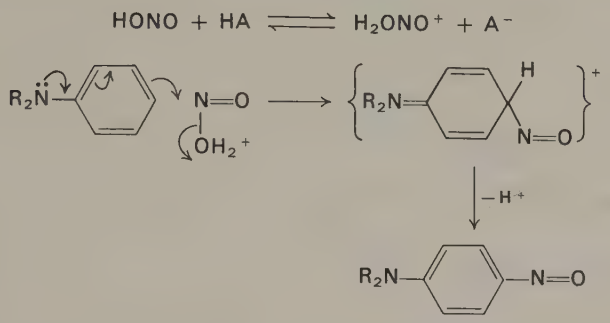
The role of step (2) in the reactions of amines with nitrous acid will be amplified by examples in the discussion to follow.

32-2 Tertiary amines

The reaction of a tertiary *aliphatic amine* with nitrous acid is simply the protonation of the amine. It leads to no consequences in the form of stable products, and upon the addition of a base the amine is recovered unchanged.

A tertiary *aromatic amine* reacts with nitrous acid to undergo nuclear nitrosation (unless the *ortho* and *para* positions are occupied by substituents). This is a typical electrophilic substitution reaction and can be formulated in accordance with our general view of this kind of reaction.

In the simplest terms, the nitrosating agent can be regarded as a nitrosonium-ion carrier such as $H_2\overset{+}{O}$—NO, the protonated form of nitrous acid:



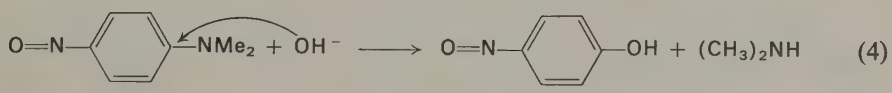
(3)

The nitrosonium ion is much less electrophilic than the nitronium ion, NO_2^+, and attacks only strongly nucleophilic aromatic nuclei. Phenols are readily nitrosated, as are tertiary aromatic amines; but aromatic rings bearing substituents less strongly activating than hydroxyl or amino groups, or deactivating substituents, are not attacked by nitrosating agents.

It is not possible to describe all nitrosating reagents in terms of a single nitrosonium-ion-carrying species, for because of the equilibria that can exist in a strongly acid solution of nitrous acid, the nitrosonium-ion carrier may be the protonated nitrous acid, N_2O_3 (O_2N—NO), BrNO (in HBr), or even the nitrosonium ion itself, NO^+. Here, as in halogenation, nitration, and acylation, it is not always possible to be specific about the actual identity of the attacking electrophile. Thus, the summary equation (3) given above must be regarded as representative only.

p-Nitrosodialkylanilines are easily prepared by adding sodium nitrite to a solution of the dialkylaniline in hydrochloric acid.

p-Nitrosodimethylaniline is a brilliant green compound; its hydrochloride is yellow. When it is treated with hot sodium hydroxide solution, dimethylamine is liberated and *p*-nitrosophenol (as the sodium salt) is formed:



(4)

This reaction (Section 30-5) constitutes a useful method for the preparation of some secondary amines by the following sequence: dialkylation of aniline, nitrosation, and alkaline cleavage in the above manner. The displacement of the dialkylamine will be recognized as a typical aromatic nucleophilic displacement reaction, carried to completion in this case by the formation of the anion of the *p*-nitrosophenol. Treatment of *p*-nitrosodimethylaniline with sodium methoxide results in the liberation of dimethylamine and the formation of *p*-nitrosoanisole.

Exercise 1

Write the reaction of *p*-nitrosodimethylaniline and sodium methoxide, and compare it with alcoholysis of an amide with sodium methoxide.

Exercise 2

Starting with *N*-benzylaniline, devise a synthesis for ethylbenzylamine, $CH_3CH_2NHCH_2C_6H_5$.

32-3 Secondary amines

The reaction of a secondary aliphatic or aromatic amine with nitrous acid results in *N*-nitrosation:

$$(CH_3)_2NH + HONO \longrightarrow (CH_3)_2N{-}NO \qquad (5)$$

N-nitrosodimethylamine

(6)

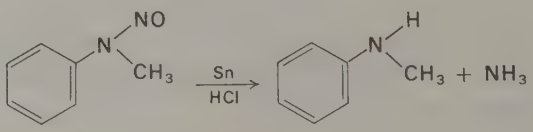
N-nitroso-*N*-methylaniline

Exercise 3

Why is nuclear nitrosation not the primary step in (6)?

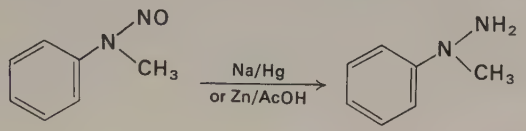
The *N*-nitroso amine is no longer basic, in contrast to the amine from which it is formed; it is not an amine, but an amide of nitrous acid, and, like amides in general, is a very weakly basic ("neutral") substance.

It will be recalled that in the preparation of *N*-ethyl-*m*-toluidine the secondary amine is purified by converting it into the neutral, ether-soluble *N*-nitroso derivative, which can be separated from the basic unethylated and diethylated toluidines, and from which the amine is regenerated by reduction. Reduction of *N*-nitroso secondary amines, with cleavage of the N—N bond, is accomplished with reducing agents such as stannous chloride or metal/mineral-acid combinations:



(7)

Mild reducing agents such as sodium amalgam or zinc and dilute acetic acid convert *N*-nitroso amines into the corresponding 1,1-disubstituted hydrazines:



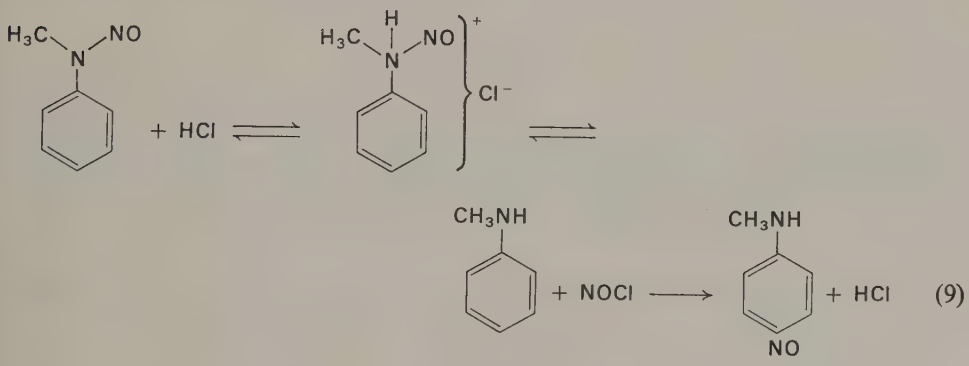
(8)

N-methyl-*N*-phenylhydrazine

N-Methyl-*N*-phenylhydrazine is a useful reagent for the characterization of sugars, forming derivatives called methylphenylhydrazones.

N-Nitroso derivatives of secondary aromatic amines rearrange under the influence of HCl or HBr to give *C*-nitroso compounds [equation (9)].

This "rearrangement" is really an intermolecular nuclear nitrosation reaction comparable in all respects to that between a nitrosating agent and a tertiary amine. *N*-Nitrosation and nuclear nitrosation are thus the separate consequences of the interrelated equilibria expressed in the following equations, and the formation of the ring-nitrosated product is the consequence of the greater thermodynamic stability of that compound. Under mildly acidic conditions, the greater nucleophilicity of the nitrogen atom leads rapidly to the *N*-nitroso derivative. When the acidity of the medium is increased, the increased availability of the more electrophilic nitrosating agent, NO^+ or NOCl, permits the establishment of the final, more favorable, equilibrium, and nuclear nitrosation is the end result. Concomitant protonation of the methylamino group stabilizes the *p*-nitroso compound.

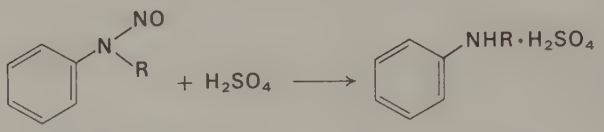


(9)

32-4 The Liebermann nitroso reaction: A diagnostic test for secondary amines

The denitrosation of *N*-nitroso compounds forms the basis of a test for these substances, called the *Liebermann nitroso reaction*. Treatment of an *N*-nitroso amine with

phenol in concentrated sulfuric acid gives a solution that turns red on dilution and blue on addition of alkali. The course of this reaction involves the following: the nitrosation of the phenol by nitrous acid formed by denitrosation of the nitrosoamine; and the condensation of the nitrosophenol with a second molecule of phenol to yield the indophenol, which is red in the unionized form and gives a blue anion with alkali:



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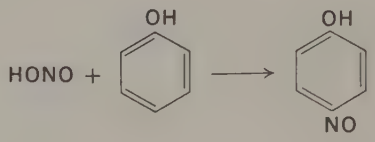

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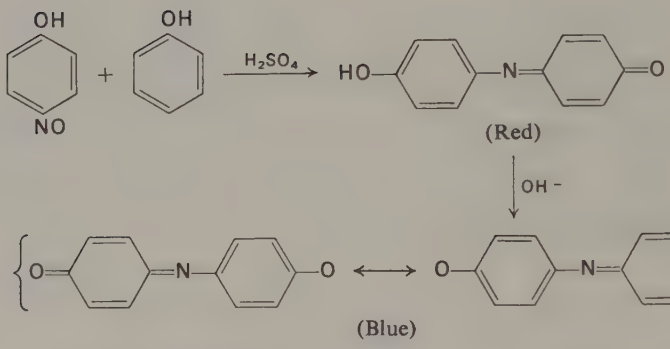


(12)

When phenol is used as the test reagent, the Liebermann reaction is undergone by *p*-nitrosophenol and by nitrous acid or nitrites; it is also used as a test for phenols, an *N*-nitrosoamine being used as the test reagent in this case.

Exercise 4

The first step in reaction (12) is a typical electrophilic substitution reaction. Formulate the course of this reaction through the sequence of stages from electrophilic attack upon phenol to the formation of the final product, the indophenol. Note that the essential feature of the reaction is the formation of a bond between the nitrogen atom of the nitrosophenol and the carbon atom *para* to the OH group of the phenol.

32-5 The reaction of primary amines with nitrous acid

The reaction between a primary amine and nitrous acid leads, probably through a transitory stage of *N*-nitrosation, to a *diazonium* salt. The overall reaction, written without mechanistic detail, is

$$R{-}NH_2 + HONO \xrightarrow{HA} \left.R{-}N_2^+\right\} A^- + 2H_2O$$

The reaction is usually carried out by adding sodium nitrite to a solution of the amine in HCl; in that case, the final solution contains the diazonium chloride ($A^- = Cl^-$). The formation and fate of aliphatic diazonium salts has been described in Chapter 16.

32-6 The nature of the diazotization reaction and the structure of the diazonium ion

The structure of the diazonium ion is best discussed for the case of the aromatic diazonium salts, since these are relatively stable compounds that can be prepared and preserved in solution and can often be isolated as pure substances.

The reaction of nitrous acid with a primary aromatic amine appears, from studies of the mechanism of the reaction, to involve the free amine and the species N_2O_3 ($O{=}N{-}O{-}N{=}O$, the anhydride of nitrous acid). The initial step can be regarded as a nucleophilic attack of $-NH_2$ on N_2O_3 with displacement of NO_2^-:

$$Ar{-}\overset{\displaystyle H}{\underset{\displaystyle H}{N}}{:} \curvearrowright N{-}\overset{\displaystyle O}{\overset{\displaystyle \|}{}}{-}ONO \longrightarrow Ar{-}\overset{+}{N}H_2{-}NO + NO_2^- \qquad (13)$$

Subsequent proton exchange in the product of the initial attack (13) and loss of a molecule of water lead to the formation of the diazonium ion:

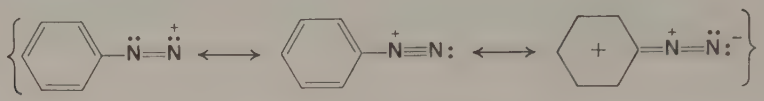
$$Ar\overset{+}{N}H_2N{=}O \rightleftharpoons \left\{ArNH{-}\overset{+}{N}{-}OH \longleftrightarrow Ar\overset{+}{N}H{=}N{-}OH\right\} \rightleftharpoons$$

$$ArN{=}N{-}\overset{+}{O}H_2 \rightleftharpoons ArN{\equiv}\overset{+}{N} + H_2O \qquad (14)$$

Exercise 5

Show the electronic details of these reactions by rewriting the above equilibria with complete electronic structures.

The relative stability of the aromatic diazonium ion is the result of resonance among the contributing structures of the hybrid:



(15)

Contributions pictured in (15) distinguish the aromatic diazonium salts from the aliphatic, since the latter are incapable of enlisting effective cooperation of the R group in this way.

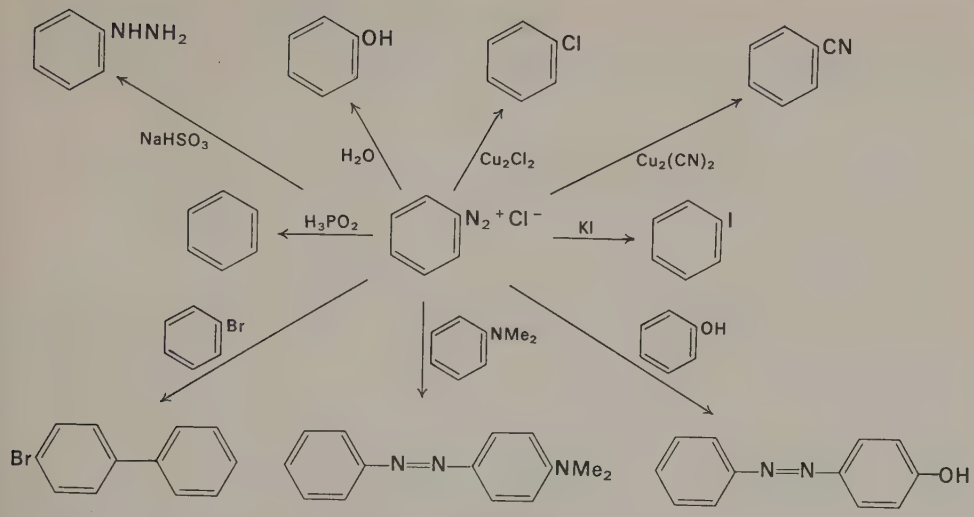
32-7 The diazotization process and the nature of diazonium salts

The diazotization reaction is ordinarily carried out by adding sodium nitrite to an ice-cooled solution of the aromatic amine in aqueous hydrochloric or sulfuric acid (usually about 3 equivalents of acid per mole of amine). The amine hydrochloride or sulfate may be present initially as a suspension, but it dissolves as the diazotization proceeds. The final solution must be kept cold (0–5°C) to avoid decomposition of the diazonium salt, and under these conditions the salt may be preserved until it is used in subsequent manipulations.

Solid diazonium salts are seldom isolated but upon occasion may be prepared in pure form by carrying out the diazotization in alcohol (using an alkyl nitrite as the source of nitrous acid) and precipitating the diazonium salt by the addition of ether, in which it is insoluble. The dry diazonium salts are very unstable, and often decompose with explosive violence. Certain complex double salts of diazonium compounds are quite stable. The fluoborates are often stable enough to be dried and stored:

$$ArN_2^+Cl^- + HBF_4 \longrightarrow \underset{\text{(A diazonium fluoborate; insoluble, stable)}}{ArN_2^+BF_4^-} + HCl \qquad (16)$$

The diazotization of aromatic amines occupies a prominent place in organic chemistry, both from the standpoint of the industrial applications of the process and the remarkable versatility of the diazonium salts in many kinds of synthetic processes. A summary of the important transformations that the diazonium salts undergo, illustrated with the simplest example, benzenediazonium chloride, is given in the following chart:

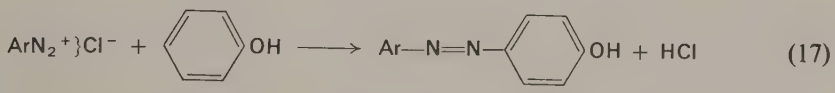


These reactions will be discussed in the sections to follow.

32-8 The diazonium ion as an electrophilic reagent

The aromatic diazonium ion is clearly *electrophilic*; it is deficient in electrons, a fact that can most easily be seen by examining the contributing structure Ar—$\ddot{N}$=$\overset{+}{N}$:, in which the terminal nitrogen atom can accommodate another pair of electrons and thus coordinate with a nucleophile.

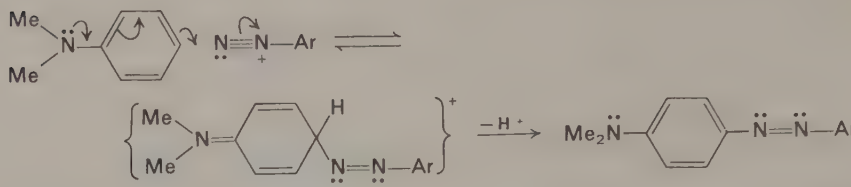
Aromatic diazonium salts are capable of attacking a sufficiently active aromatic nucleus, a typical electrophilic substitution being the result:



(17)

This reaction is *not different in kind* from the many electrophilic substitution reactions we have already examined. It differs from nitration, acylation, and halogenation *in degree*, in that the diazonium ion is not a powerful electrophile and thus can attack only reactive aromatic nuclei. Hence, the *coupling reaction* is practically confined to the reaction of diazonium salts with phenols and amines; some phenolic ethers and, in a few cases, reactive aromatic hydrocarbons, such as mesitylene, can also undergo coupling, but this is not general.

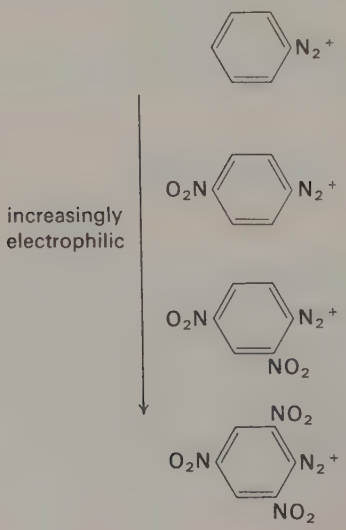
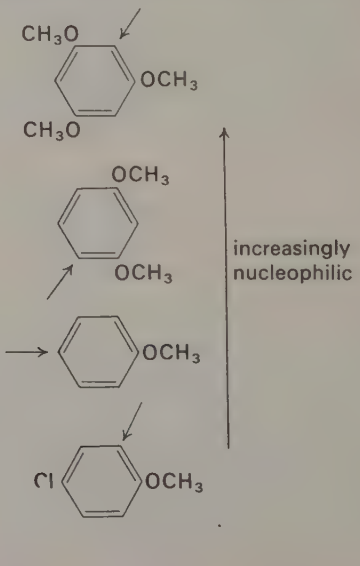
The activating influence of, for example, an amino substituent is clearly the same as the activating effect of an amino substituent in electrophilic substitutions in general:



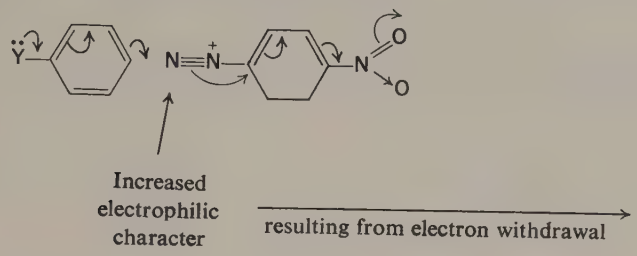
(18)

Since the electrophilic character of the diazonium ion is increased by electron withdrawal from the nitrogen atoms, electron-attracting substituents in the aromatic ring of ArN_2^+ increase the coupling ability of the ion. *p*-Nitro-, 2,4-dinitro-, and 2,4,6-trinitrobenzenediazonium salts are increasingly more reactive in coupling, and require correspondingly less active nuclei with which to react. In Table 32-1 is shown a series of increasingly electrophilic diazonium ions. It can be seen that the benzenediazonium ion will couple only with the most reactive nucleus of these (phloroglucinol trimethyl ether); but with an increasing number of nitro groups in the diazonium ion, less reactive (that is, nucleophilic) nuclei are required for successful coupling. Indeed, the trinitro compound couples with the ring bearing the deactivating halogen atom.

Table 32-1
Electrophilic diazonium ions

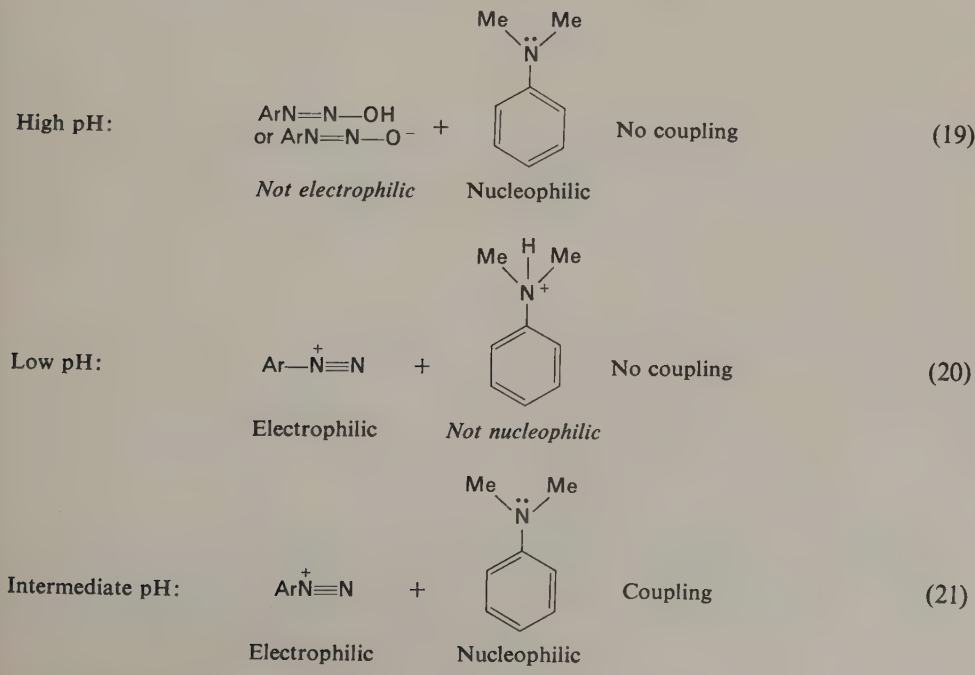
Diazonium ion	*Couples with (at position indicated by →)*
	

The effect of a single nitro group, for example, can be shown by writing the electrophilic attack in the following summary fashion:

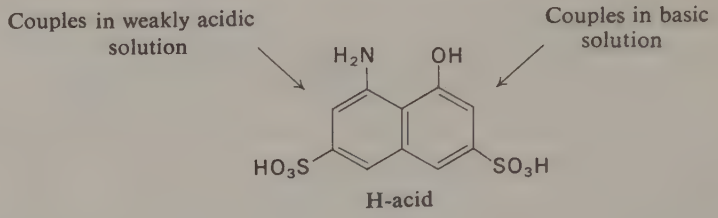


32-9 Effect of pH on the coupling reaction

Coupling is best carried out in solutions that are neither too strongly acidic nor alkaline. The reasons for this can be seen if we examine a typical case, the coupling of benzenediazonium chloride with dimethylaniline. *At high* pH, the diazonium ion is present in very low concentration, since most of it has been converted to ArN=N—OH and ArN=N—O^-. Neither ArN=NOH (the diazohydroxide) nor ArN=N—O^- (the diazotate ion) is electrophilic, and thus does not couple with the amine. *At low* pH, the dimethylaniline will be largely protonated to $ArN\overset{+}{H}Me_2$, and thus the activating effect of the $—NMe_2$ group is destroyed, since the nitrogen atom no longer possesses an unshared pair of electrons:



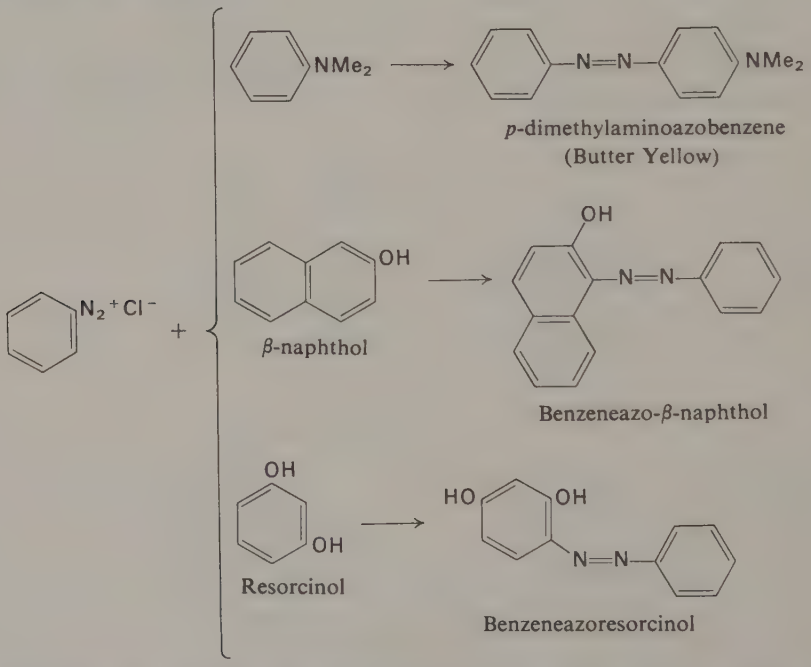
The effect of pH upon the coupling reaction is well illustrated by the coupling of the naphthalene derivative called "H-acid" with diazonium salts. At slightly acidic pH values, at which a large proportion of the amino groups are free (unprotonated), but at which ionization of the OH group is suppressed, the amino group exerts the stronger directing influence. At high pH, the hydroxyl group is ionized, and the strongly activating $—O^-$ substituent is the stronger directing influence:



H-acid

32-10 Azo compounds

The products of the diazonium coupling reactions contain the grouping —N=N—, and are called *azo compounds*:

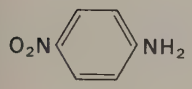


(22)

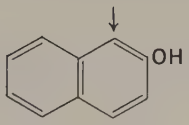
Azo compounds are colored; the simple examples are usually yellow, orange, or red, but with increasing complexity of the two partners involved in the coupling reaction an almost unlimited range of brilliantly colored substances can be formed. The

important *azo dyes* are prepared by this coupling reaction, and are known in a large variety of colors and shades. Some examples of commercial azo dyes are shown in the following:

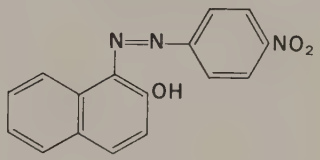
Amine diazotized



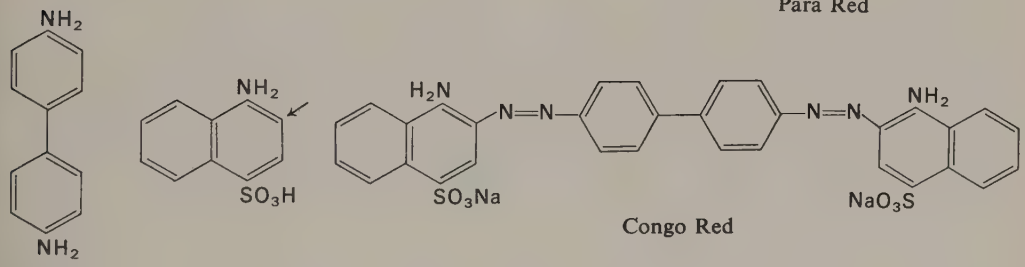
Coupled with (at ↓)



Product

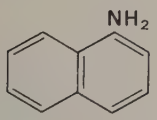


Para Red

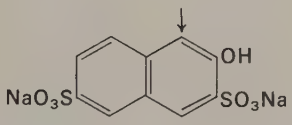


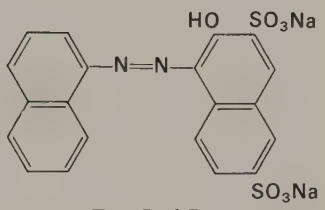
Benzidine

Congo Red



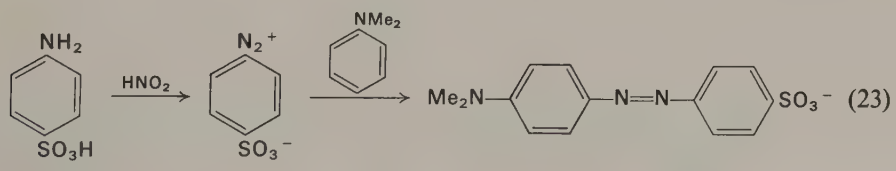
α-naphthylamine





Fast Red B

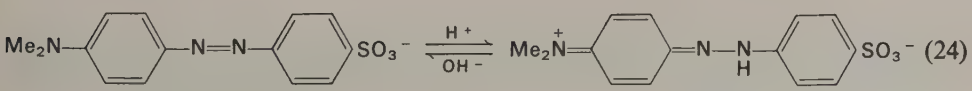
Azo compounds containing free amino or hydroxyl groups are often useful as indicators, changing color with alteration of pH. The well-known indicator methyl orange is formed by the coupling of diazotized sulfanilic acid with dimethylaniline:



Sulfanilic acid

Methyl Orange

(23)



Yellow-orange
pH 4.4

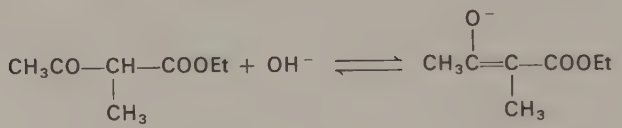
Red
pH 3.1

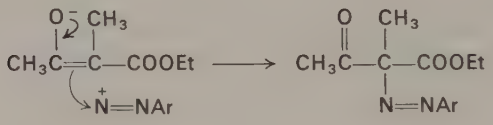
(24)

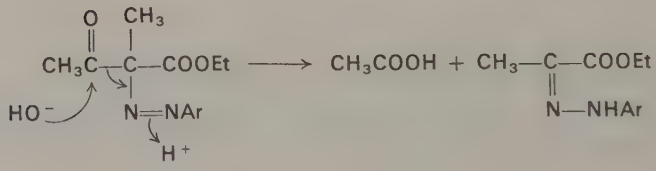
Besides their principal use as textile dyes, some azo dyes have been used as food colors. This is now regarded as hazardous because certain compounds of the class have been found to cause liver cancer in experimental animals. Butter Yellow, formerly used for coloring oleomargarines and butter, can no longer be used for this purpose. The widely used Red 2, a potential carcinogen, has recently been banned.

32-11 Reactions related to the azo coupling reaction

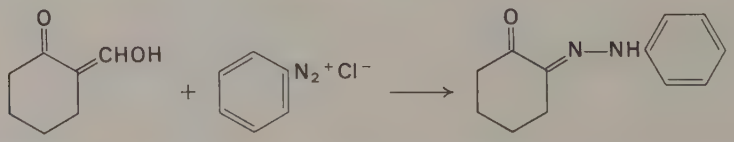
Diazonium salts react with nucleophilic compounds other than amino- or hydroxyl-activated aromatic compounds. The *Japp-Klingemann reaction* is closely allied to the azo coupling reaction, and displays both an attack of the electrophilic diazonium ion upon a β-keto ester and a subsequent cleavage of a β,β-disubstituted β-keto ester. The reaction is carried out at intermediate pH, at which both OH^- and H^+ may be utilized to play the roles shown in the following equations:


(25)


(26)


(27)

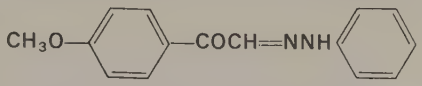
Another example of a Japp-Klingemann reaction, the details of which should be worked out by the reader, is the following:


(28)

An examination of the products of these two examples of the Japp-Klingemann reaction discloses that they are phenylhydrazones of an α-keto ester and of an α-diketone.

Exercise 6

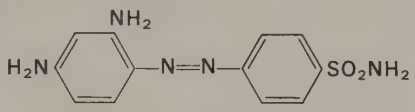
The reaction of *p*-methoxyphenylacetylene with benzenediazonium chloride at intermediate pH ultimately yields the following compound:



Show the course of this reaction by formulating the steps through which it proceeds.

32-12 Prontosil and sulfa drugs

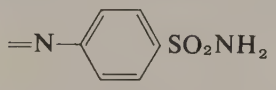
One of the most fascinating stories of the role of organic chemistry in medicine involves a group of antibacterial azo dyes, of which an important member is 4′-sulfonamido-2,4-diaminoazobenzene, Prontosil:



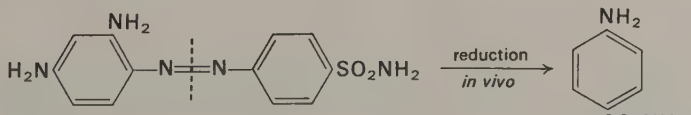
Prontosil

The discovery of the antibacterial action of Prontosil (and of a number of other azo compounds containing the 4′-sulfonamido group) was the result of the systematic testing of hundreds of such compounds, as part of a program of study based upon an early idea of Paul Ehrlich that it might be possible to find a dye that would selectively stain, or dye, a bacterial cell and thus destroy it. Prontosil was one such dye tested; and though it was found to be active against streptococcal infections *in vivo*, it was quite ineffective outside the body.

It was soon recognized that the active drugs of this type contained the grouping



and investigators in France (Tréfouël, Bovet, Fourneau) reasoned that perhaps the activity of the drug had nothing to do with its properties as a dye, but may have been the result of its conversion, by reduction, into *p*-aminobenzenesulfonamide:



Sulfanilamide

(29)

This reasoning led to the testing of sulfanilamide, and brilliant verification of the hypothesis that this was indeed the active drug. Since that time, attention has turned from azo dyes to the study of substituted sulfanilamides, and today an extensive list of such drugs is in clinical use as effective agents against a wide variety of bacterial diseases.

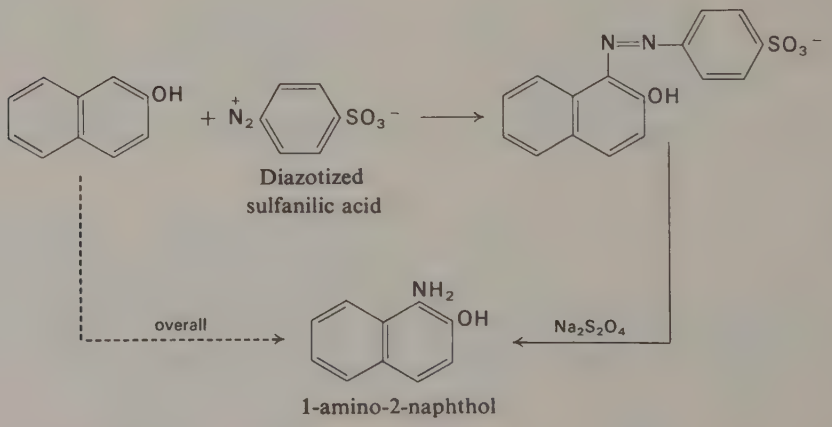
Thus, though azo dyes of the Prontosil type have been superseded by the sulfa drugs, they have an important place in the historical development of this still indispensable class of therapeutic agents.

32-13 Reduction of azo compounds

The *in vivo* reduction of the azo linkage in Prontosil is an example of a well-known and valuable reaction of azo compounds. Reduction by various means—catalytic, metal-acid combination, sodium hydrosulfite ($Na_2S_2O_4$)—leads to rupture of the —N=N— linkage and formation of two $—NH_2$ groups:

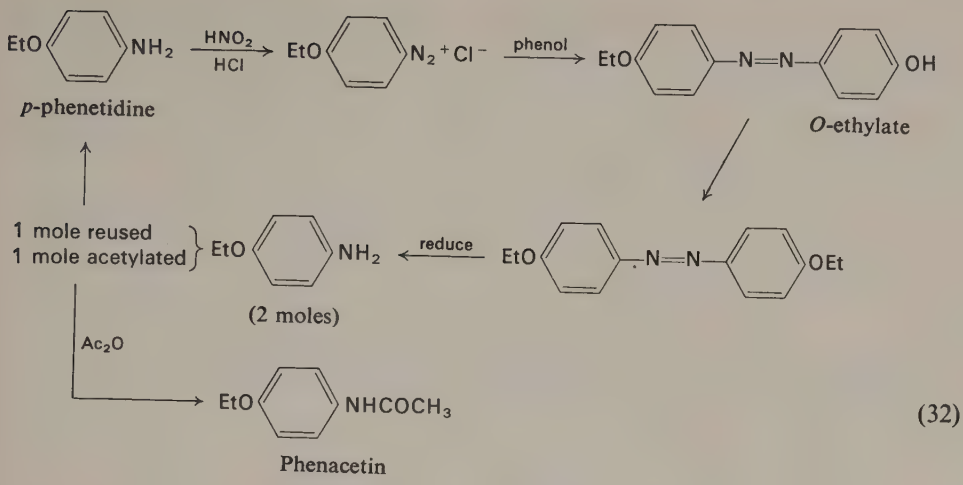
$$Ar—N{=}N—Ar' \xrightarrow{\text{reduction}} ArNH_2 + Ar'NH_2 \qquad (30)$$

By a combination of coupling with a diazonium salt and reduction of the azo compound, the introduction of amino groups can be readily accomplished:



(31)

An example of the reduction of azo compounds to amines in the technical preparation of a drug is the conversion of phenol into *p*-phenetidine and thence phenacetin:

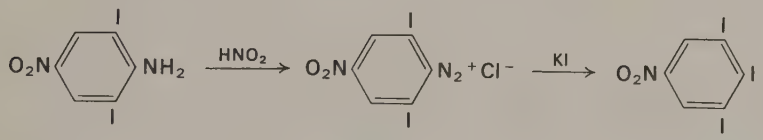


(32)

32-14 The replacement of the diazonium group with loss of nitrogen

The great utility of the diazotization reactions in synthetic operations depends upon the ability of diazonium salts to undergo replacement of the $-N_2^+$ grouping by halogen, cyano, hydroxyl, or hydrogen. This kind of reaction is called the "replacement" reaction of diazonium salts, and is typified by the following.

Replacement by halogen (Sandmeyer reaction). Treatment of a diazonium salt with one equivalent of potassium iodide in aqueous solution results in the evolution of nitrogen and the formation of the corresponding aryl iodide:



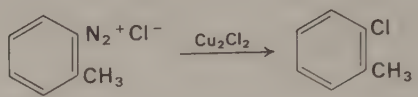
(33)

Exercise 7

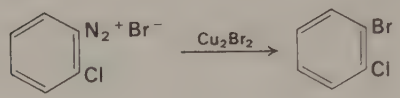
What product would be formed if 3,4,5-triiodonitrobenzene were treated with potassium phenoxide?

The replacement of the diazonium group by chlorine and bromine does not take place upon similar treatment of the diazotized amine with potassium chloride or

bromide. However, if cuprous chloride or cuprous bromide is used the replacement occurs in good yield:

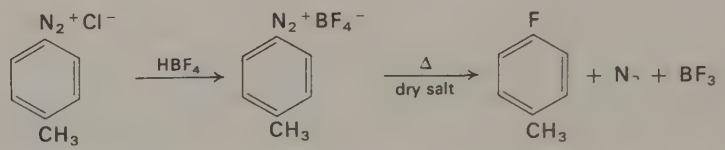


(34)



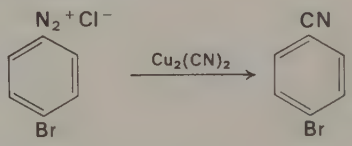
(35)

Replacement of $—N_2^+$ by fluorine is best carried out by a special method that involves heating of the dry diazonium fluoborate:



(36)

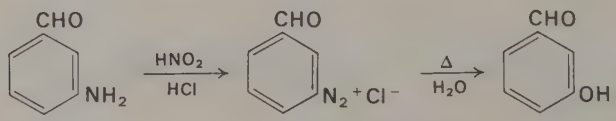
Replacement by the cyano group. Treatment of the diazonium salt with cuprous cyanide yields the corresponding aryl cyanide:



(37)

The usefulness of this reaction can be recognized when it is recalled that the cyano group can be hydrolyzed to the carboxyl group, and can be converted into $—CH_2NH_2$ by reduction or into —COR by treatment with the Grignard reagent RMgX.

Replacement by the hydroxyl group. Addition of the diazonium salt solution to hot dilute acid results in the formation of a phenol:

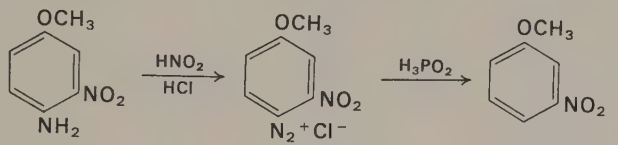


(38)

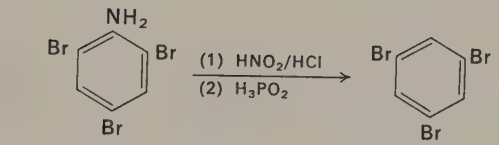
Since phenols couple with diazonium salts it is usually advantageous to add the diazonium salt solution slowly to the aqueous acid under conditions that permit the phenol to be removed by steam distillation as it is formed. The yields of phenols in this reaction vary with the degree and nature of substitution on the ring and with the

nature of the salt (the anion) used. In general, the reaction does not give yields as satisfactory as the other replacement reactions that have been described.

Replacement by hydrogen. A very useful reaction of diazonium compounds is their "reduction" with either ethanol or, better, hypophosphorous acid. The result of this procedure is the removal of $-N_2^+$ and its replacement by hydrogen:



m-nitroanisole (39)



(aniline + Br_2/H_2O) (40)

Exercise 8

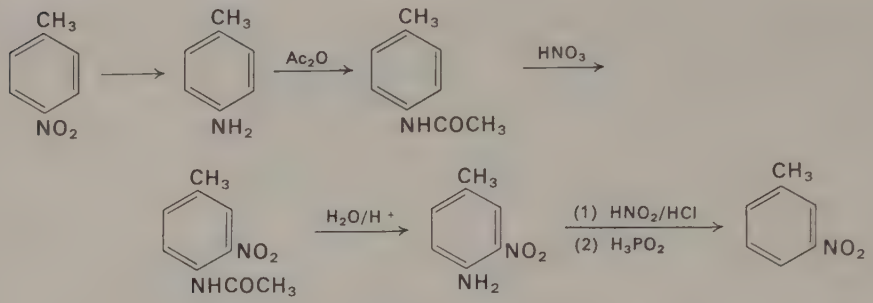
Devise a synthesis of *m*-nitroanisole starting with *m*-dinitrobenzene.

32-15 Replacement reactions in the synthesis of aromatic compounds

The utility of the various replacement reactions so far described in synthetic manipulations is very great indeed. Since nitration is so widely applicable a process, and the reduction of the nitro group to the amino group is so readily accomplished, the replacement of $-N_2^+$ by halogen, cyano, hydrogen, and so on offers a ready means of preparing a wide variety of substituted benzenes. Moreover, the replacement by hydrogen allows us to introduce a nitro or amino group in order to *direct orientation*, and then to remove it at a later time.

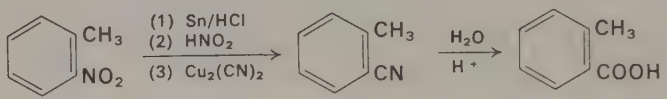
Suppose we wish to prepare *m*-nitrotoluene. Since nitration of toluene does not give the *m*-nitro compound, it cannot be made directly; moreover, the methyl group cannot be introduced into nitrobenzene by a Friedel-Crafts reaction, since nitrobenzene

does not enter into this reaction. It can be made by the following method from commercially available *p*-nitrotoluene:



(41)

Another example is the preparation of *o*-toluic acid from commercially available *o*-nitrotoluene:

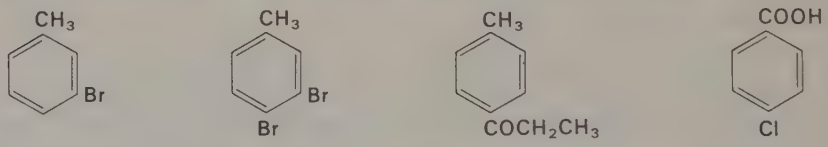


(42)

o-toluic acid

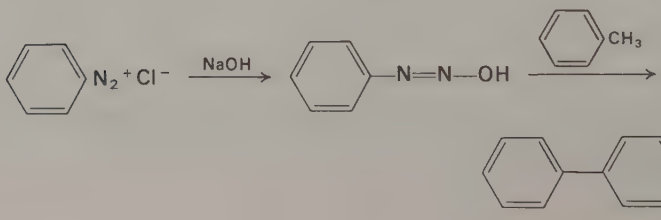
Exercise 9

Show the preparation of the following, starting from *p*-nitrotoluene.



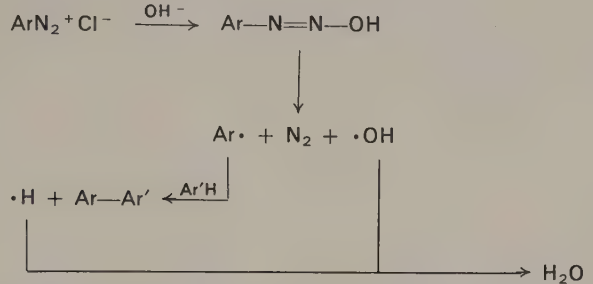
32-16 The coupling of aromatic nuclei (Gomberg reaction)

The reaction of aromatic diazohydroxides with aromatic nuclei is a reaction different in type from either the coupling reaction or the displacement reaction. It is carried out by adding alkali to a well-stirred mixture of the diazonium solution and an aromatic compound, such as toluene:



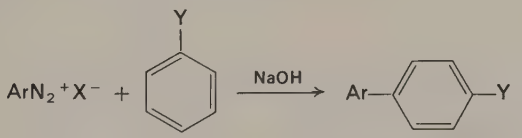
(43)

Under the alkaline conditions of the reaction, the diazonium compound is converted into the diazohydroxide. This, being a nonionic compound, is extracted into the toluene layer, where it undergoes decomposition with loss of nitrogen and coupling ensues. It is probable that the diazohydroxide decomposes to yield an *aryl radical*, and that ions are not the reacting species:



(44)

It is significant that orientation of the *entering* aryl group (that is, the one derived from ArN_2^+) is usually *ortho-para* (largely *para*) regardless of the nature of the substituent in the ring into which substitution occurs:



(45)

(Y = Br, CH_3, NO_2)

If the attacking species were Ar^+ we would expect that reaction with nitrobenzene would lead to *m*-$ArC_6H_4NO_2$, and not, as is observed, *p*-$ArC_6H_4NO_2$.

Exercise 10

Why is this statement true? Explain.

The yields of biphenyls prepared in this way are often poor, but the reaction is so readily performed that it has considerable utility in the synthesis of derivatives of biphenyl.

32-17 Diagnostic uses of diazonium reactions

A useful application of diazotization and coupling to yield an azo compound is a test for the presence of the nitro group or of the primary amino group in an aromatic ring.

If the unknown substance is reduced, diazotized, and treated with an alkaline solution of β-naphthol, the formation of a red azo compound is evidence that the original compound contained a nitro group. Similarly, an aromatic amine can be classified as primary if it can be diazotized and coupled with β-naphthol to form a red dye.

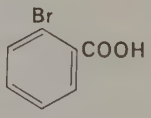
When this test is augmented by colorimetric measurement of the intensity of the red color, it can be employed as an analytical method for measuring aromatic nitro or primary amino compounds present in micro amounts; for example, in the atmosphere.

Exercise 11

Devise a quantitative method (giving practical details) for determining the amount of nitrobenzene in the atmosphere of an industrial plant in which nitrobenzene is being manufactured.

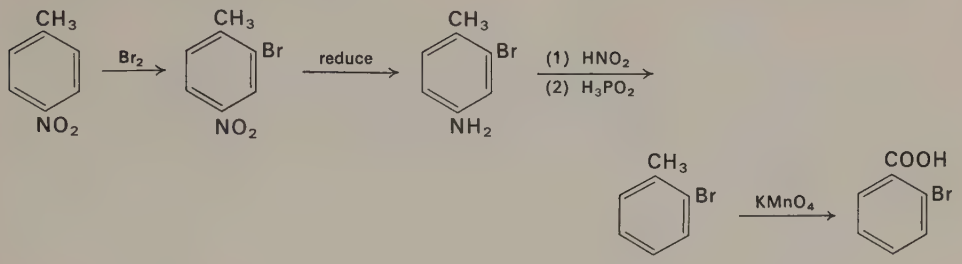
32-18 Syntheses involving orientation problems

The various means of introducing, removing, and altering substituents in aromatic rings serve to prepare a nearly unlimited array of compounds. Many of the possible synthetic operations are illustrated in examples given throughout the text; in the following paragraphs are described the solutions to a few specific problems of synthesis.

1. Synthesize 

This cannot be prepared by bromination of benzoic acid, and no satisfactory method is available for the *direct* introduction of —COOH into bromobenzene. The desired compound can be prepared by oxidation of *o*-bromotoluene. The preparation of *o*-bromotoluene by Friedel-Crafts alkylation of bromobenzene is impractical because the orientation of the first methyl group would be largely *para*, and polyalkylation (and probably partial debromination) would ensue. The nitration or bromination of toluene to a mixture of *o*- and *p*-nitro- or bromotoluene would be practicable, and would be an acceptable method, since the separation of the *o*- and

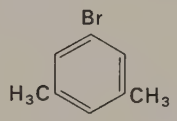
p-nitro- or bromotoluenes could be accomplished. The following is a method that requires no separation of isomers:



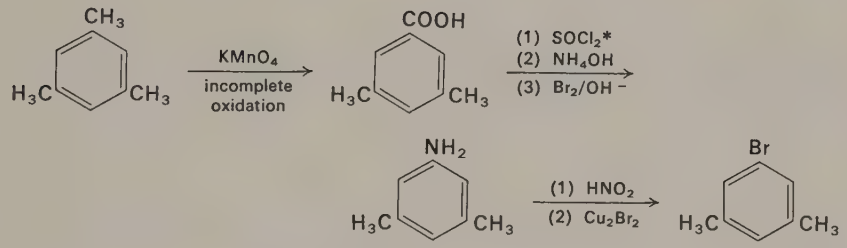
Exercise 12

How could *o*-bromobenzoic acid be prepared from *o*-nitrotoluene?

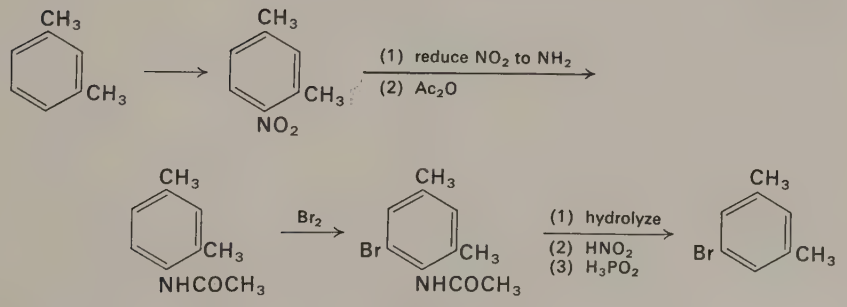
2. Synthesize



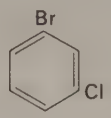
(*a*)

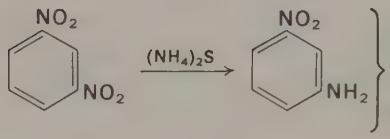


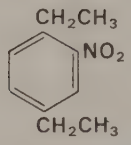
(*b*)

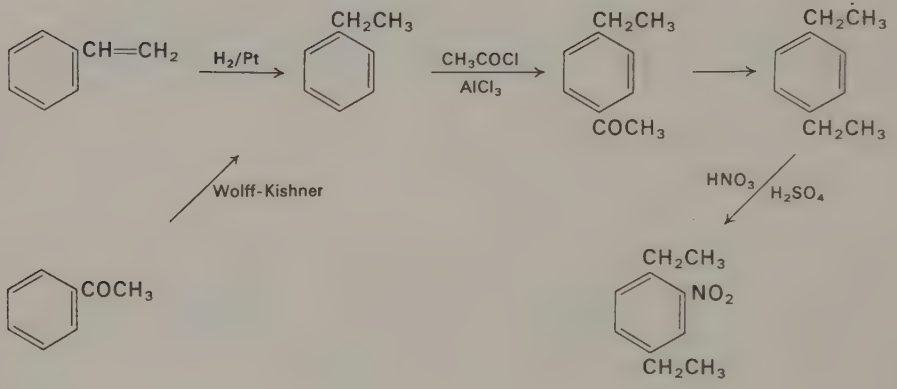


* This transformation of a carboxylic acid into an amine is called the Hofmann reaction. It is described in Section 34-8.

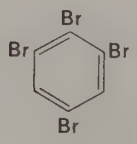
3. Synthesize 

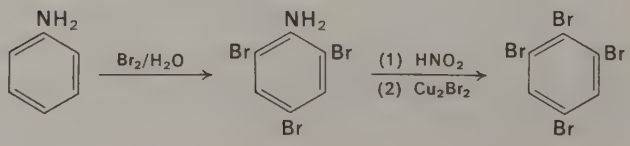


4. Synthesize 

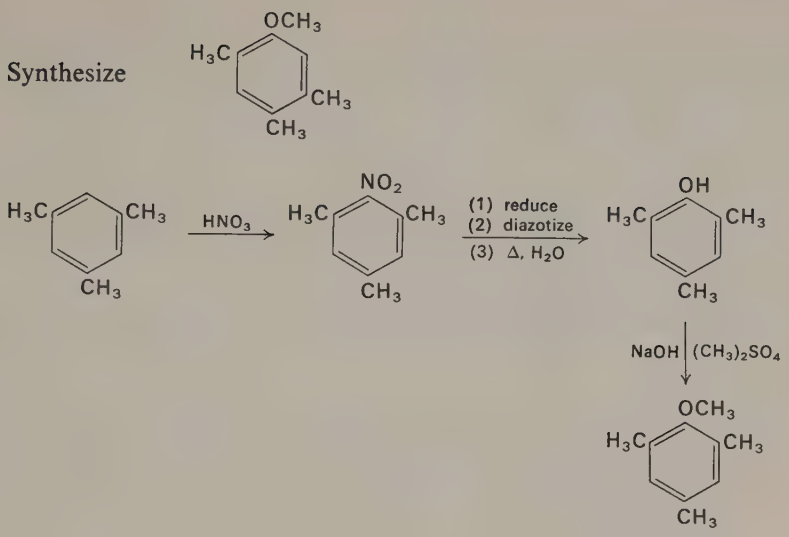


The nitro group must be introduced as the last step, since it would not survive the reduction steps, and it would not be practicable to attempt to acetylate *o*-ethylnitrobenzene, even if this were available.

5. Synthesize 



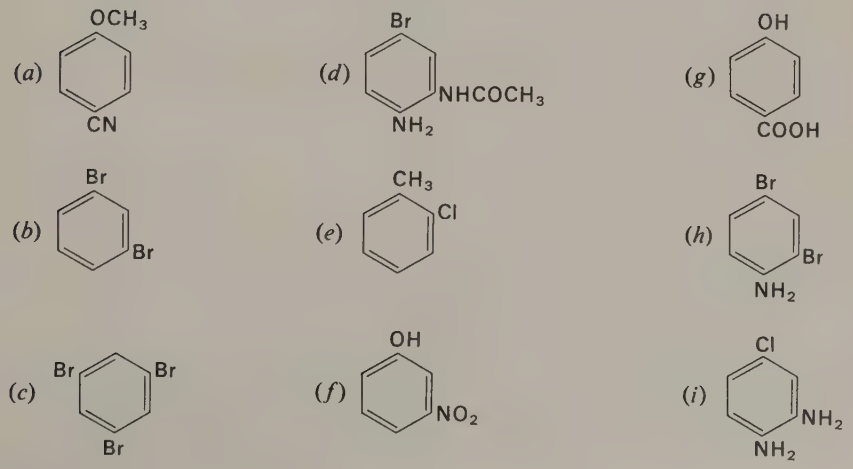
6. Synthesize



Problems

1. Write the equation for the reaction of nitrous acid (that is, sodium nitrite and aqueous mineral acid) with each of the following: (*a*) *N*-methylaniline, (*b*) di-*n*-butylamine, (*c*) triethylamine, (*d*) *p*-chloroaniline, (*e*) *m*-toluidine, (*f*) *N*,*N*-diethylaniline.

2. Starting with any monosubstituted benzene, devise syntheses for



3. Of the following compounds, select those that will couple with benzenediazonium chloride to yield an azo compound. Write the reactions. (*a*) benzene, (*b*) toluene, (*c*) phenol, (*d*) *N*,*N*-diethylaniline, (*e*) anisole, (*f*) resorcinol, (*g*) β-naphthol, (*h*) *o*-nitrotoluene, (*i*) benzoic acid, (*j*) *o*-cresol.

4. Show how you could prepare the following compounds, starting with benzene and using the diazo reaction at some stage in the synthesis. (*a*) benzoic acid, (*b*) anisole, (*c*) *p*-hydroxyazobenzene, (*d*) *p*-dibromobenzene, (*e*) *p*-aminophenol.

5. Look up in *Organic Syntheses* the description of the diazotization of an aromatic amine. Using this description as a model, write out complete and detailed experimental directions for the diazotization of 17.0 g of *o*-bromoaniline.

6. Show how you could distinguish between the compounds in each of the following pairs. Use chemical methods, and describe the experimental result of each test (color reaction, solubility, and so on). (*a*) *N*-methyl-*o*-toluidine and *N*,*N*-dimethylaniline, (*b*) *m*-toluidine and cyclohexylamine, (*c*) acetanilide and *p*-aminoacetophenone, (*d*) aniline hydrobromide and *p*-bromoaniline, (*e*) phenol and anisole, (*f*) *m*-aminophenol and *m*-toluidine, (*g*) *p*-bromoaniline and *p*-aminobenzyl bromide.

7. How could you separate a mixture of aniline, acetanilide, and *m*-aminophenol into the pure components?

8. Describe the method you would use to prove the structure of *m*-toluidine. (Degradative, analytical, and synthetic means may be employed.)

9. Write equations showing the chemical changes that would take place when an acidic solution of benzenediazonium chloride is made increasingly more alkaline, until it is finally strongly alkaline.

10. What would you expect to obtain as the product if a solution of *p*-aminobenzylamine were diazotized and the resulting solution allowed to warm up until nitrogen evolution was at an end?

11. Although *N*,*N*-dimethylaniline couples readily with benzenediazonium chloride, 2,6,*N*,*N*-tetramethylaniline does not. Explain.

33

Phenols and aromatic hydroxycarbonyl compounds

In Chapter 32 we saw that aromatic amines display special properties setting them apart from aliphatic amines, and thus require special treatment as a class. In the same way, phenols will be discussed apart from aliphatic hydroxy compounds such as alcohols because, although some aspects of their reactivity are similar to those of alcohols, much of their chemistry depends upon reactions involving the aromatic ring. The hydroxyl group attached directly to the ring has a profound influence upon nuclear reactivity, and in this respect there is little similarity between the chemistry of phenols and the chemistry of alcohols.

Aromatic hydroxycarbonyl compounds are included in this chapter because the synthesis of most of them depends upon the influence of the phenolic hydroxyl group upon the substitution reactions by which they are prepared.

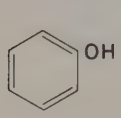
Many aromatic hydroxycarbonyl compounds are well-known and abundant products of natural (biosynthetic) processes. Many plant pigments belong to this class of compounds. Some of them are described in this chapter, and a more detailed discussion of their biosynthesis will be found in Chapter 39.

The chemistry of phenolic compounds extends to their oxidation products known as quinones. Many of these are important compounds: some are medicinal agents of great therapeutic value, others are natural vitamins, and still others are well-known

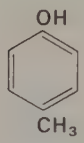
plant pigments. Quinones are discussed briefly to introduce the student to the ways in which they can be synthesized and how some of them can be used.

33-1 Characteristic properties of phenols

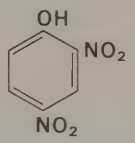
Phenols are aromatic hydroxy compounds in which the hydroxyl group is attached directly to the aromatic ring:



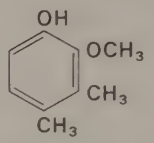
Phenol



p-cresol



2,4-dinitrophenol

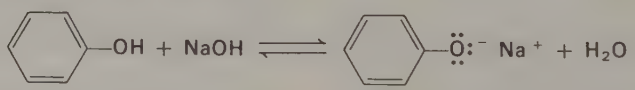


2-methoxy-3,4-dimethylphenol

Phenols bear a formal resemblance to alcohols and indeed undergo some reactions in common with them; but they deserve special consideration because of the profound effect of the ring upon the properties of the hydroxyl group and the influence of the hydroxyl group upon the properties of the ring.

The differences between, for example, phenol and 1-hexanol are very great. Phenol is appreciably acidic ($K_a = 10^{-10}$); consequently, the basic character (nucleophilic character) of the hydroxyl group is diminished. In neutral or acid solution, in which the unionized hydroxyl group reacts, 1-hexanol is more reactive than phenol toward reagents such as acid halides and anhydrides and other substances that react by accepting the unshared electron pair on the oxygen atom of —OH.

Under basic conditions, however, phenol is an excellent nucleophile, the nucleophilic species being the *phenoxide ion*:



(1)

Phenols can be distinguished from alcohols, if both are water-insoluble, by the solubility of the phenols in aqueous alkali; since simple phenols are very weak acids, they do not dissolve in aqueous sodium bicarbonate solution and so can be distinguished from carboxylic acids, which are bicarbonate-soluble. These properties make possible a convenient means of separating phenols and carboxylic acids: if an alkaline solution of a phenol and a carboxylic acid is saturated with carbon dioxide, the phenol separates, while the acid remains in solution as the salt. After removal of the phenol by filtration or extraction, acidification of the remaining aqueous solution with a mineral acid liberates the carboxylic acid, and permits its isolation.

Phenol is a very toxic substance and is corrosive to living tissue by virtue of its destructive action on proteins. Its common name, "carbolic acid," is indicative of this property rather than of its acid strength. Phenol was first used, in the nineteenth century, for antisepsis and was the first substance to be used generally in surgical operations and in the disinfection of hospital premises and equipment. Although phenol has been superseded in medicine by other, more effective antiseptics, commercial preparations containing mixtures of simple phenols (for example, cresols) are still marketed as household disinfectants. The term "phenol coefficient" refers to a number that compares the effectiveness of bactericidal substances against a standard solution of phenol.

Other therapeutic uses of certain substituted phenols will be described later in this chapter.

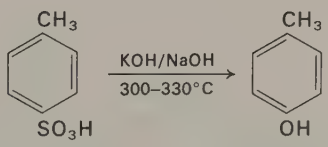
33-2 Synthesis of phenols

Several methods for introducing a hydroxyl group into the aromatic ring, discussed in other chapters, are recalled here:

1. The synthesis of phenol itself on a technical scale by the high-pressure and high-temperature hydrolysis of chlorobenzene.
2. The transformation of the aromatic amino group into a hydroxyl group by diazotization and hydrolysis of the diazonium salt.
3. Replacement of aromatic halogen, when it is *ortho* or *para* to an activating group such as nitro or nitroso, by hydrolysis. In this category also is the hydrolysis of *p*-nitrosodimethylaniline to *p*-nitrosophenol.

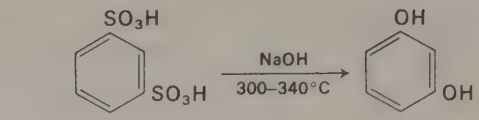
A general method of preparing phenols is the fusion of aromatic sulfonic acids with alkali. This is a valuable industrial method, and is used for the manufacture of a number of phenols of technical importance. Several examples of the reaction are the following:*

(2)

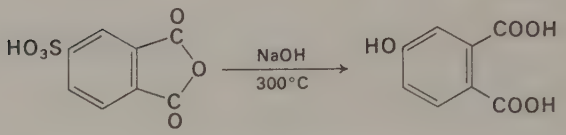


(3)

* In these reactions it is, of course, the sodium or potassium salt of the sulfonic acid that is present in the alkaline reaction mixture. Further, the immediate product of the reaction is the alkali metal salt of the phenol. A final acidification step would be used to liberate the free phenol.



(4)

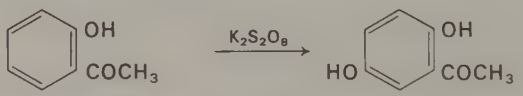


(5)

This method is important in the industrial preparation of phenols. It is limited by the availability of the necessary sulfonic acid, and by the possible sensitivity of other substituents to the severe conditions used. A presently important technical method of preparing phenol involves the interesting rearrangement of cumene hydroperoxide that is described in Chapter 34.

Other methods of preparing phenols fall into numerous diverse classes of reactions. There are a few useful methods of introducing a hydroxyl group directly into the aromatic nucleus (that is, by replacement of hydrogen); syntheses of phenols nearly always involve the replacement of some substituent by hydroxyl.

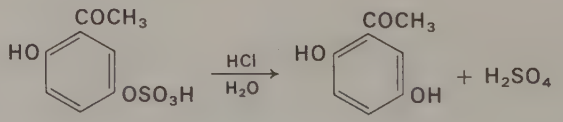
The direct oxidation of phenols with potassium persulfate does allow the introduction of an additional hydroxyl group into the ring. This is of most usefulness in the synthesis of polyhydroxy compounds of rather complex structures, chiefly because it is often more convenient to introduce a single hydroxyl group into a molecule of moderately complex structure than to build up the final structure in other ways:



(6)

o-hydroxyacetophenone

In the above equation, only the final product is shown. An intermediate sulfuric acid ester of the final phenol is formed; this is seldom isolated, but is hydrolyzed with aqueous HCl to the products:



(7)

Exercise 1

The exact mechanism of this oxidation reaction has not been established with certainty. Both free-radical and ionic mechanisms have been proposed. Using the simpler expression for persulfuric acid, HO—OSO_2OH, devise a rational course for the reaction that gives the sulfate ester of equation (7) by an ionic mechanism.

33-3 Effect of substituents upon the acidity of phenols

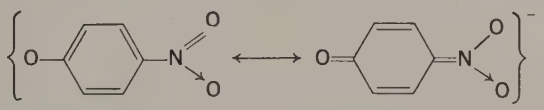
The substitution of electron-attracting groups onto the ring of aniline decreases the basic strength of the amine. It would be anticipated that the same effect would result in the case of similar substitution of phenol, and this is what is found. However, since phenol is ordinarily characterized not by the basicity of its —OH group but by the acidity of the hydrogen atom of this group, and in view of the reciprocal relationship between acidity and basicity of a function, the result is that *base-weakening substituents in aniline are acid-strengthening substituents in phenol*:

Phenol	K_a
unsubstituted	1.3×10^{-10}
3-nitro	1.0×10^{-8}
4-nitro	6.5×10^{-8}
2,4-dinitro	8.3×10^{-5}
2,4,6-trinitro	4.2×10^{-1}

Exercise 2

Express the above dissociation constants as pK_a values.

2,4-Dinitrophenol is a somewhat stronger acid than acetic acid, and 2,4,6-trinitrophenol is nearly in the class of "strong" acids. Indeed, the latter is commonly called picric acid. It is to be noted that *m*-nitrophenol is a weaker acid than *p*-nitrophenol. This shows that the effect of the nitro group upon the acidity is due to more than the inductive effect, since this should be more effective in the *m* position (closer to —OH) than in the *p* position. The resonance effect of the nitro group in stabilizing the anion



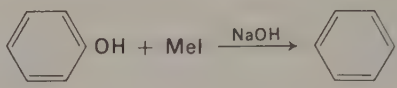
is important in contributing to the ease with which the proton can be removed.

Exercise 3

Inspect the structure of *m*-nitrophenol and show that no comparable structures, in which the negative charge resides on the nitro group, can be written for the anion.

33-4 Oxygen alkylation and oxygen acylation of phenols

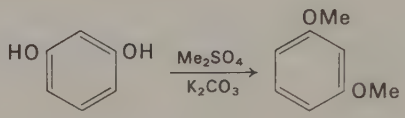
Alkylation of phenols can be accomplished readily by alkyl halides, alkyl sulfates, or alkyl sulfonates in the presence of aqueous alkali:



(8)

(9)

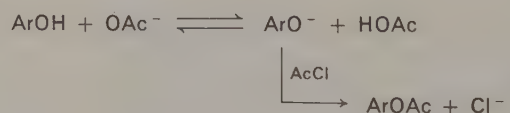
An alternative method of carrying out the alkylation of many phenols is by the use of an alkyl sulfate in the presence of anhydrous potassium carbonate, with acetone as a solvent:



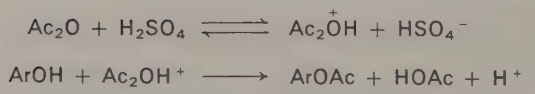
(10)

The similarity of these alkylations, which are simple nucleophilic displacement reactions, to the Williamson ether synthesis is apparent. The difference is one of degree, and lies in the experimental conditions used. The Williamson synthesis of dialkyl ethers requires the use of an alkoxide, usually prepared by the addition of sodium or potassium to an excess of the alcohol.

The acylation of phenols can be accomplished by acid chlorides or anhydrides, a trace of sodium acetate (when acetic anhydride is the acylating agent) or pyridine, or a strong mineral acid (sulfuric, perchloric) to catalyze the reactions: the base by providing phenoxide ion, the acid by increasing the electrophilic character of the acid anhydride.



Base-catalyzed acylation (11)



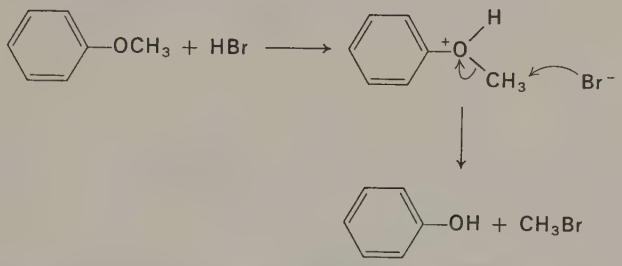
Acid-catalyzed acylation (12)

In the *O*-acylation of phenols with the less reactive aromatic acid chlorides (*Schotten-Baumann reaction*), aqueous alkali is used; again, the phenoxide ion formed is the actual nucleophile that reacts with the acid derivative.

The use of pyridine as the basic catalyst in the *O*-acylation of alcohols with aromatic acid chlorides probably involves the formation of an intermediate *N*-acyl pyridinium salt, whose reaction with the alcohol in a second step leads to the ester.

33-5 Cleavage of phenyl alkyl ethers

Phenyl alkyl ethers can be cleaved (hydrolyzed) by concentrated aqueous hydriodic and hydrobromic acids. While this procedure is not an important preparative method for phenols (since phenyl alkyl ethers are not commonly available raw materials), it is of importance in laboratory operations involved in the proof of the structures of organic compounds. The cleavage probably proceeds by way of a nucleophilic attack of the halide ion on the protonated phenyl ether; the reaction is illustrated for the case of the cleavage of anisole by HBr:



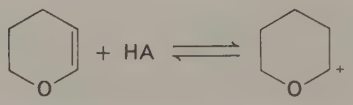
(13)

The cleavage of methyl and ethyl ethers of phenols by hydriodic acid is the basis for an important analytical method, called the *Zeisel alkoxyl determination.* A weighed sample of the ether is heated with concentrated HI, and the methyl or ethyl iodide is volatilized and passed into an alcoholic solution of silver nitrate. The precipitated silver iodide is weighed, and the percentage of alkoxyl thus determined. The Zeisel method of alkoxyl determination is capable of a degree of accuracy that is comparable with that obtained in such other organic analytical methods as carbon-hydrogen, nitrogen, and halogen determinations.

The *O*-alkylation of phenolic hydroxyl groups is often carried out as a prelude to the performance upon another part of the molecule of reactions which would not be possible in the presence of free hydroxyl groups. In most cases, *O*-acylation would not be an acceptable alternative, for the hydrolysis of the *O*-acyl linkage under many reaction conditions—particularly in alkaline media—would defeat the purpose of the protective maneuver. On the other hand, although an *O*-methyl ether would be stable under many experimental conditions, the later removal of the protecting methyl group often requires undesirably drastic conditions. The ideal "protecting" group that would be stable under alkaline reaction conditions, or when Grignard reagents are used, would be an ether that would be cleaved under mildly acidic conditions, or

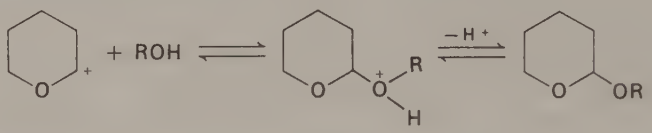
that could be removed by other means. Two such protecting groups that are commonly used are *O*-benzyl groups and those formed by reaction of the phenolic hydroxyl groups with dihydropyran.

Dihydropyran, a commercially available reagent, is a vinyl ether. In the presence of a proton donor (a trace of mineral acid may be used) it is readily protonated in the equilibrium



(14)

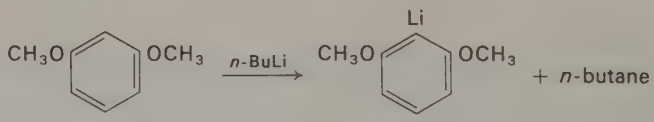
The electrophilic tetrahydropyranyl ion is capable of reacting with a hydroxyl group in the equilibrium



(15)

When dihydropyran is used in excess the tetrahydropyranyl ether is formed in substantially quantitative yield and, after neutralization of the trace of acid catalyst, can be isolated and used in subsequent reactions. It will be noted that the tetrahydropyranyl ether *is an acetal, and thus is stable to alkaline reaction conditions; but it is very readily hydrolyzed by aqueous acid, with regeneration of the original hydroxyl group*. The reaction is applicable to both phenolic and alcoholic hydroxyl groups, and can also be used to prepare tetrahydropyranyl esters of carboxylic acids.

An example of the use of tetrahydropyranylation is a convenient synthesis of certain phenolic carboxylic acids. When resorcinol dimethyl ether is allowed to react with *n*-butyllithium, a nuclear hydrogen atom is replaced, with the formation of the aryllithium compound:



(16)

Carbonation, followed by hydrolysis, yields 2,6-dimethoxybenzoic acid. Demethylation of this acid, with the formation of 2,6-dihydroxybenzoic acid, can be accomplished with hydrogen iodide or hydrogen bromide, but the yields are often unsatisfactory. An alternative course, which is easily carried out and gives good yields, involves the use of the *bis*-tetrahydropyranyl ether, which reacts with butyllithium in the same way as does the dimethyl ether. After the lithium derivative is carbonated, mild acid hydrolysis of the reaction mixture causes removal of the tetrahydropyranyl

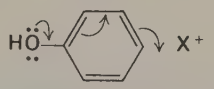
groups, and 2,6-dihydroxybenzoic acid is obtained without the need for a separate dealkylation step.

Phenolic *O*-benzyl ethers are much more readily cleaved by acids than are methyl ethers, but have the special advantage that the removal of the benzyl groups is easily accomplished by catalytic hydrogenolysis:

$$ArOCH_2C_6H_5 \xrightarrow[Pd]{H_2} ArOH + C_6H_5CH_3 \qquad (17)$$

33-6 Nuclear reactivity of phenols

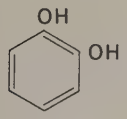
The nucleophilic properties of a saturated alcohol are of necessity confined to the oxygen atom of the hydroxyl group, with its unshared electrons. In phenols, however, the hydroxyl group can reinforce the nucleophilic properties of the nucleus, and thus is a powerful influence in aiding electrophilic attack on the ring:



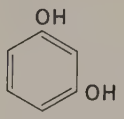
(18)

Nucleophilic response — Electrophilic demand

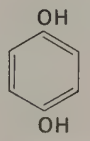
Di- and trihydroxybenzenes, such as catechol, resorcinol, hydroquinone, pyrogallol, hydroxyhydroquinone, and phloroglucinol,



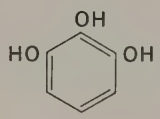
Catechol



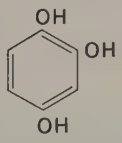
Resorcinol



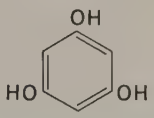
Hydroquinone



Pyrogallol



Hydroxyhydroquinone

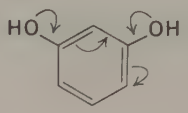


Phloroglucinol

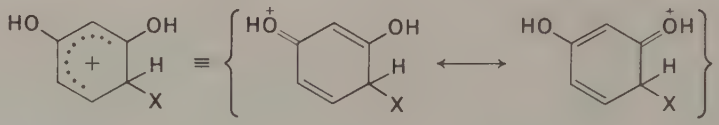
are much more reactive to nucleophilic substitution than is phenol. Indeed, substitution into the rings of resorcinol and phloroglucinol is extraordinarily facile.

Resorcinol, with two *meta*-disposed hydroxyl groups, is subject to electrophilic attack at the 4-position by reagents that are too weakly electrophilic to attack benzene

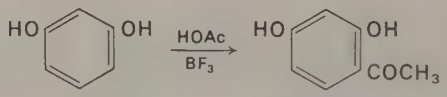
or monophenols. It is apparent that the electron-donating powers of the two hydroxyl groups are *both* directed to the 4-position, since it is *ortho* to one and *para* to the other:



Hence, in the transition state for electrophilic substitution, both —OH groups can participate in stabilization of the positively charged complex:



Resorcinol can undergo nuclear acylation by acetic acid in the presence of sulfuric acid, zinc chloride, or boron trifluoride:

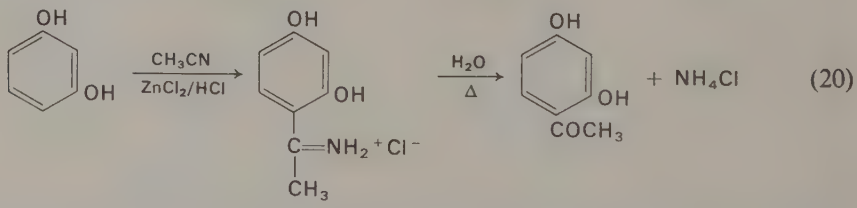


Resacetophenone

(19)

Less highly activated benzene derivatives (for example, benzene or phenol) will not undergo nuclear acetylation under these conditions.

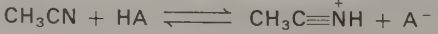
Nuclear acylation of resorcinol can also be accomplished by an alkyl cyanide, zinc chloride, and hydrogen chloride. The reaction is carried out in dry ether solution at ice-bath temperature (*Hoesch reaction*):



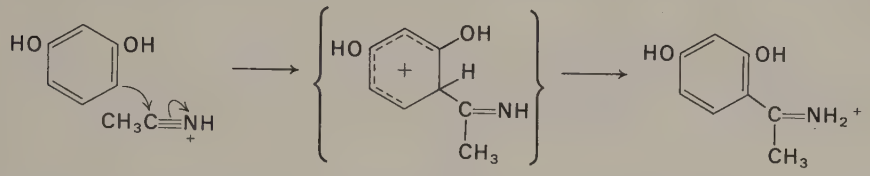
(20)

The close mechanistic relationship of the Hoesch synthesis to the Friedel-Crafts acylation can be seen upon consideration of the details of the reaction.

1. In the presence of the strong acids HCl and $ZnCl_2$ (conveniently regarded together as H_2ZnCl_4) the nitrile undergoes protonation:

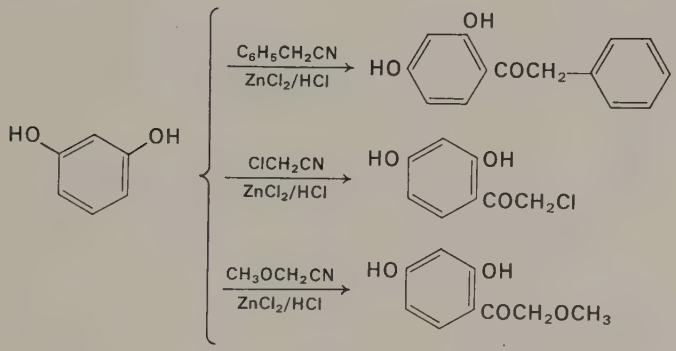


2. Nucleophilic attack by the resorcinol nucleus upon the electrophilic carbon atom of $CH_3C{\equiv}\overset{+}{N}H$ leads to an intermediate of the usual kind:



The product of the reaction is the protonated imine (Schiff base), which is readily hydrolyzed to the free ketone.

The Hoesch reaction is applicable to the preparation of ω-substituted acetophenones by the use of the appropriately substituted acetonitrile (the final ketone is shown in each case):



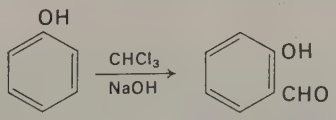
(21)

Nitrosation and diazo coupling occur readily with resorcinol.

Phloroglucinol, in which three hydroxyl groups are capable of aiding directly the nucleophilic character of the ring, is more reactive than resorcinol, and undergoes the Hoesch reaction under milder conditions.

33-7 The Reimer-Tiemann reaction. Carbenes

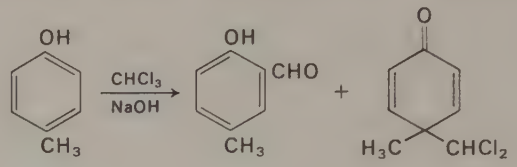
Phenols undergo the *Reimer-Tiemann reaction* with chloroform in the presence of sodium hydroxide to yield hydroxybenzaldehydes. Phenol itself gives salicylaldehyde:



(22)

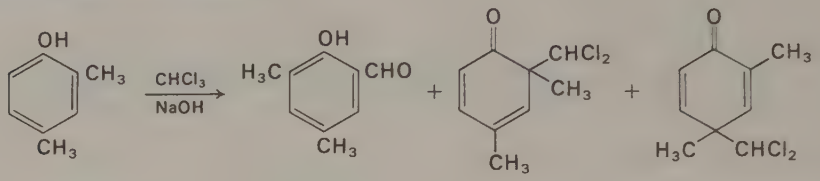
Salicylaldehyde

That an intermediate is formed containing the $—CHCl_2$ group, which is ultimately hydrolyzed to —CHO, is indicated by the observation that *p*-cresol yields, in addition to 5-methylsalicylaldehyde, 4-methyl-4-dichloromethyl-2,5-cyclohexadienone:



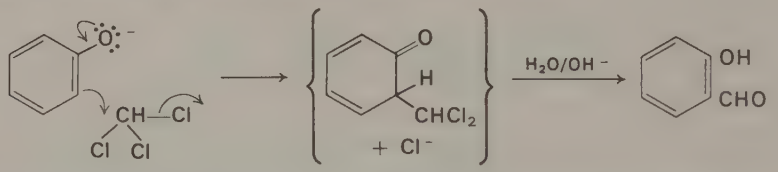
(23)

2,4-Xylenol reacts as follows:



(24)

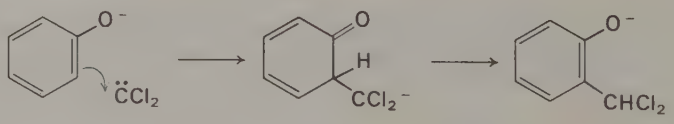
Although the Reimer-Tiemann reaction was for a long time formulated as a nucleophilic attack of the phenoxide ion upon chloroform,



it has been established recently that the reaction involves the divalent carbon compound $:CCl_2$, dichlorocarbene:

$$CHCl_3 + OH^- \rightleftharpoons :CCl_3^- + H_2O$$
$$:CCl_3^- \longrightarrow Cl^- + :CCl_2 \quad \text{(Dichlorocarbene)} \tag{25}$$

Dichlorocarbene, in which the carbon atom lacks two electrons of having an octet, would be expected to be exceedingly reactive as an electrophile, and to react with the phenoxide ion as follows:

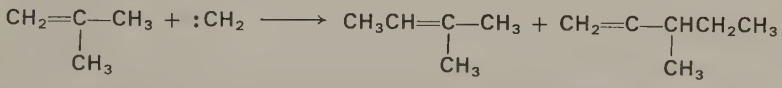


(26)

It can be seen that the difference between these two mechanisms lies chiefly in the details—at which stage and under what circumstances the chloride ion is lost. This is most important from the point of view of the theoretical aspects of the reaction.

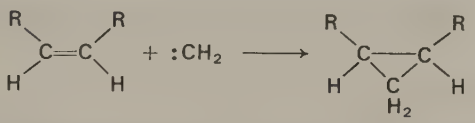
In particular, the existence (however transitory) of the divalent carbon compound is of great theoretical interest. Other evidence, not directly related to the reaction we are discussing here, supports the view that intermediate "carbenes" are indeed capable of existence.

Carbenes, like other compounds in which carbon exists in an "abnormal" valence state (carbonium ions, carbanions, free radicals), are very reactive. Although the most thoroughly studied carbene is probably the dichlorocarbene formed from chloroform by the action of strong bases, carbenes of other kinds can be formed in a variety of ways. Carbene itself, or methylene, has been observed as a highly reactive intermediate when diazomethane, CH_2N_2, is subjected to irradiation with ultraviolet light or is decomposed by pyrolysis. Depending upon the method used for the preparation of the compound, which may be represented simply by the formula $:CH_2$, the two electrons may be an electron pair, with opposite spins, or they may be single electrons, with like spins, in which case the compound is a diradical. The first of these is designated a "singlet" state, the second (the diradical) a "triplet." Singlet methylene is a highly reactive compound. It undergoes "insertion" reactions, in which the CH_2 group is introduced into a bond, as in the reaction



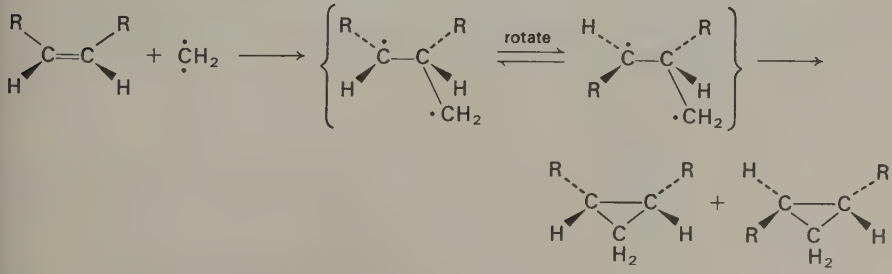
(27)

and adds to carbon-carbon double bonds to form cyclopropanes:



(28)

Carbene produced by the photochemical decomposition of diazomethane appears to be in the singlet state, for the addition shown in the above equation is stereospecific. The degree of stereospecificity can, however, be altered by the experimental conditions, indicating that the change singlet → triplet can occur. Addition of triplet methylene to a double bond would lack stereospecificity because the two-step character of diradical addition would lead through a monoradical that could undergo isomerization by rotation about the single bond:

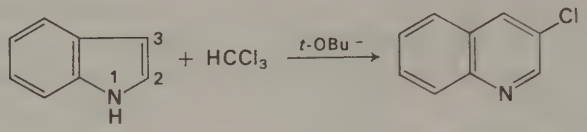


(29)

The addition of carbenes to carbon-carbon double bonds is not limited to olefinic double bonds; aromatic rings are attacked, giving products that can be formulated as arising from the addition of the carbene to a double bond of the Kekulé form of the benzene ring.

Exercise 4

The reaction of dichlorocarbene (from chloroform and potassium *t*-butoxide) with indole proceeds in the following way:



Indole 3-chloroquinoline

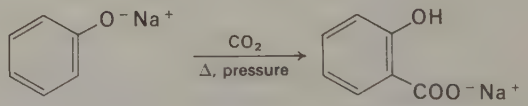
Devise a reasonable course for this transformation, starting with the addition of the dichlorocarbene to the 2,3-double bond of indole.

Exercise 5

The Reimer-Tiemann reaction with 6-hydroxy-1,2,3,4-tetrahydronaphthalene yields two products: one is the expected hydroxyaldehyde. What is the structure of the other?

33-8 The carboxylation of phenols

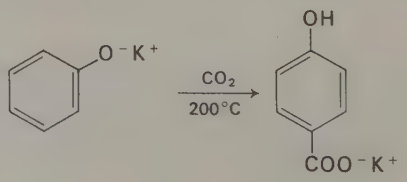
Phenol, as the sodium salt, reacts with carbon dioxide at 120–140°C (under pressure) to yield the sodium salt of salicylic acid (the *Kolbe reaction*):



(30)

Salicylic acid
(as sodium salt)

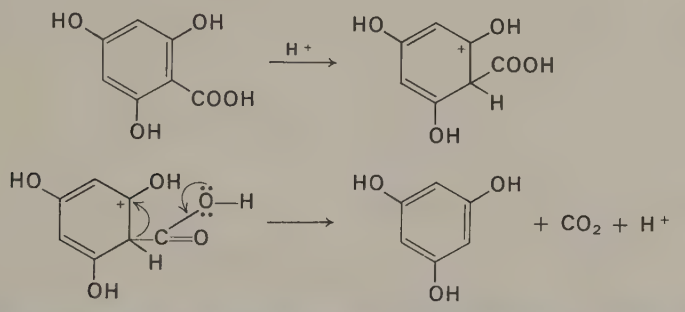
At a higher temperature (220°C) potassium phenoxide reacts with carbon dioxide to yield largely *p*-hydroxybenzoic acid:



(31)

Although the carbon atom of CO_2 is electrophilic (recall the addition of RMgX, and the fact that OH^- adds to give bicarbonate ion), its ability to effect an electrophilic attack upon an aromatic nucleus is not demonstrated with any but a highly nucleophilic ring. The carboxylation of phenoxide ions is thus an excellent demonstration of the reciprocal relationship between the electrophilic "attacking" reagent and the nucleophilic ring.

The carboxylation of more nucleophilic phenols takes place with correspondingly greater ease. Phloroglucinolcarboxylic acid is prepared by heating phloroglucinol with aqueous potassium bicarbonate; pyrogallol behaves similarly. The *decarboxylation* of polyhydroxybenzoic acids by acids takes place readily, a behavior that is easily accounted for, since the decarboxylation reaction in these cases is an *electrophilic displacement of CO_2 by hydrogen ion*:



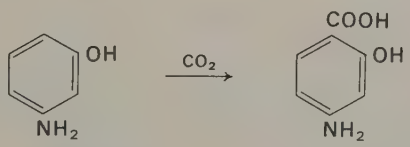
(32)

It will be apparent that the carboxylation and decarboxylation reactions follow the same course.

33-9 Therapeutic uses of salicylic acid derivatives

Salicylic acid is a very important compound. Its acetyl derivative is *aspirin*, one of the most widely used and useful drugs known. Aspirin is a mild analgetic agent, a febrifuge, and an effective drug in the treatment of rheumatoid arthritis (salicylic acid and its salts are also used for the latter disease). About 30 million pounds (40 billion five-grain tablets) of aspirin are consumed yearly in the United States alone.

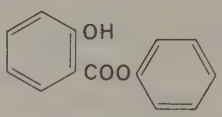
In recent years the drug 4-aminosalicylic acid (*p*-aminosalicylic acid, PAS) has come into clinical use in the treatment of tuberculosis. It has a tuberculostatic action, and is commonly used in conjunction with streptomycin and isonicotinic acid hydrazide (isoniazid). PAS can be prepared by the Kolbe carboxylation of *m*-aminophenol:



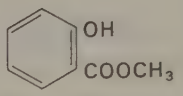
(As sodium salt) 4-aminosalicylic acid

(33)

Other salicylic acid derivatives of physiological significance are phenyl salicylate ("salol") and methyl salicylate (oil of wintergreen). The latter occurs in nature in certain plants:

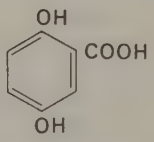


Salol

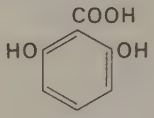


Oil of wintergreen

Gentisic acid and γ-resorcylic acid have also been used for some of the purposes for which salicylic acid has been employed (rheumatic diseases):



Gentisic acid

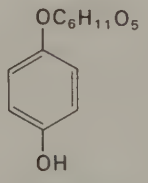


γ-resorcylic acid

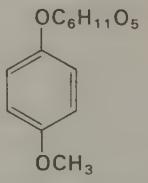
33-10 Naturally occurring phenols

Phenols, and in particular phenolic carbonyl compounds, occur widely in nature. They are particularly prevalent in plants, where they are found as sap-soluble pigments of flowers and fruits and as a large and varied group of glycosides (Chapter 15) in which one or more of the phenolic hydroxyl groups is combined with a sugar in glycosidic linkage.

A well-known phenolic glucoside is *arbutin*, the mono-β-glucoside of hydroquinone; the monomethyl ether often accompanies it in the plant (*Arbutus uva-ursi*) in which it is found.



Arbutin

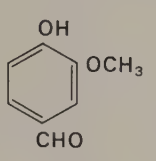


Methylarbutin

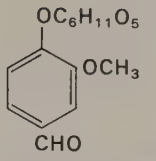
Exercise 6

Write the structure of arbutin using the Haworth formula for the sugar. Arbutin is a β-D-glucopyranoside.

By far the greater number of natural phenols are substituted phenols or their glycosides. Salicin has been described earlier (Chapter 15). *Vanillin*, an important flavoring material, is one of man's most extensively used condiments. It occurs in nature as the odorous constituent of the vanilla bean (an orchid), and as the glucoside in some other plants.

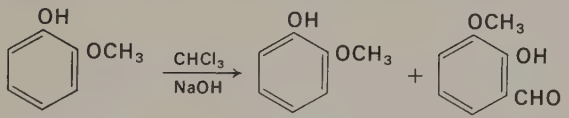


Vanillin



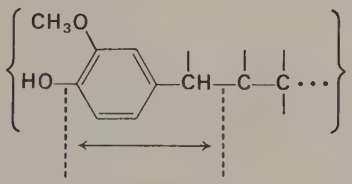
Vanillin glucoside

Vanillin can be prepared by the Reimer-Tiemann reaction, starting with guaiacol (catechol monomethyl ether), from which it is formed along with *o*-vanillin:



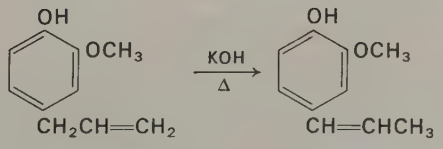
Guaiacol Vanillin *o*-vanillin (34)

Another source of vanillin is lignin, a byproduct of paper pulp manufacture. Lignin is a complex polymeric structural material of woody plants, and contains as a structural unit the fragment



Yields vanillin

(combined in a manner too complex to permit its detailed consideration here). Upon oxidation of lignin, vanillin is formed in sufficiently high yield to make the process economically feasible. Vanillin is also prepared by oxidation (chromic acid, ozone, or nitrobenzene) of *isoeugenol*. Isoeugenol is prepared by isomerization of *eugenol*, found in clove oil:



Eugenol Isoeugenol (35)

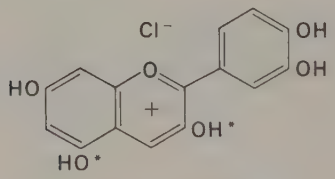
Phenolic compounds are not synthesized from simple precursors by animals as they are by plants (in which the ultimate source of all carbon compounds is CO_2). Plants require no accessory supplies of carbon compounds, but animals require a variety of organic substances at an advanced level of synthetic elaboration. Among these are compounds containing aromatic rings; and from such starting materials the animal organism is able to perform further structural alterations to produce, among other kinds of compounds, phenols (see Chapter 39).

Exercise 7

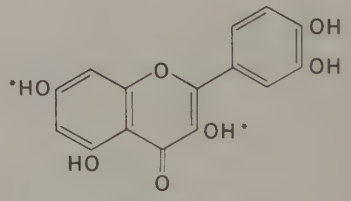
The isomerization of eugenol to isoeugenol requires vigorous treatment with strong alkali. Explain how the isomerization occurs.

33-11 Phenolic plant pigments

The phenolic compounds of plants are of a wide and varied range of structural types, from the simple phenols so far described (arbutin, salicin, vanillin) to very complex compounds. Among the latter are many of the naturally occurring pigments of plants, typified by the red *anthocyanidin* pigment, cyanidin (chloride), and the yellow *flavone* pigment, quercetin:



Cyanidin chloride



Quercetin

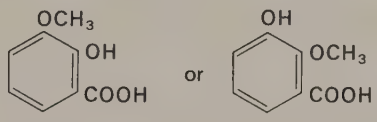
Both of these compounds occur as glycosides, the sugar residues usually being attached at one of the starred hydroxyl groups. Numerous related compounds, including anthocyanins (the term used for the anthocyanidin glycosides) and flavones with fewer or with more hydroxyl groups than the two examples given above, occur in plants. Anthocyanin pigments are responsible for most of the red, violet, and blue colors of flowers and fruits. The monoglucoside of cyanidin is *chrysanthemin*, named from its occurrence in scarlet chrysanthemums, and the diglucoside is *cyanin*, which, curiously, is the pigment of both the blue cornflower and the red rose. The difference in color of a single pigment in different plant tissues is probably due to the presence

in plant tissues of metallic ions (iron, aluminum), whose complexes with the anthocyanin pigments display a range of color.

33-12 Recognition and characterization of phenols

Simple phenols are characterized by their solubility in alkali and insolubility in sodium bicarbonate, although it must be recalled that certain substituted phenols (for example, *p*-nitrophenol) are much stronger acids then phenol itself. Most—but not all—phenols give strikingly colored complexes with ferric salts. The *ferric chloride color* is a valuable diagnostic test for phenols, but it must be recognized that other types of compounds also give colors with this reagent. The ferric chloride color of hydroxamic acids has been mentioned earlier; and enols of many kinds give ferric chloride colors (for example, acetoacetic esters).

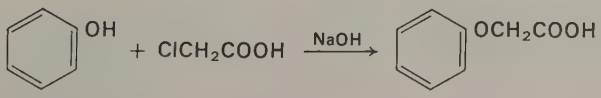
Occasionally the kind of color given by a phenol with ferric chloride is a clue to its structure. Catechol and many other *o*-dihydroxy benzene derivatives give green colors. Salicylic acid gives a deep purple color; and many *o*-hydroxy aldehydes and ketones give more intensely red to purple colors than do simple phenols. These subordinate criteria must be used with caution, but when the experimentalist who is using the test is aware of the limits of the context in which his work lies, they are often valuable. For example, if an unknown compound were thought to be either



the appearance of a purple ferric chloride color would be a strong indication that the first of these structures is the correct one, since the characteristic grouping of salicylic acid is present in this structure, but not in the other.

Another useful diagnostic test for phenols having unsubstituted *ortho* or *para* positions is the use of a diazotized amine. The formation of an azo dye is readily recognized by the intense color that usually characterizes these compounds. The converse of this—the use of β-naphthol in the test for a primary aromatic amine—has been dealt with in Chapter 32.

Phenoxyacetic acids, prepared by the reaction of phenols with chloroacetic acid in alkaline solution, are valuable derivatives for the characterization and identification of phenols:



(36)

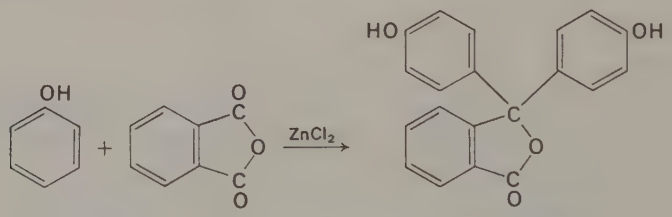
The phenoxyacetic acids are usually crystalline compounds with characteristic melting points. They possess the additional and valuable property of being carboxylic acids that can be titrated with standard alkali. Thus, they provide a means of determining the equivalent weight (the molecular weight in the case of monophenols) of the phenol. The advantage of knowing the molecular weight of an unknown phenol when establishing its structure is obvious.

Exercise 8

An unknown phenol, which contained bromine but no other elements except C, H, and O, formed a phenoxyacetic acid when treated with chloroacetic acid in alkali. Titration of 0.245 g of the derivative with 0.100 *N* NaOH required 10.0 ml of the standard alkali. What is a possible structure for the phenol?

33-13 Phenolphthalein and fluorescein

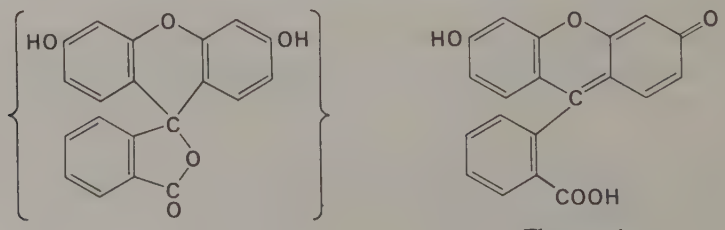
When phenols are heated with phthalic anhydride in the presence of a strong acid catalyst (for example, zinc chloride), condensation to form "phthalein" dyes results. In the case of phenol, the reaction proceeds as follows:



(37)

Phenolphthalein

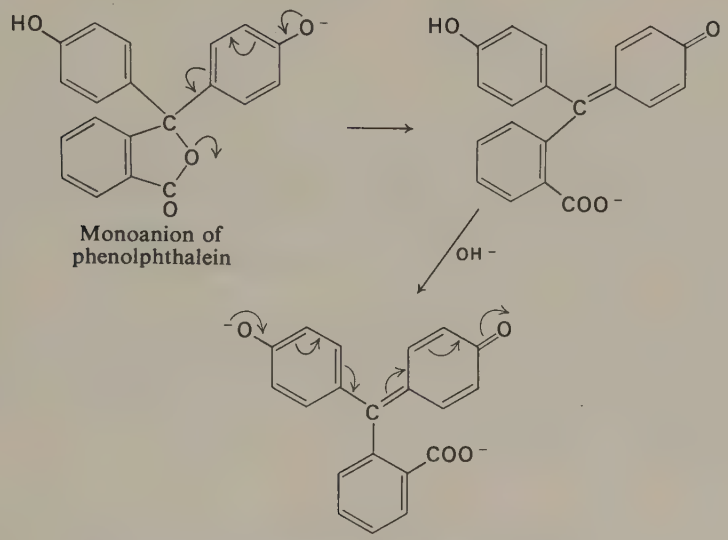
When resorcinol is used in place of phenol, the product is fluorescein:



Fluorescein

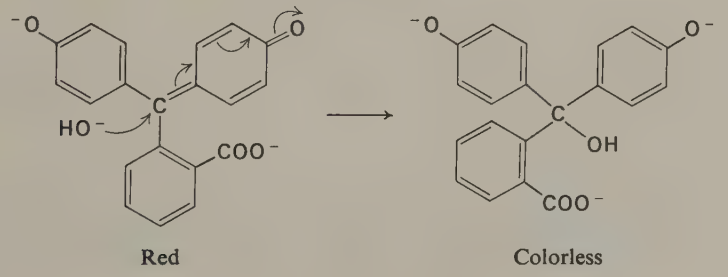
Since phenolphthalein is colorless, the structure written for it above is satisfactory; but fluorescein is a colored compound, and thus probably has the isomeric quinone-like structure.

The use of phenolphthalein as an acid-base indicator depends upon its color change in alkaline solution from colorless to red. The structural change accompanying the ionization is as follows:



(38)

With an increase in the concentration of hydroxide ion (high pH) the red color disappears and the solution again becomes colorless. This change results from the attack of the hydroxide ion shown in the following:

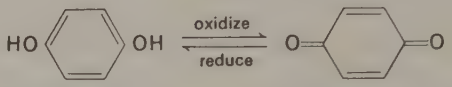


(39)

It can be understood why a high pH is needed to bring this about, since a trinegative ion must be produced (that is, the negative OH ion must attack the doubly negatively charged phenolphthalein ion).

33-14 Quinones and hydroquinones

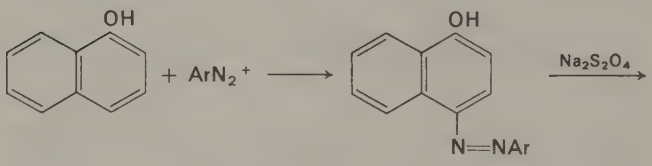
Aromatic 1,2- and 1,4-dihydroxy compounds are readily oxidized to the corresponding *quinones*:

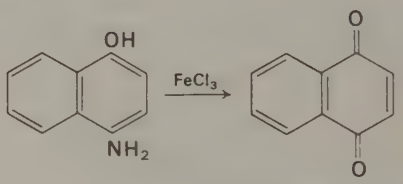


Hydroquinone — *p*-benzoquinone (quinone) (40)

Conversely, quinones are readily reduced to hydroquinones (quinols). Quinones are also obtainable in other ways: by oxidation of *o*- and *p*-aminophenols, and in many cases by direct oxidation of monohydric phenols and aromatic amines. Indeed, the most practicable method of preparing *p*-benzoquinone itself is by the oxidation of aniline.

The ready oxidation of *p*-aminophenols to quinones permits one to prepare quinones, and thus hydroquinones, from simpler phenols by (1) diazonium coupling to give an azo compound, (2) reduction of the azo compound, and (3) oxidation of the amine so formed; for example:



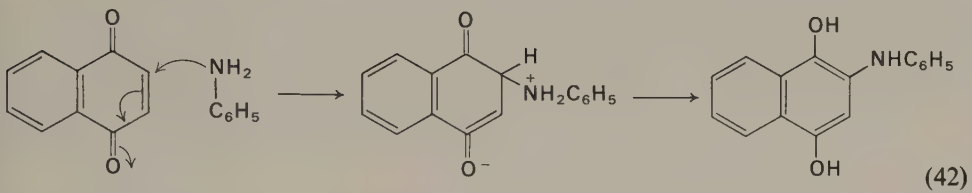


1,4-naphthoquinone (41)

Ortho-quinones, although less stable than *p*-quinones, can be prepared by analogous methods, such as the oxidation of *o*-dihydroxy and *o*-hydroxyamino compounds. The oxidation of catechol by silver oxide gives *o*-benzoquinone, a red crystalline compound.

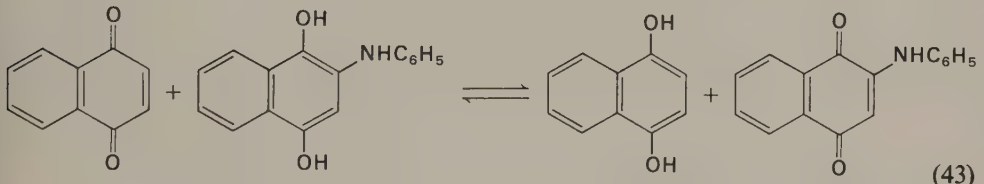
Quinones are not aromatic compounds; rather, they are α,β-unsaturated carbonyl compounds, and their reactions are best interpreted in this way. The addition of amines to quinones is a reaction that will be recognized as a nucleophilic addition to

the conjugated system. The reaction between aniline and 1,4-naphthoquinone proceeds as follows:



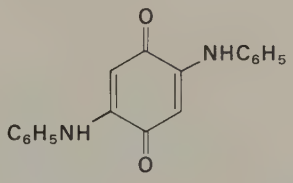
(42)

The hydroquinone derivative that is the product of the addition reaction can be oxidized by the original quinone, and the position of the following equilibrium depends upon the relative oxidation-reduction potentials of the two quinone-hydroquinone systems:

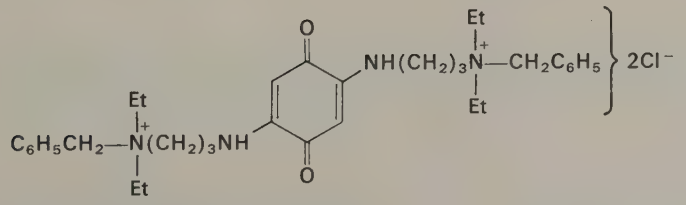


(43)

With *p*-benzoquinone, two molecules of the amine add in successive stages to yield as the final product the disubstituted quinone:

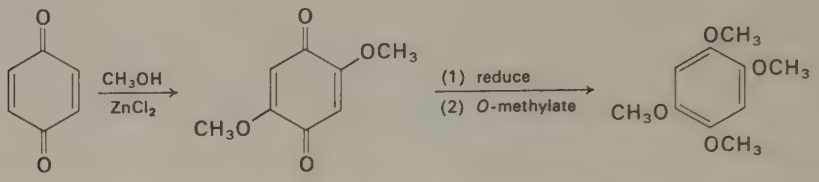


The compound Mytolon, a clinically useful muscle-relaxant (curare-like) compound, is prepared in this way:



Mytolon

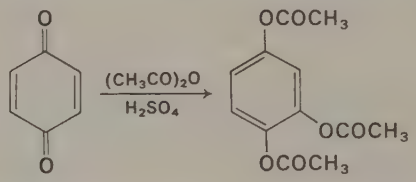
Compounds more weakly nucleophilic than amines add to quinones under the catalytic effect of strong acids. The addition of methanol to *p*-benzoquinone proceeds in the following way:



(44)

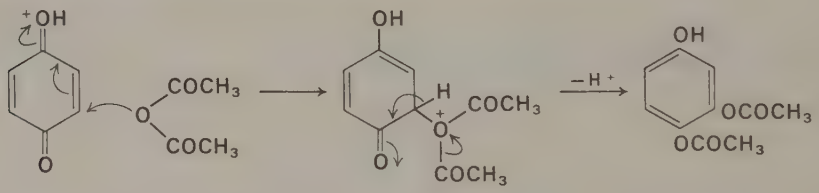
As shown in the second stage of this reaction, the method is useful for the preparation of tetraalkoxybenzenes.

Acid-catalyzed addition of acetic anhydride to *p*-benzoquinone (the *Thiele reaction*) leads to the formation of 1,2,4-triacetoxybenzene:



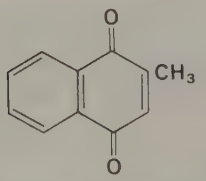
(45)

The course of the reaction can be described by the following steps:

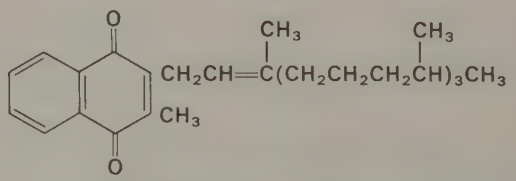


(46)

Quinones of many kinds are important compounds, both because of their widespread occurrence in nature as the products of plant and animal metabolism, and because of their use in medicine. 2-Methyl-1,4-naphthoquinone is a clinically useful "vitamin K," which is used to combat certain diseases characterized by reduced clotting power of the blood. "Natural" vitamin K also possesses the 1,4-naphthoquinone structure, but carries at the 3 position a complex hydrocarbon chain:



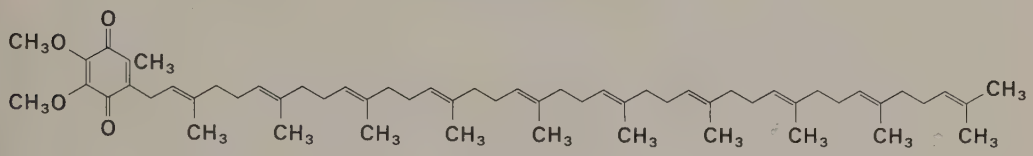
(Synthetic) vitamin K



(Natural) vitamin K_1
2-methyl-3-phytyl-1,4-naphthoquinone

Natural vitamin K_1 is found in green plants and is an important dietary constituent that plays a role in the maintenance of the coagulant properties of blood.

A group of quinones typified by the one shown below, but differing in the length of the chain of five-carbon-atom units, are widely distributed in living cells, in which they play important roles in metabolism, probably by electron transfer involving reversible quinone-hydroquinone interconversion:



Coenzyme Q_{10}

Other quinones occur in plants, lichens, fungi, and marine organisms, in many of which they are responsible for yellow, orange, and red colors.

Problems

1. Arrange the following compounds in order of decreasing strength as acids: (*a*) phenol, (*b*) *o*-nitrophenol, (*c*) *m*-bromophenol, (*d*) *o*-bromophenol, (*e*) 2,4,6-trimethylphenol, (*f*) *p*-hydroxybenzoic acid, (*g*) 2,4,6-tribromophenol, (*h*) 2,4-dinitrophenol, (*i*) benzyl alcohol.

2. Devise practical syntheses for the following, using as the aromatic starting material any monosubstituted benzene derivative: (*a*) *p*-bromophenol, (*b*) resorcinol (*m*-dihydroxybenzene), (*c*) aspirin, (*d*) *o*-methoxybenzoic acid, (*e*) *p*-aminoanisole, (*f*) *p*-*n*-butylphenol, (*g*) 2-hydroxy-5-methylbenzaldehyde, (*h*) 3,4-dimethoxybenzoic acid.

3. Devise procedures for separating the following mixtures into their pure components. Use chemical means of separation. (*a*) phenol, benzoic acid, benzyl alcohol; (*b*) anisole, salicylaldehyde, benzaldehyde; (*c*) aniline, picric acid, *p*-cresol; (*d*) β-naphthol, β-naphthylmethyl ether, β-naphthoic acid; (*e*) salicylic acid, salicylaldehyde, phenol, methyl salicylate.

4. A phenolic compound (A), $C_7H_8O_2$, is completely destroyed when oxidized with $KMnO_4$. When A is treated with dimethyl sulfate in alkali it is transformed into B, $C_8H_{10}O_2$. Oxidation of B with $KMnO_4$ gives in excellent yield an acid (C), $C_8H_8O_3$. Write a possible structure for A. Are any other structures possible for A? If so, how could you distinguish them?

5. Contrast the chemical behavior of phenol and benzyl alcohol, using at least four different types of reactions to illustrate your discussion.

6. A glucoside (A), $C_{12}H_{16}O_7$, is soluble in dilute aqueous alkali, from which it is recovered unchanged upon acidification. It can be hydrolyzed with hot dilute HCl, or by emulsin, to yield D-glucose and a phenolic aglucone (B). Exhaustive methylation of A yields an alkali-insoluble product (C). The methylated glucoside (C) can be hydrolized to yield 2,3,4,6-tetra-*O*-methylglucose and a phenol (D), $C_7H_8O_2$. Both B and D can be methylated with dimethyl sulfate and alkali to a neutral compound (E), $C_8H_{10}O_2$. Bromination of E gives *only one* monobromo derivative. Write the structures of the lettered compounds.

7. Picein, $C_{14}H_{18}O_7$, is a naturally occurring glucoside. It is nonreducing, but forms an oxime and a phenylhydrazone. After hydrolysis with a β-glucosidase or with dilute acid, it yields D-glucose and a compound (A), $C_8H_8O_2$. Compound A is soluble in alkali but not in sodium bicarbonate solution, and when treated with dimethyl sulfate and alkali is transformed into a neutral compound (B), $C_9H_{10}O_2$. Compound B gives a positive iodoform reaction, and from this reaction is isolated, along with iodoform, an acid (C), $C_8H_8O_3$. The acid C can be synthesized by permanganate oxidation of *p*-cresyl methyl ether. Picein reacts with HIO_4, consuming 2 moles of the reagent and forming 1 mole of formic acid and no formaldehyde. Draw the Haworth projection formula for picein and write the reactions described.

34

Molecular rearrangements

One of the most intellectually fascinating—and often the most mechanistically significant—aspects of the chemical transformations of organic compounds is the alteration of structure that accompanies the shift of an atom or group from one position in the molecule to another. This may be as simple and unexceptional as the shift of a hydrogen atom (prototropy) or a change in the position of a carbon-carbon double bond; or it may involve a change in the carbon skeleton of a compound by the shift of a methyl or other group, or a change in the size of a ring.

This chapter describes the rearrangements most commonly encountered by the organic chemist. The student should note with care that in the discussion of these reactions the emphasis is placed upon the nature of the transformations and upon the energetic considerations that account for them. Since reactions tend to run "downhill" energetically, rearrangements occur because an unstable precursor is transformed into a product with greater stability. Although some rearrangements are equilibrium reactions in which both the rearranged and unrearranged product are present, most rearrangements proceed to practical completion.

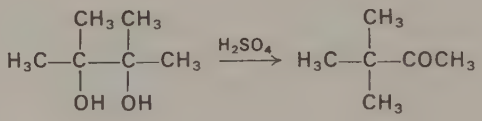
Special note should be taken of the fact, which this chapter stresses, that many rearrangements appearing at first sight quite disparate in kind are simply variations on a theme, and are different expressions of the same mechanistic principle.

34-1 Electron-deficient atoms

One of the problems confronting the organic chemist, and one to which he must always be alert, arises from the fact that the relative arrangement of atoms in an organic compound may alter in the course of a reaction, and a *rearrangement* may occur. A rearrangement may be simple, as in the shift of a double bond from one position to another,

$$CH_3CH_2CH{=}CH_2 \overset{H_2SO_4}{\rightleftharpoons} CH_3CH{=}CHCH_3$$

or somewhat more complex, as in the pinacol rearrangement,



or it may involve extensive changes in structure in which more than one atom or group changes its point of attachment.

The fact that rearrangements do occur is of great value to the chemist. Many rearrangements have considerable practical value in permitting ready synthetic routes to desired products that would otherwise require involved and lengthy methods of preparation. But there is another use in the occurrence of rearrangements: by the study of their nature and course a theoretical insight can be gained into the fundamental aspects of organic reactions. Thus, far from complicating the study of organic chemistry, rearrangements serve as a basis upon which to correlate and elucidate the principles of organic reactions, and help to disclose common fundamental modes of behavior of organic compounds.

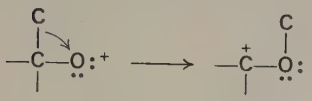
We have seen that many organic reactions owe their inception to the deficiency of electrons on an atomic nucleus, and the consequent satisfaction of this deficiency by a donor, or nucleophilic reagent, which is capable of providing electrons to the deficient atom, forming a new bond. Examples that may be recalled briefly are the electrophilic character of carbon in the carbon-halogen bond, the electron-poor carbon atom of the carbonyl group, the boron atom of the neutral tricovalent boron compounds, and the very electrophilic carbonium carbon atom.

It will also be recalled that in some cases the generation of an electron-deficient carbon atom, as by ionization of a C—Cl or C—$\overset{+}{O}H_2$ bond, is followed by a molecular rearrangement to a more stable carbonium ion.

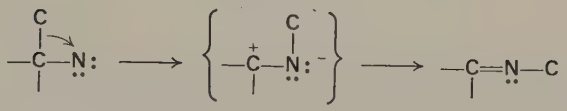
Most of the rearrangements with which we shall be concerned consist in the breaking of a carbon-carbon bond, and the "migration" of the group so liberated

to form a new bond with another carbon atom or with an oxygen or nitrogen atom:

(1)



(2)



(3)

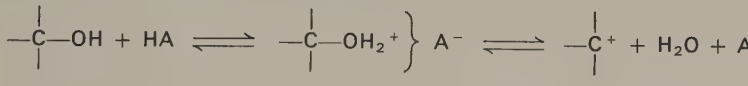
The common feature of the three kinds of rearrangements is that the atom B in equation (4) is electron deficient, and the migration of A with its binding pair of electrons satisfies this deficiency:

[General expression for equations (1), (2), (3)] (4)

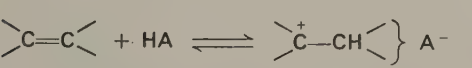
It appears to be a corollary of this that if the compound or ion A—X—B, in which B is electron deficient, rearranges to X—B—A, leaving X electron deficient, X must be better able to tolerate the electron deficiency. The gain in stability of X—B—A over A—X—B is the driving force for the rearrangement.

34-2 Carbonium-ion rearrangements

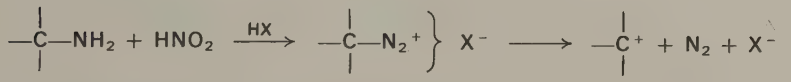
The generation of an electron-deficient carbon atom (a carbonium ion) can be accomplished in a number of ways; for example:



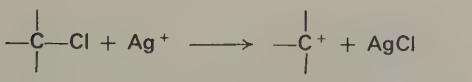
(5)



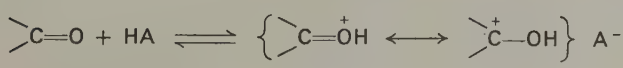
(6)



(7)



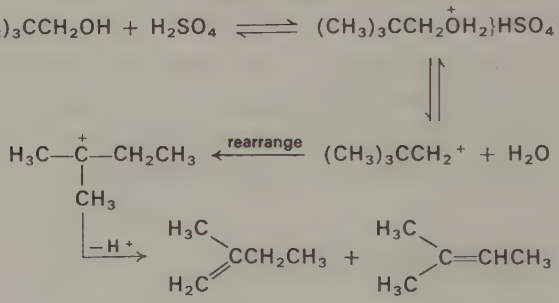
(8)



(9)

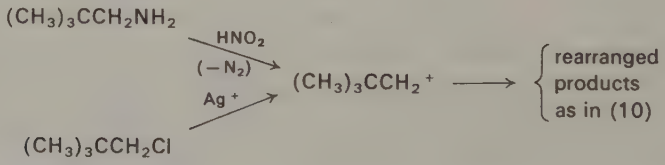
It will be recalled that while the protonation of the alcoholic hydroxyl group is a consequence of its basic nature, and always occurs to a degree that depends upon the strength of the protonating acid, the formation of a "free" carbonium ion according to (5) does not invariably follow, but occurs only when the resulting carbonium ion possesses stabilizing features such as the resonance contributions of the attached methyl groups in $(CH_3)_3C^+$, or of the alkoxyl group and aromatic ring in

We can now recognize another influence that leads to the loss of H_2O from $-\overset{|}{\underset{|}{C}}-\overset{+}{O}H_2$; namely, a rearrangement to a new system of greater stability. For instance, although the acid-catalyzed reactions of saturated primary alcohols do not ordinarily proceed by way of discrete carbonium ions, dehydration of the primary alcohol neopentyl alcohol by the action of acid occurs by a reaction that is probably initiated by a dissociation of the protonated alcohol:



(10)

In accordance with the reactions indicated in (5)–(9), the treatment of neopentylamine with nitrous acid (11), or of neopentyl chloride with a silver salt (12), will produce a comparable result:



(11)

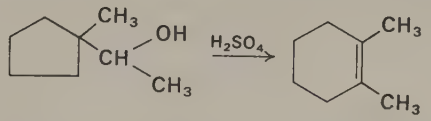
(12)

This kind of rearrangement is called the *Wagner-Meerwein rearrangement*, so called because of the studies of Wagner and Meerwein on the chemistry of terpenes, the chemistry of which is replete with structural changes brought about by skeletal alterations initiated by the generation of electron-deficient carbon atoms.

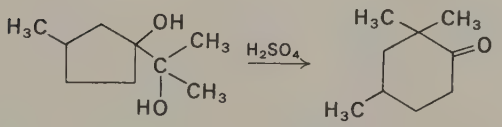
That rearrangements such as that of the neopentyl group occur, even though the generation of a primary carbonium ion is energetically very unfavorable, indicates that the migration of the methyl group occurs as the leaving group departs, and that the neighboring group participates in the process of ionization. We may formulate the general case in the following terms:

Further refinement of this concept would require much more extended comment than is possible here. It can be said that, depending upon the nature of X, R, and Y, and the degree of substitution on the two carbon atoms shown in this generalized expression, the stages shown may be discrete intermediates, stages represented by energy minima in an energy diagram for the progress of the reaction, or stages that represent only a formal dissection of a reaction course that leads through a single intermediate. Thus, equations (10), (11), and (12) should be regarded as didactic rather than realistic expressions for the overall course of the reaction.

Other examples of rearrangements that proceed by way of carbonium ions are:



(13)



(14)

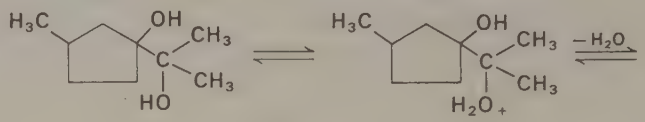
Reaction (14) is an example of the pinacol rearrangement, which is mechanistically closely related to the Wagner-Meerwein rearrangement.

Exercise 1

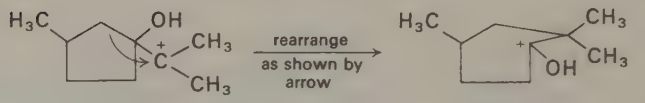
Formulate the stages in the rearrangements in (13) and (14).

In the rearrangement that takes place in (10) the driving force is the transformation of the primary carbonium ion into the more stable tertiary carbonium ion by the migration of the methyl group. In the pinacol rearrangement [for example, (14)] the

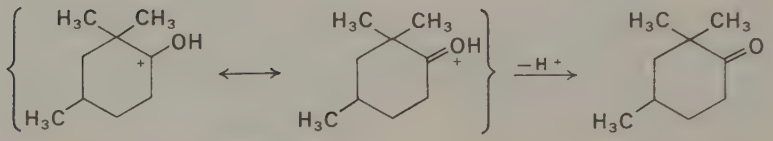
protonation (15) and loss of a water molecule to give (16) is followed by a rearrangement that leads to the generation of the resonance-stabilized conjugate acid of a carbonyl group (17):



(15)

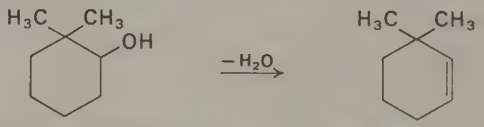


(16) (= 17)



(17)

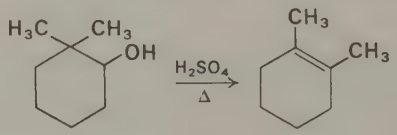
It is evident that in any reaction in which a carbonium ion is generated, the possibility of the occurrence of a rearrangement of the Wagner-Meerwein or pinacol type must be kept in mind. Suppose, for example, it were desired to carry out the reaction



(18)

2,2-dimethylcyclohexanol 3,3-dimethylcyclohexene

The usual methods of dehydration of alcohols by treatment with strong acid catalysts proceed by way of protonated species that can lead to carbonium ion intermediates. Indeed, an attempt to bring about the dehydration of 2,2-dimethylcyclohexanol by treating the alcohol with hot dilute sulfuric acid leads to the rearranged olefin:

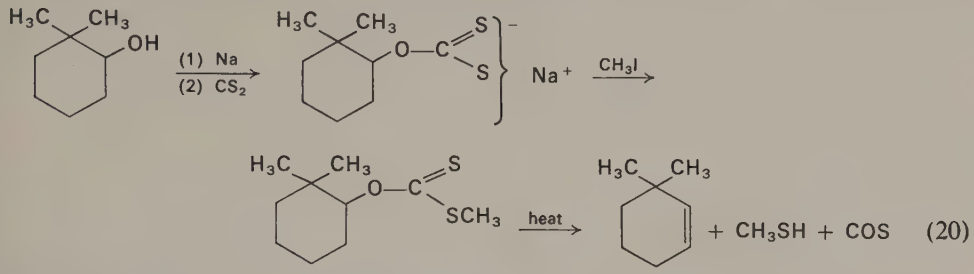


(19)

34-3 Dehydration without rearrangement

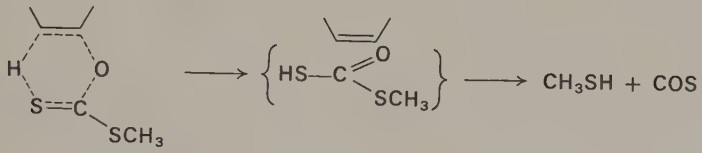
The dehydration of 2,2-dimethylcyclohexanol to 3,3-dimethylcyclohexene can be accomplished by a reaction in which a carbonium ion is not an intermediate. A proce-

dure for carrying this out, known as the xanthogenate method, involves the pyrolytic decomposition of a thioester, prepared as follows:



(20)

The formation of a cyclic transition state

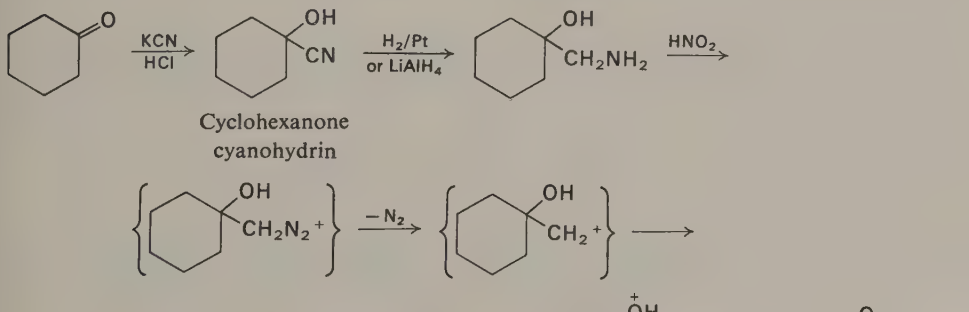


(21)

provides for a concerted rupture of the C—O bond simultaneous with the deprotonation. The pyrolysis of esters of other kinds (for example, benzoates and acetates) is also employed.

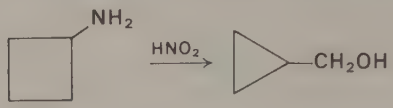
34-4 Aliphatic diazonium compounds

The action of nitrous acid upon aliphatic primary amines is very apt to lead to rearrangements, since the tendency for the aliphatic diazonium compounds to decompose, yielding nitrogen and carbonium ions, is very high indeed. When the amino group is adjacent to a carbinol carbon atom, as in 1-aminomethylcyclohexanol (the synthesis of which is shown), pinacol-like rearrangement occurs:



(22)

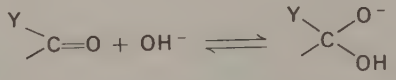
Ring contractions as well as expansions are observed in cyclic systems:



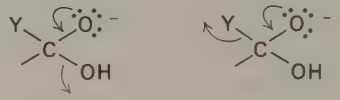
(23)

34-5 Base-induced rearrangements

The addition of a strong base (for example, OH^-) to a carbonyl group, as in the following partial expression,

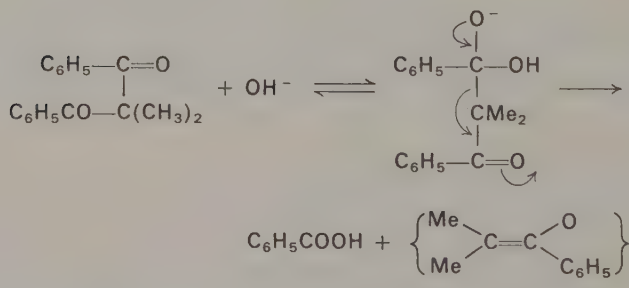


may lead to a number of consequences other than the simple reversal of the addition with expulsion of OH^- (24). That is, the anionic $—O:^-$ can regain its carbonyl character in two ways:



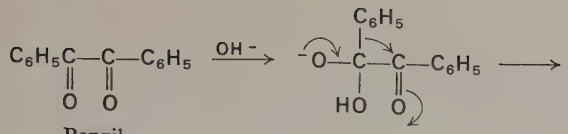
(24) (25)

Examples of (25) that we have already encountered, which are not rearrangements as we are now using the term, include many of the reactions of acid derivatives (for example, hydrolysis of esters, where Y = OR) and the cleavage of β-dicarbonyl compounds; for example:

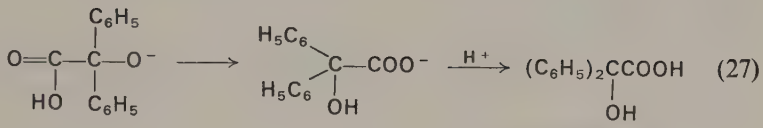


(26)

A third course to which (25) applies consists in a *migration* of Y to an adjacent electron-deficient center. A typical example of this is the *benzilic acid rearrangement*, so called because its prototype is the rearrangement of benzil into benzilic acid:



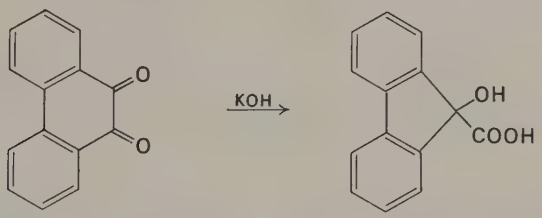
Benzil



Benzilic acid (27)

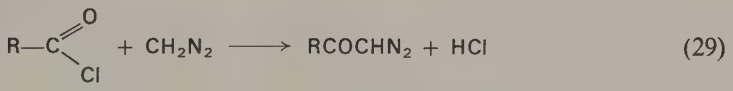
In this case the driving force for the rearrangement is the combination of the influences of the electrophilic carbonyl carbon atom *to which* the phenyl group migrates and of the anionic oxygen furnishing the electron pair to the carbon *from which* the phenyl group has migrated. An examination of the rearrangement of benzil to benzilic acid reveals that this is indeed an oxidation-reduction reaction: benzil, with two carbonyl groups, is transformed into benzilic acid, with one hydroxyl group and one carboxyl group.

Ring contractions can occur when the migrating "group" is a member of a cyclic system. For example, in the benzilic acid rearrangement of phenanthrene-9,10-quinone (phenanthraquinone), the product is a fluorene derivative:



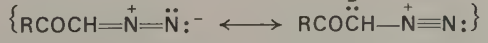
Phenanthrene-9,10-quinone Fluoren-9-ol-9-carboxylic acid (28)

The *Wolff rearrangement* of diazoketones to carboxylic acid derivatives may be included in this general category. Diazoketones are prepared by the action of diazomethane upon acid chlorides:



(29)

The structure of this diazoketone is that of a resonance hybrid of the important contributing forms



Diazoketones of this kind react with water, alcohols, and ammonia to give, respectively,

acids, esters, and amides that contain one more $—CH_2—$ group than the acid (RCOOH) from which the acid chloride was derived. The overall method is commonly known as the *Arndt-Eistert synthesis* and is a valuable way of extending a carbon chain. By successive Arndt-Eistert reactions a synthetic sequence such as the following can be accomplished:

$$RCOOH \longrightarrow RCH_2COOH \longrightarrow RCH_2CH_2COOH$$

The rearrangement step occurs in the following way. The loss of nitrogen from the diazoketone leaves an electron-deficient carbon atom, to which the group R can migrate as in equation (1):

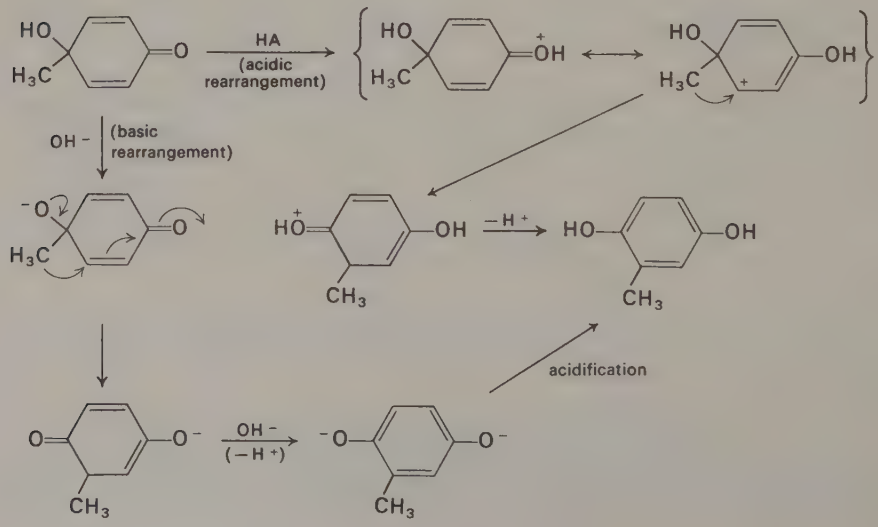
$$RCOCHN_2 \xrightarrow{-N_2} \left\{ R—C(=O)—\ddot{C}H \right\} \xrightarrow{\text{shift of R:}} RCH{=}C{=}O$$

A ketene

The resulting *ketene* (which can be isolated in some cases) then reacts with water, alcohol, or ammonia, depending upon the manner in which the reaction is carried out, to give the final product:

$$RCH{=}C{=}O \begin{cases} + EtOH \longrightarrow RCH_2COOEt \\ + H_2O \longrightarrow RCH_2COOH \\ + RNH_2 \longrightarrow RCH_2CONHR \end{cases}$$

An illuminating example of a compound that undergoes rearrangement under both acidic and basic conditions is the following:

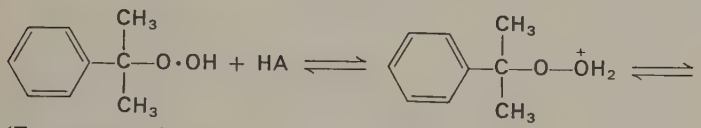


(30)

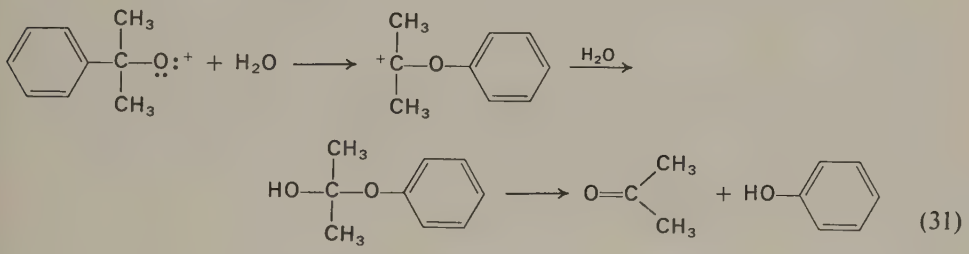
34-6 Rearrangements involving electron-deficient oxygen

The participation of electron-deficient oxygen atoms in organic reactions is a feature of many reactions in which oxidation is the overall process. In general terms, the change has been pictured in (2). The subsequent fate of the rearranged product, which is still "onium" in nature, will depend upon structural factors that can best be described by examining the following examples.

The treatment of cumene hydroperoxide with acid leads to the formation of acetone and phenol; the process is used industrially for the large-scale production of these important chemicals:



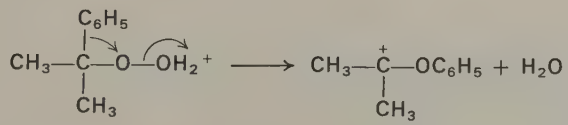
(From cumene by air oxidation in the presence of a catalyst)



Hemiketal of phenol and acetone

(31)

It is emphasized here, as in earlier discussions, that dissociation of H_2O from the protonated intermediate is shown as a discrete process as a convenience, since it is not always possible to distinguish that process from the nearly equivalent one in which the shift of the migrating group is *a part of the step* in which H_2O departs. That is, the equations might better be written

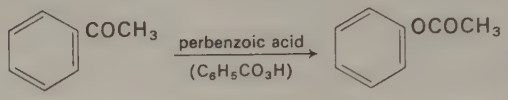


(32)

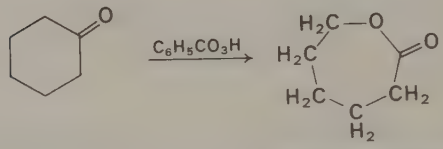
However, since the incipient dissociation, or tendency for the dissociation, of H_2O from $-O-\overset{+}{O}H_2$ lends the residual oxygen atom positive character, writing the equation for the reaction in discrete steps serves to emphasize the mechanistic basis for the change.

34-7 The Baeyer-Villiger reaction. Oxidation of ketones to esters and lactones

A reaction that has a mechanistic basis similar to that of the preceding example is the oxidation of ketones to esters (or lactones, in the case of cyclic ketones) by peroxy acids. The reaction, in two examples, is as follows:

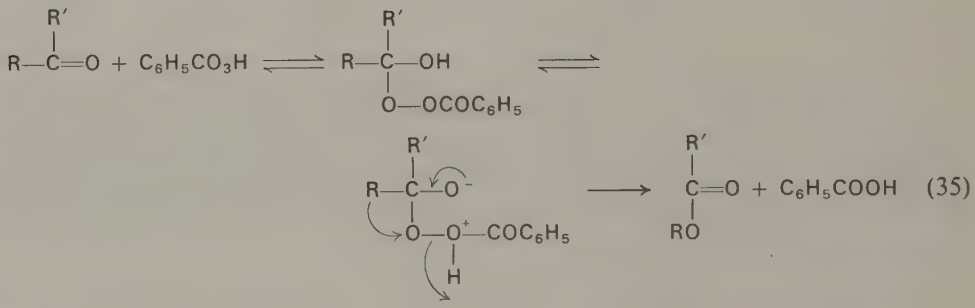


Acetophenone — Phenyl acetate (33)



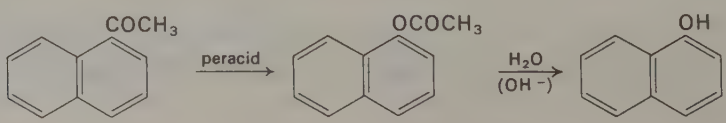
Cyclohexanone — 6-hydroxyhexanoic acid lactone (34)

The addition of the peroxy acid [perbenzoic acid will be used as the example, but other peroxy acids, such as peroxyacetic, peroxytrifluoroacetic, and persulfuric (Caro's acid) are also used] to the ketonic carbonyl group may be written in the following way:



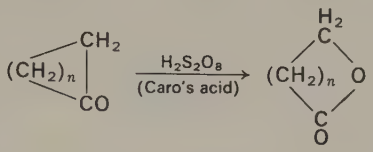
(35)

The oxidation of ketones to esters in this way is a very useful reaction. It serves as a means of displacing an acyl group from the aromatic ring, with the formation of a phenol (as the ester); for example,



(36)

It has also been used to produce large-ring lactones from large-ring ketones:

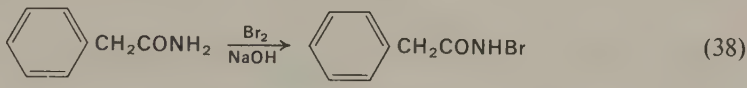


(37)

The formation of a multi-membered lactone from the corresponding ketone is evidence that *the reaction does not proceed by oxidation of the ketone to a hydroxy acid, and subsequent lactonization.* In such a case a cyclic ketone of $n = 4$ or more in (37) would be expected to yield a polymeric linear lactone.

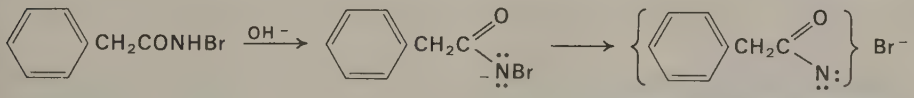
34-8 Rearrangements involving electron-deficient nitrogen

The *Hofmann degradation* of amides results in the overall transformation $RCONH_2 \rightarrow RNH_2$, which clearly involves the formation of a carbon-nitrogen bond between the carbon atom of the R group and the amide nitrogen atom. The reaction is carried out by treating the amide with bromine in alkaline solution (to yield an intermediate *N*-bromoamide that can be, but seldom is, isolated), the final stage being brought about by alkaline hydrolysis under the alkaline conditions employed. The stages in the reaction are shown in (38)–(40):

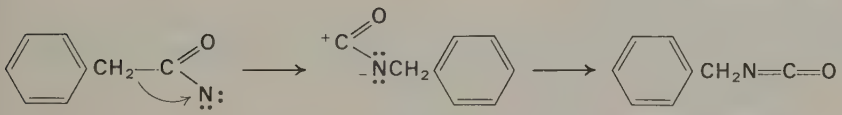


(38)

The final, or rearrangement step, can be described by the simplified equations



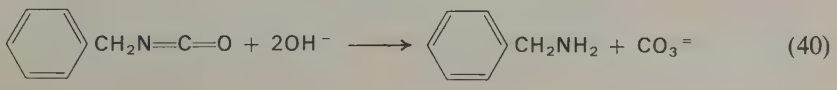
Electron-deficient nitrogen atom [cf. (3)]



(39)

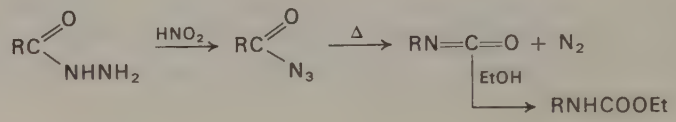
Benzyl isocyanate

The isocyanate (which can be isolated) is hydrolyzed by alkali to yield the amine and carbon dioxide (as carbonate):



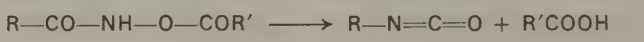
(40)

The *Curtius reaction* is quite different from the Hofmann reaction in the manner of its performance, but it is *mechanistically very closely allied to it*; it consists in the treatment of an acyl hydrazine (a hydrazide) with nitrous acid, with the formation of an acyl azide. The azide rearranges to the isocyanate on heating in an inert solvent (for example, benzene); if the reaction is carried out in alcoholic solution, the isocyanate reacts with the solvent to form a *urethane*:



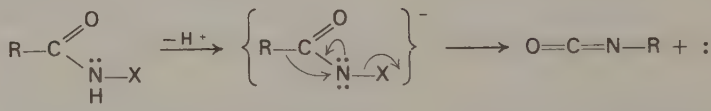
(41)

A third reaction of the same kind is the *Lossen rearrangement* of hydroxamic acids. Hydroxamic acids, or their *O*-acyl derivatives, rearrange upon heating, with the loss of —OH or *O*-acyl and migration of the R group to nitrogen:



(42)

All of these rearrangements can be seen to proceed by a common course, which can be summarized in the expression

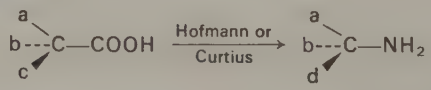


(43)

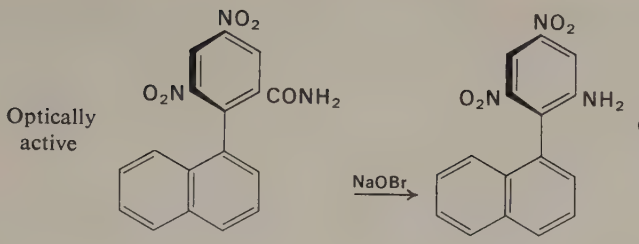
in which :X is Br^- in the Hofmann reaction, N_2 in the Curtius reaction, and $OCOR^-$ in the Lossen reaction.

An example of the Lossen rearrangement that occurs in nature is the formation of isothiocyanates from mustard oil glycosides, described in Chapter 15. In this case the compound that undergoes the rearrangement is a derivative of the hydroxamic acid derived from a thio acid, RCOSH.

A noteworthy feature of the Hofmann and Curtius reactions is that if the R group in RCOOH is asymmetric its configuration is retained:



This has been demonstrated experimentally by the Hofmann rearrangement of the following amide, in which the optical activity is due to the restricted rotation about the bond joining the two aryl groups:



(44)

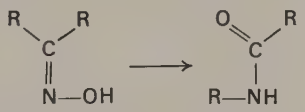
Had the biaryl system become free at any time during the rearrangement (by loss of $-CONH_2$, for example), rotation and racemization would have occurred.

Exercise 2

Show how acetophenone can be converted into (*a*) phenol and (*b*) aniline, by means of reactions described in this chapter. Write the equations.

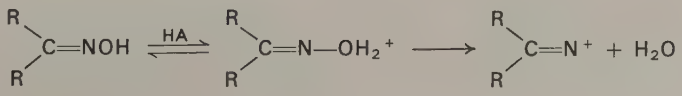
34-9 The Beckmann and Schmidt rearrangements

The *Beckmann rearrangement* consists in the conversion of an oxime into an amide by the migration of a group from carbon to nitrogen:



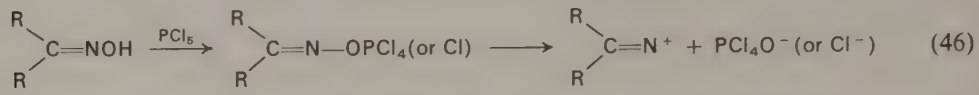
The Beckmann rearrangement can be brought about by a variety of reagents, all of them characterized by a common feature: they all act to permit the removal of the —OH group from nitrogen in such a way as to create an electron deficiency on nitrogen. In the following equations illustrating this step, a discrete, positively charged nitrogen atom is written; as will be discussed in greater detail further on, this is a simplification that requires additional elaboration.

Strong acids, such as sulfuric acid, can aid the departure of the OH group by protonation:



(45)

Phosphorus halides can aid the departure of the OH group by replacement of OH by halogen, or by conversion of the oxime into a phosphoric ester:

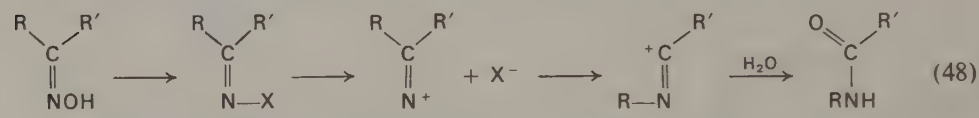


(46)

In some cases tosylation brings about the rearrangement by converting OH into the excellent leaving group —OTos:

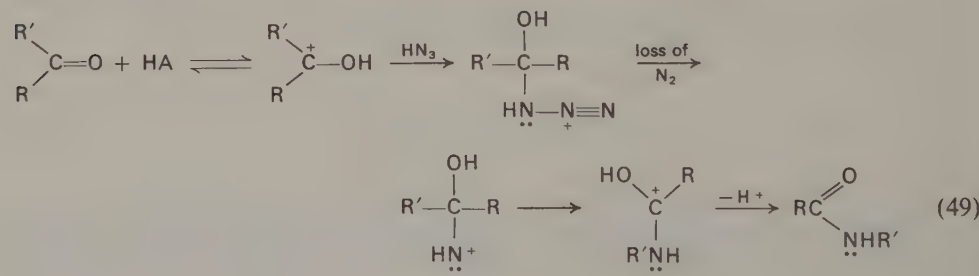
(47)

The result of any of these procedures is to alter the hydroxyl group of =N—OH to a group X that is apt to ionize as $:X^-$. The complete equation for the Beckmann rearrangement, including a final hydrolysis, is represented by the following:



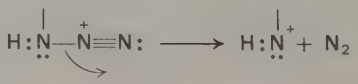
(48)

In the *Schmidt reaction* a ketone reacts with hydrazoic acid to form an amide, with the simultaneous evolution of nitrogen. The reaction can be described by the following sequence of steps:



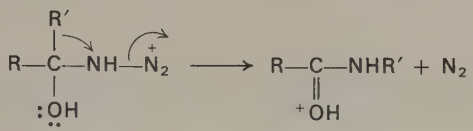
(49)

As before, it can be seen that the loss of nitrogen from the $—N_3$ fragment leads to an electron-deficient nitrogen atom:



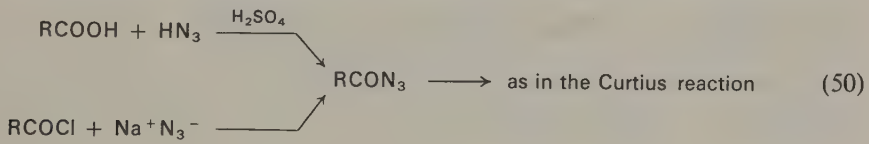
Again, it should be borne in mind that the details of each reaction that has been formulated above describe the *nature and course* of the reaction, and are not in all cases the *mechanism* of the reaction. For example, the course of the Schmidt reac-

tion can be recognized as involving a shift of the R group to an electron-deficient nitrogen, whether the loss of nitrogen precedes the migration of R as a discrete phase, or whether the nitrogen leaves as the group migrates:



The difference between these details represents a difference in *mechanism*; that such details have not been made explicit in the discussion throughout this chapter is partly because a given reaction may follow one course or another, depending upon the particular structure of the substance involved, and partly because in some cases such details are not known with certainty. In the case of the Beckmann rearrangement, the simplified "mechanism" involving an intermediate $\diagdown C{=}N^+$ would lead to erroneous predictions of the stereochemical course of the rearrangement; this is discussed in the following section.

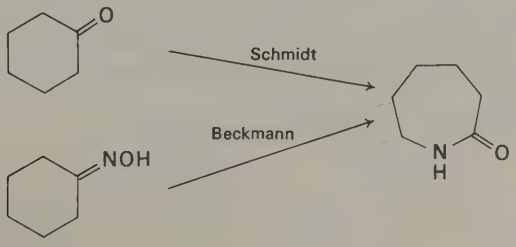
The degradation of carboxylic acids to amines by hydrazoic acid is also called the Schmidt reaction. An alternative but equivalent procedure is to treat the acid chloride with sodium azide. In either case, the acid is converted into the acyl azide just as in the Curtius reaction, and the subsequent course of the reaction is the same:



(50)

34-10 The intramolecular nature of the Beckmann and Schmidt rearrangements

The intramolecular nature of the Beckmann and Schmidt rearrangements is shown by the fact that cyclohexanone (via Schmidt) or its oxime (via Beckmann) is converted into the seven-membered cyclic amide (lactam):



(51)

(52)

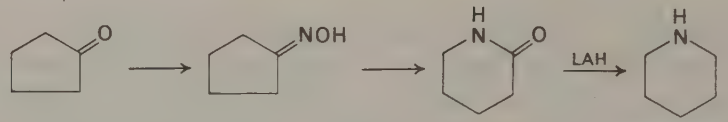
This result demonstrates that the amide is not formed from an intermediate amino acid.

Exercise 3

Devise syntheses for (*a*) methylethylamine; (*b*) benzanilide; and (*c*) 5-aminopentanoic acid, using the Beckmann or Schmidt reaction.

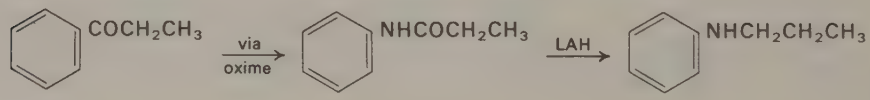
Cycloheptanone oxime undergoes the Beckmann rearrangement to yield the eight-membered lactam, and the macrocyclic ketones of 8 to 20 members can be converted into large-ring lactams.

A synthetic sequence involving a Beckmann rearrangement and leading finally to an amine can be carried out with aid of lithium aluminum hydride (LAH), which can reduce the amide linkage —CO—NH— to —CH_2NH—. For example, piperidine can be prepared from cyclopentanone,



Piperidine (53)

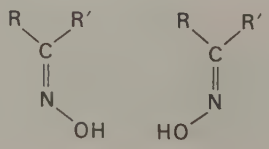
and propiophenone can be converted to *N*-*n*-propylaniline:



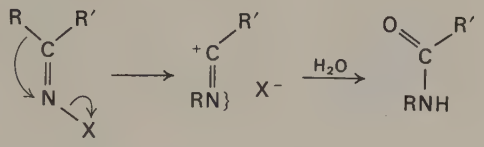
(54)

34-11 The stereochemistry of the Beckmann rearrangement

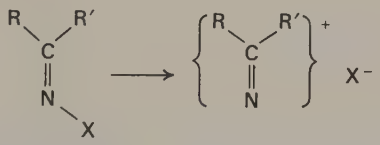
In the unsymmetrical ketoxime R—C(=NOH)—R′ there would appear to be two possible results of a Beckmann rearrangement: RCONHR′ and R′CONHR. With a given oxime, however, but one product is obtained, and it can be concluded that the course of the rearrangement is directed by the configuration of the oximino group. It will be recalled that an unsymmetrical ketone (R—CO—R′) can give rise to two oximes:



It has been shown experimentally that the Beckmann rearrangement proceeds with a *trans* migration, the migrating group entering from the rear as the —OH (or derived) group leaves the nitrogen atom:

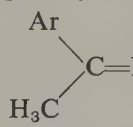


With reference to the remarks concerning the course and mechanism of the reaction it can now be seen that a discrete stage

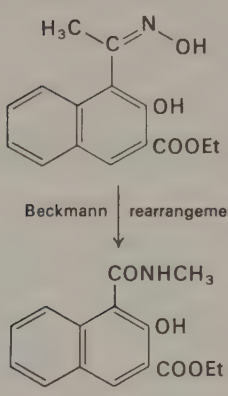


of the reaction is unlikely, since it would be anticipated that a species $R_2C{=}N^+$ would not retain a fixed configuration, and that both R and R′ migration would occur. It thus appears the that *shift of a group from C to N occurs as X departs*, thus preserving the stereochemical specificity of the reaction.

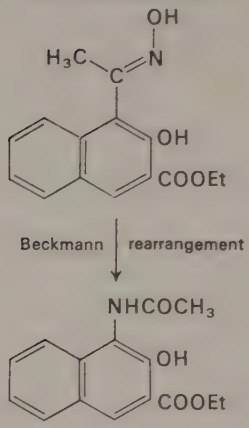
One of several experimental demonstrations of the stereochemical specificity of the Beckmann rearrangement is the following. Ethyl 1-acetyl-2-naphthol-3-carboxylate forms two oximes, which differ in the stereochemistry at the C=N bond. One of the oximes can be resolved into enantiomorphic, optically active forms; the other is not resolvable. It will be seen from the structures of these two oximes that the compound in which the naphthyl group and the *N*-hydroxyl group are *syn* disposed will suffer restriction to the rotation of the oximated acetyl group (the blocking substituents in the naphthalene nucleus are the 2-hydroxyl group and the hydrogen atom in the 8 position), while in the isomeric oxime the *N*-hydroxyl group and the 2-hydroxyl group are not in a position to interfere with free rotation. The resolvable oxime, in which the methyl group is *trans* to the *N*-hydroxyl group undergoes Beckmann rearrangement with migration of the methyl group (55). The nonresolvable oxime undergoes Beckmann rearrangement with migration of the aromatic group (56).

The fact that certain ketones yield oximes that give only one Beckmann-rearrangement product is accounted for by the fact that one of the two possible oximes is formed preferentially, probably for steric reasons. For example, aryl methyl ketones always yield arylamine derivatives. This indicates that in  , the hydroxyl group is oriented *away from the bulky aryl group*, and thus the aryl group migrates to nitrogen in the rearrangement.

(55) Resolvable

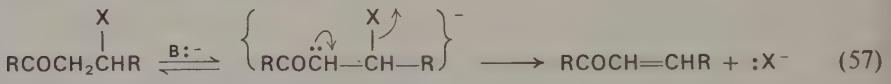


(56) Non-resolvable



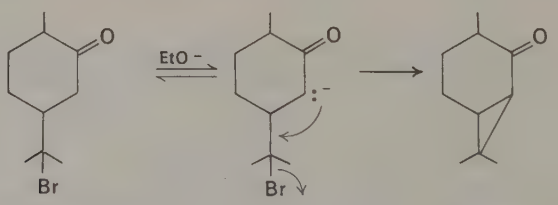
34-12 Rearrangements of carbonyl compounds induced by bases

The generation of an α-carbanion by the attack of a strong base upon a carbonyl compound can in certain cases lead to a sequence of events that results in a molecular rearrangement. Halogenated ketones react with bases in various ways; β-halogenated ketones undergo a ready elimination reaction:



(57)

γ-Halogenated ketones often react with bases to form cyclopropane derivatives. These may be stable compounds that can be isolated, such as carone, formed by the action of alcoholic potassium hydroxide on dihydrocarvone hydrobromide:

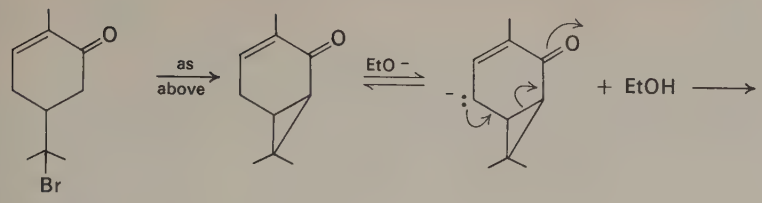


(58)

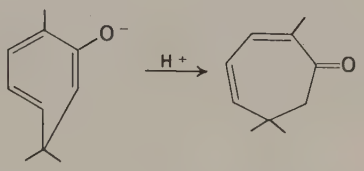
Dihydrocarvone hydrobromide

Carone

Carvone hydrobromide, however, undergoes a similar second reaction by the action of the alcoholic alkali upon the cyclopropane formed. The methylene group present in the system $-CH_2-C=C-C=O$ is an active methylene group, for the anion $\{-\ddot{C}H-C=C-C=O\}^-$ is stabilized by resonance. As a consequence, the following reaction course leads to the eventual formation of the seven-membered ring compound eucarvone:



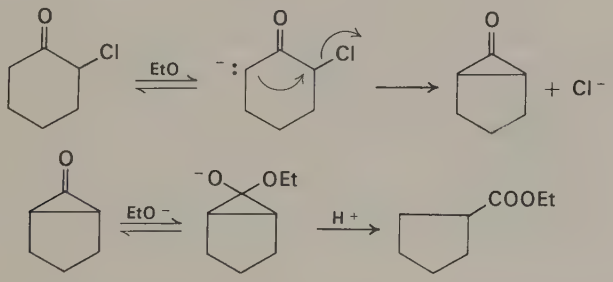
Carvone hydrobromide



(59)

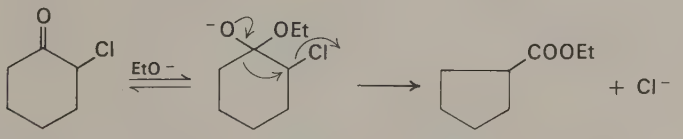
Eucarvone

The *Favorskii rearrangement* bears a close resemblance to the reactions just discussed. A representative example of this reaction is the action of alkali upon 2-chlorocyclohexanone. In this case the formation of an intermediate cyclopropanone derivative has been shown to occur, the subsequent cleavage of which by alkali leads to a cyclopentanecarboxylic acid derivative:



(60)

An alternative formulation for the course of the Favorskii rearrangement of 2-chlorocyclohexanone appears reasonable:



(61)

Experiment has shown, however, that when the 2-chlorocyclohexanone is labeled with radioactive carbon (^{14}C) at the 2 position, the resulting cyclopentanecarboxylic acid contains half of the radioactivity on the α carbon atom and half on the β carbon atom. This shows that a symmetrical intermediate, as in (60), is formed in the reaction.

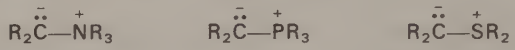
Reactions closely allied to the Favorskii rearrangement, but in which a cyclopropanone intermediate cannot be formed, are known; these probably proceed by another mechanism.

Exercise 4

If the Favorskii rearrangement proceeded as in (61), and 2-chloro-2-^{14}C-cyclohexanone were used, what would be the location of ^{14}C in the product?

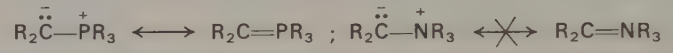
34-13 Ylids. Sommelet and Stevens rearrangements

Ylids are compounds containing an anionic carbon atom in a position adjacent to a quaternary nitrogen, phosphorus, or sulfur atom:



Phosphorus ylids, used in the synthesis of olefins by the Wittig reaction, have been described (Section 20-4).

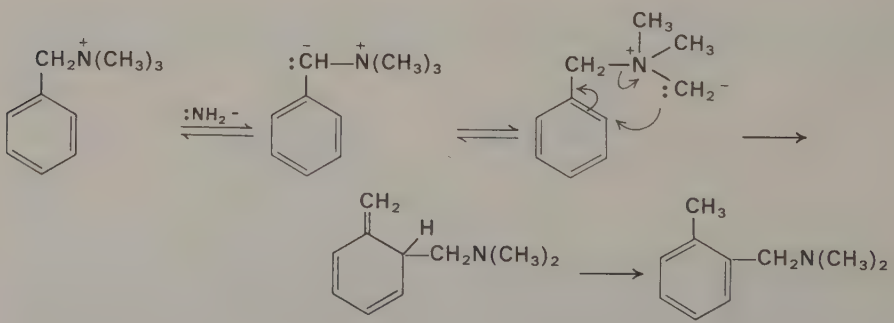
Nitrogen ylids cannot assume the alternative pentacovalent structure that is one of the contributing forms of the structures of phosphorus and sulfur ylids,



(62)

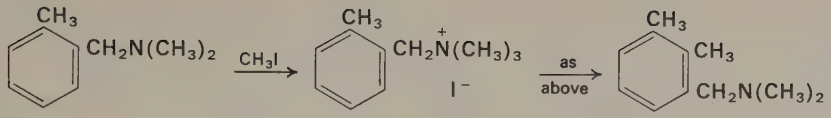
for the use of a fifth orbital of nitrogen is energetically proscribed. We should therefore expect to find that nitrogen ylids are exceptionally powerful nucleophiles by reason of the unshared electron pair on the anionic carbon atom.

Nitrogen ylids can be formed by the attack of a strong base (sodamide or an organolithium compound) upon a proton adjacent to a quaternary nitrogen atom. The ylid formed from benzyltrimethylammonium salts (only the cation is shown in the following equations) arises and reacts in the following way:



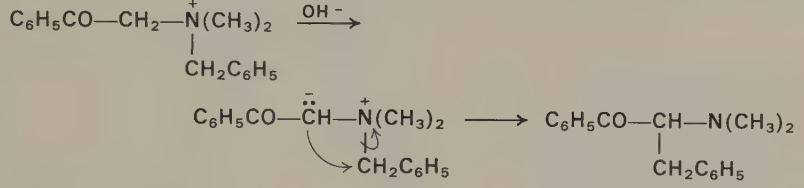
(63)

This reaction (the *Sommelet reaction*) is a nucleophilic substitution into the benzene ring. Repetition of this process by quaternization of the *o*-methylbenzyldimethylamine and treatment of the quaternary salt with sodamide introduces a second methyl group. The process may be repeated:



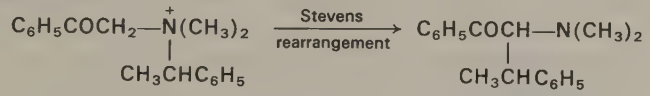
(64)

The *Stevens rearrangement* bears a resemblance to the reactions of nitrogen ylids but differs in that the initial ylid is stabilized by additional contributions due to the presence of a carbonyl group in the position adjacent to the anionic carbon atom. This additional activation afforded to the *alpha* hydrogen atoms makes it possible to carry out the Stevens rearrangement with aqueous alkali:



(65)

When the migrating group is asymmetric (for example, α-methylbenzyl instead of benzyl) and the compound optically active, the rearranged product is found to retain its optical activity, and the asymmetric carbon retains its original configuration:



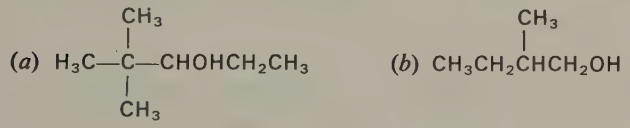
(66)

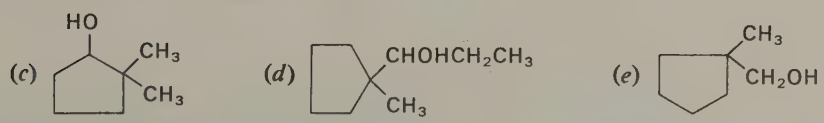
Optically active

Optical activity and configuration retained

Problems

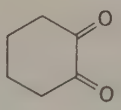
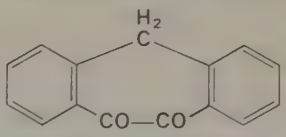
1. Predict the result of the sulfuric-acid-catalyzed dehydration of the following alcohols (show all expected *olefinic* products, but it will not be necessary to assess their relative proportions):

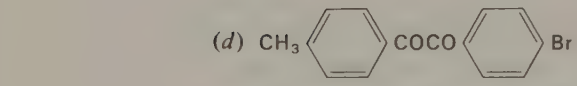




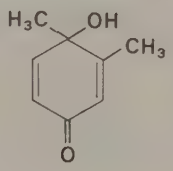
2. What products would you expect from the diazotization of methylamine in aqueous solution? In ethanol solution?

3. Formulate the benzilic acid rearrangement of the following α-diketones:

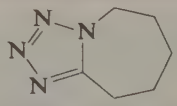
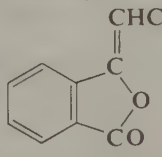
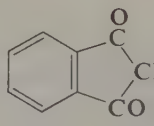
(*a*) $CH_3COCOCH_3$ (*b*)  (*c*) 

(*d*) 

4. What product would result from the treatment of



with sulfuric acid?

5. How could you prepare 2,5-dimethylphenol starting with 2,5-dimethylpropiophenone?
6. Starting with succinic acid, devise a synthesis of 5-hydroxypentanoic acid.
7. (*a*) Of what use is the Hofmann (or Curtius) degradation of amides in the introduction of substituents into the aromatic ring? (*b*) Show how you could convert acetophenone into benzenediazonium chloride.
8. Formulate the following transformations:
   (*a*) acetophenone → acetanilide
   (*b*) phenyl isopropyl ketone → *N*-isobutylaniline
   (*c*) adipic acid → piperidine
   (*d*) benzoic acid → hydrocinnamic acid (β-phenyl propionic acid).
9. When the Schmidt reaction is performed upon cyclohexanone, one product is *Metrazole*, a convulsant drug with the structure  Suggest the manner of its formation. (HINT: How would HN_3 react with the carbonyl group of an amide?)
10. The lactone  reacts with sodium methoxide in methanol to give the sodium salt of  . Formulate the course of this reaction.

35

Heterocyclic compounds. Alkaloids

In one of the most widely used compendia of organic chemistry,* the number of pages devoted to aliphatic compounds is 1391; to alicyclic compounds, 1049; to aromatic compounds, 1533; and to heterocyclic compounds, 2130.

Although the number of pages devoted to a subject is not necessarily an index of its relative importance, it is clear that heterocyclic chemistry comprises a large section of organic chemistry and thus deserves special attention. Much of heterocyclic chemistry (and indeed, of the other areas enumerated) is descriptive and rests upon a basis of principles that are not all unique to the field. But one reason for the large volume of literature that must be devoted to this area is the enormous variety of *kinds* of compounds it embraces. Not only are such "hetero" elements as oxygen, nitrogen, sulfur, and phosphorus included in heterocyclic rings, but many ring systems contain two, three, or more of one or more of these "hetero" atoms.

Heterocyclic chemistry, however, does have a unique place in organic chemistry. Much of it is not simply a repetitious extension of general principles. It also includes

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* *The Chemistry of Carbon Compounds*, 1951–1962. Edited by E. H. Rodd. Elsevier, New York. A second edition, still incomplete, edited by S. Coffey, will have somewhat different pagination but will probably correspond roughly to these divisions.

many reaction types that have no direct or obvious counterparts in alicyclic or aromatic chemistry. More important to organic chemistry as a practical science is the fact that many medicinals and innumerable naturally occurring compounds are heterocyclic.

Since the breadth of heterocyclic chemistry, as noted at the beginning of these remarks, is so great, it is clearly necessary that its treatment in a general textbook be limited and selective. This chapter will be confined to several of the more common and representative kinds of heterocyclic systems, and will stress those aspects of their behavior that best illustrate general principles of organic reactivity. Some descriptive sections will deal with heterocyclic compounds of special interest and importance.

35-1 Classification of heterocyclic compounds

The classical reference work of organic chemistry is Beilstein's *Handbuch der Organischen Chemie* (Encyclopedia of Organic Chemistry). In "Beilstein," organic compounds are organized into three large divisions: acyclic, homocyclic, and heterocyclic.

Acyclic compounds are those in which the carbon atoms are arranged only in straight or branched chains; no rings are present. Acyclic compounds are typified by the aliphatic hydrocarbons, alcohols, ketones, amines, and so forth.

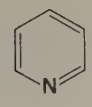
Homocyclic compounds are those in which a ring, either alicyclic or aromatic, is present. For example, the cycloalkanes, benzene, and naphthalene and their derivatives are classified in this category. Although the term "homocyclic" can refer to a ring containing but one kind of atom of any kind, in practice only rings of carbon atoms need be considered.

Heterocyclic compounds are cyclic compounds in which a ring containing more than one kind of atom is present. Heterocyclic rings may contain, in addition to carbon, one or more atoms of nitrogen, oxygen, or sulfur.*

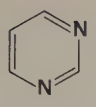
Because of the great number of combinations of carbon, nitrogen, oxygen, and sulfur atoms that can be present in rings of various sizes, the heterocyclic compounds include by far the greatest number of different *kinds* of compounds of any of the three main divisions. The following are a few typical heterocyclic compounds. Others have been encountered in earlier chapters.

There are a number of kinds of compounds that are, strictly speaking, heterocyclic compounds, but ordinarily are not treated as such. These include such compounds as lactones and acid anhydrides, which are related, respectively, to the corresponding open-chain hydroxyacids and dicarboxylic acids by simple hydrolysis. Cyclic acetals and hemiacetals are similarly related to open-chain aldehydes and ketones, and indeed

* Hetero atoms other than nitrogen, oxygen, and sulfur are known; for example, phosphorus and selenium; but these are less common.

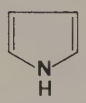


Pyridine



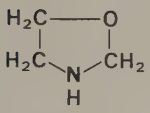
Pyrimidine

Furan

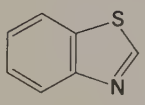


Pyrrole

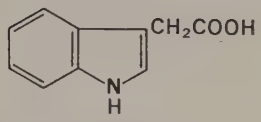
Oxazole



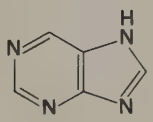
Oxazolidine



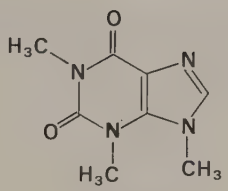
Benzothiazole



3-indoleacetic acid



Purine



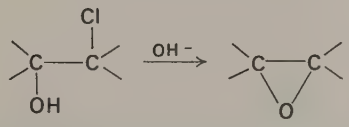
Caffeine

in this class of substances are found the sugars and their derivatives, which are generally treated separately as a discrete group. It is clear that classification rests upon somewhat arbitrary grounds.

35-2 Oxygen-containing heterocyclic compounds. Methods of formation

Saturated oxygen heterocycles are cyclic ethers, and can be formed by the same kinds of reactions that lead to acyclic ethers. A number of examples of cyclic ether formation have already been encountered in earlier chapters.

The formation of ethylene oxides by the intramolecular displacement of halide ion is the cyclic counterpart of the Williamson ether synthesis

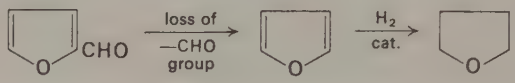


(1)

The commercially important ethylene oxide* is manufactured by this method from ethylene chlorohydrin, which in turn is prepared from ethylene.

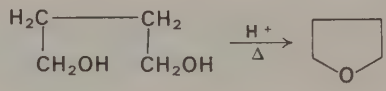
* The preparation of ethylene oxide by the direct oxidation of ethylene is the most important industrial method for producing the compound.

Another important group of oxygen heterocycles includes furan and its derivatives: furfuraldehyde, furfuryl alcohol, and tetrahydrofuran. The central compound of this group, and the raw material from which the others are prepared, is furfuraldehyde, made by the combined acid hydrolysis and dehydration of the pentose-containing polysaccharides present in certain vegetable materials, such as oat hulls and corn cobs (Chapter 15). Furan, prepared by the catalytic removal of the formyl group from furfuraldehyde, can be hydrogenated to tetrahydrofuran:



(2)

Tetrahydrofuran is also manufactured by the acid-catalyzed (H_3PO_4) dehydration of 1,4-butanediol. This reaction is the cyclic counterpart of the preparation of diethyl ether from ethanol:

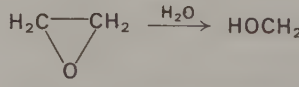


(3)

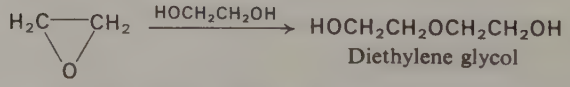
In general, reactions that lead to the formation of carbon-oxygen bonds in non-cyclic compounds can, when applied to bifunctional molecules, lead to ring formation. Three-, five-, and six-membered rings are easiest to prepare, and constitute the most important groups of the oxygen heterocycles.

35-3 Chemical behavior of oxygen heterocycles

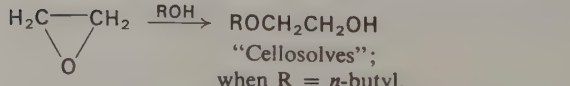
Ethylene oxide is the raw material from which many important compounds are prepared. The strained three-membered ring is readily opened by nucleophilic attack, and in consequence of this high degree of reactivity, ethylene oxide undergoes many reactions that lead to ethylene glycol derivatives. Hydrolysis and alcoholysis yield ethylene glycol and various ethylene glycol ethers that have become important industrial solvents:



(4)

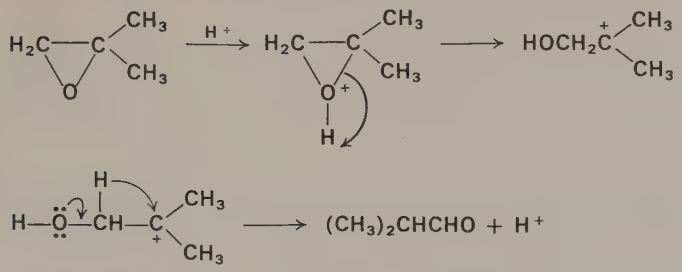


(5)



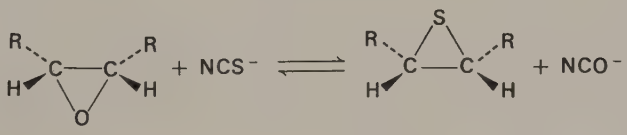
(6)

Substituted ethylene oxides often rearrange under acidic conditions:



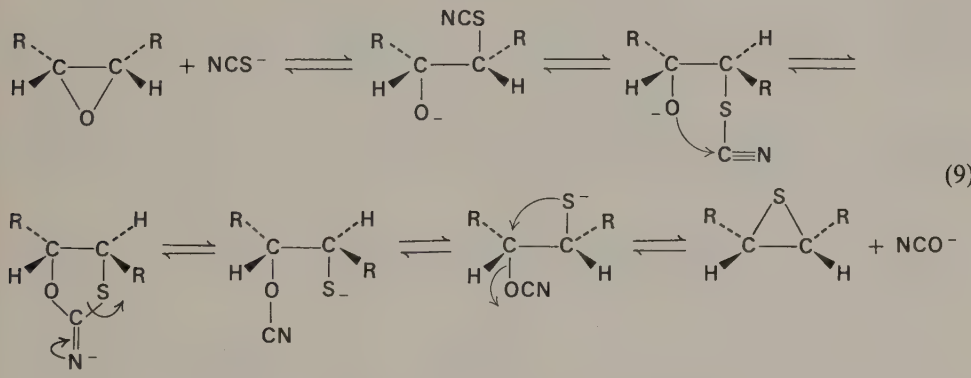
(7)

The reaction of ethylene oxides with sodium thiocyanate or selenocyanate provides an informative example of a sequence of interrelated equilibrium reactions in which the position of the final equilibrium depends essentially upon the relative nucleophilicity of sulfur and oxygen. The overall reaction



(8)

can be described by the following equilibria:*



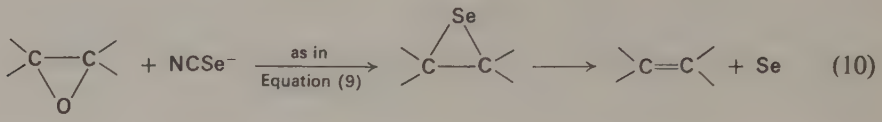
(9)

The position of the final equilibrium is such that the product of the reaction is the ethylene sulfide. It is to be noted that the position of the sulfur-containing ring is opposite to that of the original oxide ring.

---

* The student should examine equation (9) with care, noting the stereochemical disposition of the groups at each step.

When sodium selenocyanate is used, the final product is the cyclic selenide. This compound spontaneously loses selenium to form the olefin:

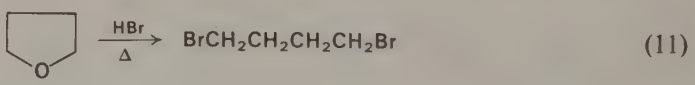


(10)

The latter reaction can be used as a preparative means of regenerating an olefin from its oxide; or, since the precipitated selenium forms a dark red-brown deposit, it can be used as a test for the presence of the ethylene oxide grouping.

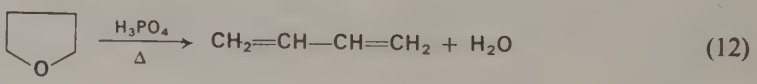
Since the ease with which ethylene oxide rings are opened is in part the result of the strain associated with the three-membered ring, it is to be expected that four-membered oxide rings would also be subject to ready ring opening, but that the five- and six-membered cyclic oxides would be stable. This is the case. Tetrahydrofuran and tetrahydropyran are stable substances, having much the same chemical characteristics as the analogous acyclic ethers such as diethyl ether. *Tetrahydrofuran* is a solvent widely used in modern laboratory practice. It has the chemical inertness of diethyl ether but possesses somewhat different solvent characteristics that lend it to certain special uses. It is a useful solvent in reactions involving the Grignard reagent, in lithium aluminum hydride reductions, and in the preparation of organolithium compounds.

Although tetrahydrofuran is a stable, ether-like compound, its ring can be opened, just as acyclic ethers can be cleaved, by the use of strong hot hydrobromic acid:



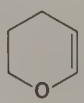
(11)

Tetrahydrofuran can be dehydrated catalytically (by passing its vapors over an acid catalyst at an elevated temperature), and it serves as a source of butadiene:

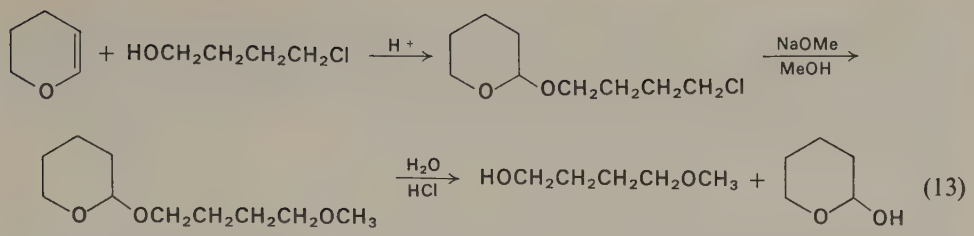


(12)

Another useful commercially available reagent is dihydropyran:

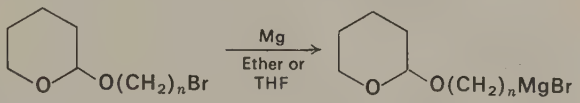


The use of dihydropyran in the protection of phenolic hydroxyl groups has been described in Section 33-5. Another example, in which an aliphatic hydroxyl compound is used, is the following:



(13)

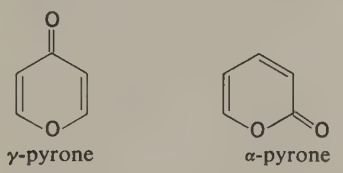
If an attempt were made to replace the chlorine in the chloro-alcohol with the methoxyl group by direct reaction with sodium methoxide, ring closure would occur. By "protecting" the hydroxyl group the desired replacement can be effected. Tetrahydropyranyl ethers of chloro- and bromo-alcohols can also be converted into Grignard reagents* (this cannot be accomplished with the free alcohols):



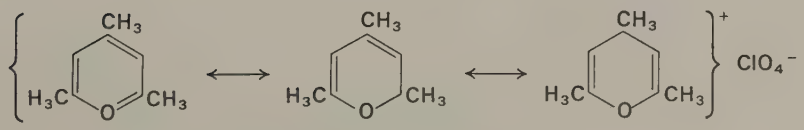
$(n > 2)$ (14)

35-4 Cyclic oxonium compounds

The ability of oxygen to sustain a positive charge makes it possible to prepare cyclic oxonium compounds of extraordinary stability. The stability of these compounds depends upon their possession, in addition to the oxonium atom, of a six-membered ring containing two carbon-carbon double bonds. The positive charge can be delocalized by a resonance stabilization that resembles the stabilization of the aromatic nucleus. The *pyrilium* salts (the name is derived from pyrone, the six-membered oxygen heterocycle) are usually isolated as chlorides, picrates, perchlorates, or ferrichlorides. An example is 2,4,6-trimethylpyrilium perchlorate:



γ-pyrone α-pyrone



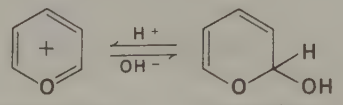
2,4,6-trimethylpyrilium perchlorate

* Except in the case of 2-haloethanol derivatives. Compounds that contain halogen and alkoxyl groups in the 1,2-positions react with magnesium to eliminate the elements of RO—MgBr and give the corresponding olefin.

The greatest interest that attaches to pyrilium salts lies in the fact that the red to blue coloring matters of plants—the anthocyanin pigments—are compounds of this class. Cyanin (chloride) is the commonest of these: it is the pigment of many red flowers and fruits, as well as of the blue cornflower.

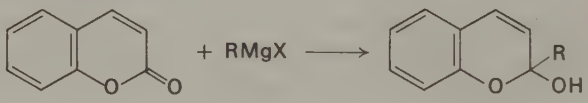
35-5 Synthesis of the pyrilium ring system

Pyrilium salts can be formed from, and in neutral solution are in equilibrium with, the corresponding "pseudobases."



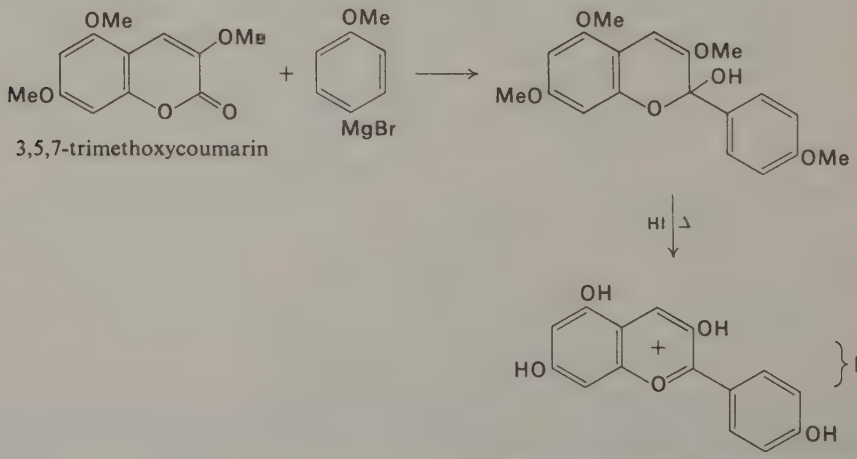
Pyrilium cation Pseudobase (15)

Thus, synthetic methods for preparing pyrilium salts are methods that lead to the hydroxy compounds of the pseudobase type. One such method, which has been applied to the preparation of a natural anthocyanidin, consists of the addition of a Grignard reagent to a coumarin:



(16)

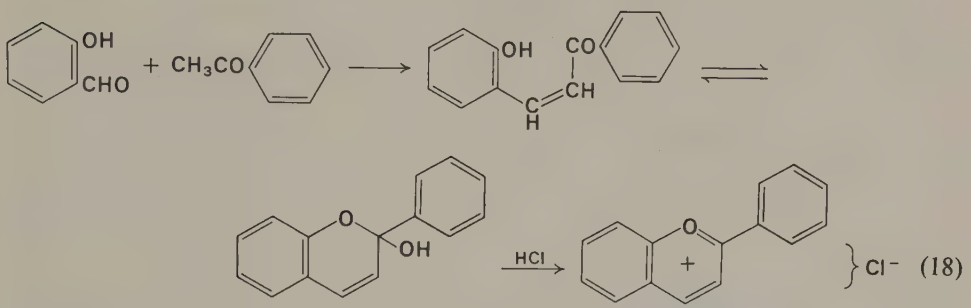
The initial addition product is a pseudo-base, which when treated with acid is converted into the pyrilium salt. Compounds of the type represented by cyanidin are called *flavylium* salts:



3,5,7-trimethoxycoumarin (17)

Pelargonidin iodide, a flavylium salt

Another general method of preparing the flavylium ring system is the aldol condensation of an *o*-hydroxyaldehyde with an acetophenone derivative. The initially formed benzalacetophenone derivative can be converted into the flavylium salt by treatment with acid:

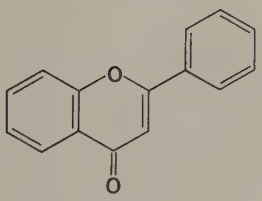


(18)

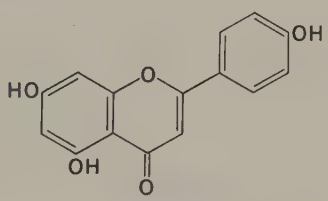
Flavylium chloride

35-6 Other six-ring oxygen heterocycles

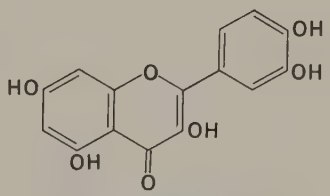
The six-membered oxygen heterocycles are a large and important group of naturally occurring compounds. Included in this class are many of the natural pigments of the plant world, many of them derived from the parent structure flavone. Some representatives of the class are the following:



Flavone



Apigenin
(in parsley, celery)

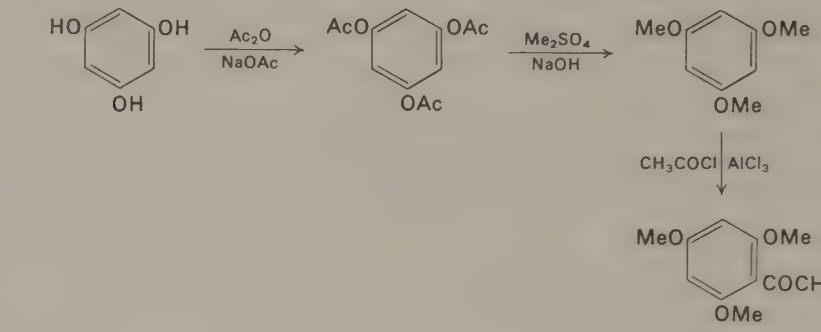


Quercetin
(widely distributed in plants)

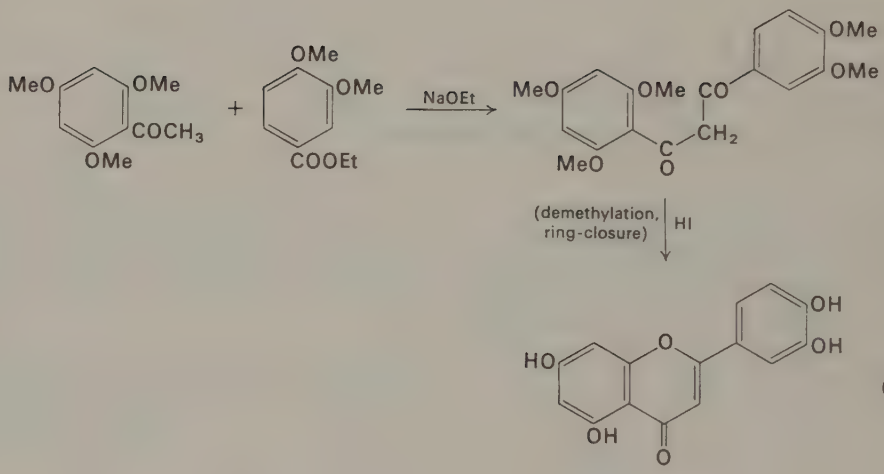
The naturally occurring flavones are hydroxyflavones; most of them occur in nature in the form of glycosides.

The synthesis of a typical natural flavone, luteolin, is shown in the following equations. A study of these reactions will disclose the fact that nearly all of them are examples of reactions that have been encountered in earlier parts of this book in other, simpler forms. One additional comment will be appropriate here: it will be noticed that phloroglucinol trimethyl ether is prepared by the simultaneous deacetylation-methylation of phloroglucinol triacetate. This is necessary in the case of phloroglucinol

because direct methylation of this compound with methyl sulfate and alkali leads to *C*-methylation.



(19)



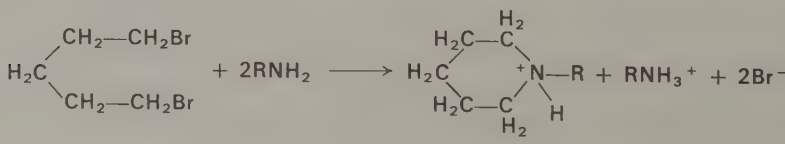
(20)

Luteolin

Each step of these synthetic sequences should be examined with care until its nature is understood.

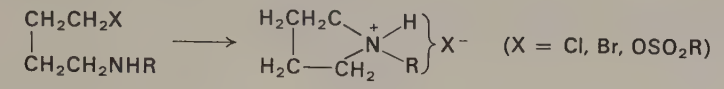
35-7 Nitrogen-containing heterocycles

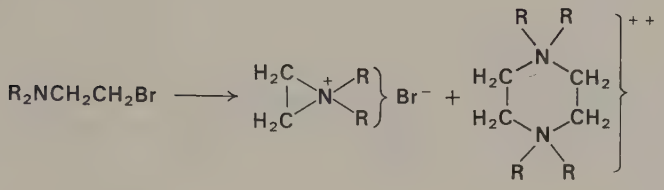
The alkylation of a primary amine with an alkyl halide leads to the formation of a tertiary amine; if, instead of an alkyl halide, an α,ω-dihalide is used, ring formation occurs:



(21)

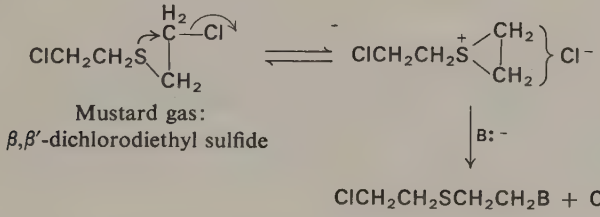
Entirely analogous to this reaction is the ring closure of halogen-substituted amines, or of sulfonyl derivatives of amino alcohols:





(22)

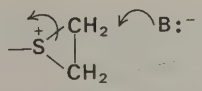
β-Haloethylamines containing a tertiary amino group undergo ring closure to cyclic quaternary ammonium salts. These three-membered imonium ions are extraordinarily susceptible to ring opening by nucleophilic attack, resembling in this respect ethylene oxides. The closure and reopening of three-membered cyclic ammonium ions is of great importance in biology and medicine. The well-known wartime "mustard gas" has as its counterparts a series of substances known as "nitrogen mustards." "Mustard gas" reacts by way of a unimolecular nucleophilic displacement to give rise to an intermediate three-membered cyclic sulfonium ion, which then reacts with an external nucleophile with ring opening (in the following equations the symbol $B:^-$ is used for a nucleophilic reagent):



Mustard gas:
β,β′-dichlorodiethyl sulfide

(23)

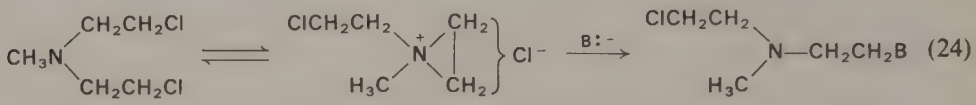
Repetition of the above reactions permits replacement of the second chlorine atom in the same way. The susceptibility of the three-membered sulfonium ring to opening by nucleophilic attack



finds parallels in several reactions that we have already encountered in earlier chapters: the opening of protonated ethylene oxide rings; the three-membered "bromonium"

ion intermediate in the addition of bromine to the carbon-carbon double bond; and the ready ring opening of cyclopropane derivatives.

The course of reaction of β-haloethylamines is the exact counterpart of the corresponding reactions of the chloroethyl sulfides:



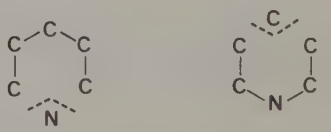
(24)

It is believed that the profound physiological effects of "mustard gas" and of the related β-chloroethylamines are the result of interactions of the above kind between these toxic agents and an enzyme or other protein component of the tissue. These have been described in Chapter 8, where these agents were included among the biological alkylating agents.

Certain synthetic applications of the bifunctional alkylating ability of compounds of the nitrogen mustard class are especially significant here because they demonstrate another means of synthesizing heterocyclic rings. For example, the reaction between the sodium derivative of phenylacetonitrile and *N*-methyl-β,β′-dichlorodiethylamine leads to the formation of a substituted piperidine; this has been described in Chapter 27. The synthesis of meperidine (Demerol) by this means illustrates a method of entry into a series of medicinally important compounds with morphine-like properties.

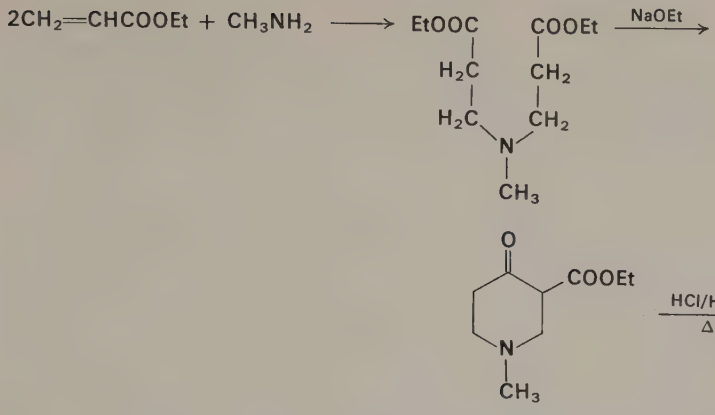
35-8 The formation of piperidine derivatives by ring closure

Piperidine and its derivatives can be prepared by methods similar to those thus far described. It will be noted that in the foregoing examples the ring has been closed by two quite different methods, one involving the formation of one or two C—N bonds, the other involving the ring closure by C—C bond formation between the 3 and 4 carbon atoms:



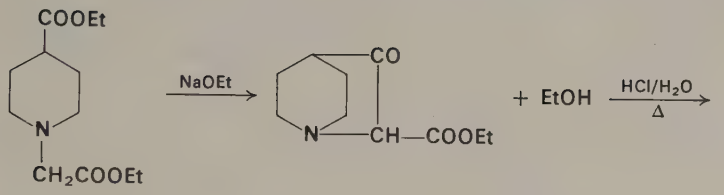
(25)

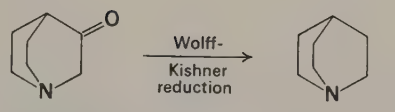
Closure of a ring between the 2,3- and 3,4-carbon atoms can also be used to form piperidine rings. Some typical syntheses are shown on page 809. Each of the reaction series shown involves a Dieckmann condensation as the first step. Hydrolysis and decarboxylation of the β-keto ester yields in each case the piperidone derivative.



(26)

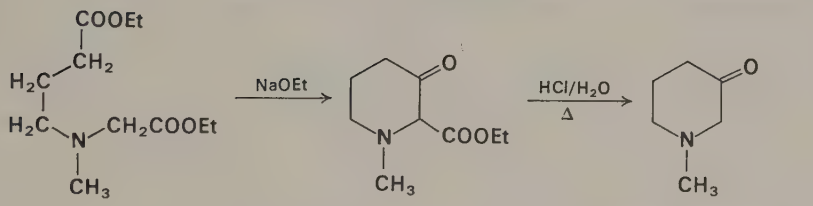
1-methyl-4-piperidone





(27)

3-quinuclidone Quinuclidine



(28)

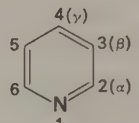
1-methyl-3-piperidone

Exercise 1

The ring-closure shown in (28) is one of two alternative courses for the cyclization. What is the other? Suggest why the one shown is the principal course of the reaction.

35-9 Pyridine

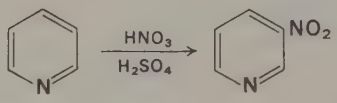
The electronic structure of pyridine resembles that of benzene, and thus it is not surprising to find that pyridine has aromatic properties that resemble those of the aromatic hydrocarbons:



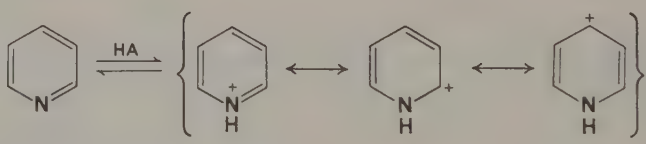
Pyridine

Benzene

The resemblance between pyridine and benzene lies in their ability to undergo electrophilic substitution reactions. But whereas the nitration of benzene, for example, takes place readily, that of pyridine is more difficult. Of course, the available positions of substitution in pyridine are not equivalent; in fact, nitration occurs largely at the β (3) position:



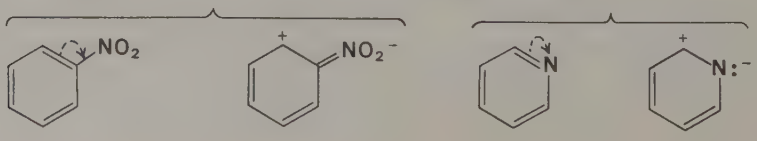
In considering this reaction, an additional point must be recognized: pyridine, with an unshared pair of electrons on the nitrogen atom, is a base (about as strong a base as aniline) and thus is largely protonated under the strongly acid conditions of nitration. The protonation of pyridine imparts to the α and γ carbon atoms a high degree of positive character:



(29)

The attack of the electrophilic reagent (for example, NO_2^+) would thus be less likely to occur at an α or γ carbon atom, since these are electron deficient, than at the β carbon atom. But attack of an electrophilic reagent at any point in the positively charged ring would be difficult, and thus the substitution reaction is slow.

It will be noted that the α and β positions of pyridine bear a formal resemblance to the *ortho* and *meta* positions, respectively, of nitrobenzene:

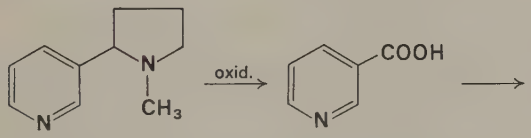


Exercise 2

What kind of reactivity would you expect to find in 2-bromopyridine?

Sulfonation and halogenation of pyridine also occur slowly under the usual conditions employed with benzene derivatives. High-temperature halogenation proceeds readily to give substitution at all three possible positions of the ring (α, β, and γ), and probably proceeds by way of free halogen atoms. Thus, the orientation would not be expected to correspond to that observed in electrophilic substitution.

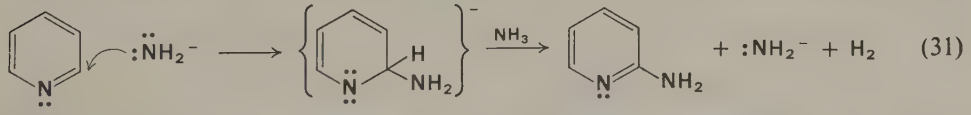
The preparation of substituted pyridine derivatives is often achieved by indirect methods. Substituents in the 3 position are often introduced by the alteration of the carboxyl group of nicotinic acid, readily obtained from nicotine, an abundant by-product of the tobacco industry:



Nicotine Nicotinic acid (30)

35-10 Nucleophilic substitution in pyridine

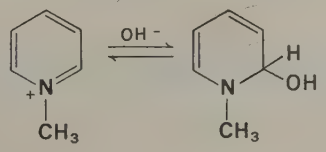
The electron-deficient nature of the 2 and 4 positions of pyridine makes these positions susceptible to ready *nucleophilic attack*. One of the most useful of the reactions of this kind is that between pyridine and sodamide, in which nucleophilic attack of the amide anion results in the formation of 2-aminopyridine:



(31)

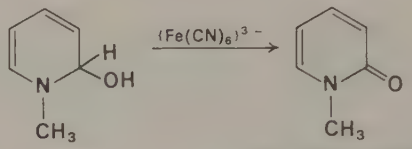
It will be noted that the 2 hydrogen atom is expelled in the oxidation state of the hydride ion ($H:^-$).

When the electrophilic character of the α position is enhanced by quaternization of the nitrogen atom, nucleophilic attack is very ready. Indeed, the coordination of hydroxide ion in aqueous alkaline solution does occur, in the equilibrium reaction



(32)

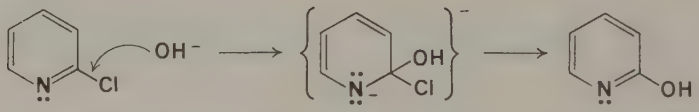
The resulting "carbinolamine" is not isolable since the equilibrium lies largely on the side of the "aromatic" pyridinium ion. But when an oxidizing agent, such as potassium ferricyanide, is present the addition compound is oxidized to the 2-keto compound *N*-methyl-2-pyridone:



(33)

N-methyl-2-pyridone

Preparation of 2-pyridone (2-hydroxypyridine) is accomplished by hydrolysis of 2-chloro(or -bromo)pyridine. This reaction, too, is a nucleophilic substitution reaction, and probably involves a nucleophilic attack upon the ring that resembles (in regard to mechanism) that which leads to dispacement of nitro-activated halogen from an aromatic nucleus:

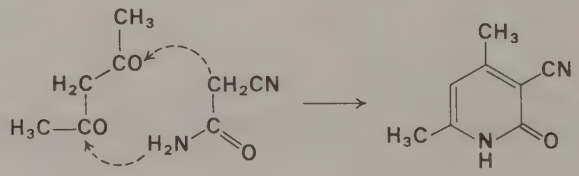


(34)

This reaction again discloses the resemblance of the α position of the pyridine ring to the position *ortho* or *para* to a nitro group in an aromatic nitro compound.

35-11 "Total" synthesis of pyridine derivatives

The synthesis of substituted pyridine derivatives from acyclic precursors can be accomplished in several ways. Among these are methods in which base-catalyzed aldol or Schiff-base condensations are involved; an example is the following:



(35)

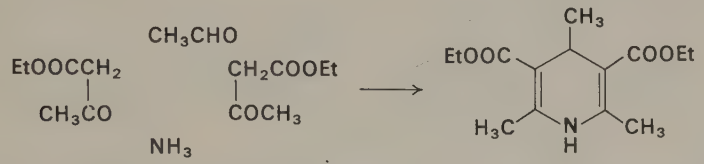
Acetylacetone + cyanoacetamide ⟶ 3-cyano-4,6-dimethyl-2-pyridone

---

Exercise 3

Formulate the steps in this condensation, showing a reasonable series of intermediate stages.

Another general method of synthesis that is adaptable to the preparation of substituted pyridines involves the condensation of ammonia, an aldehyde, and either a β-keto ester or a β-diketone. The following is a typical example:

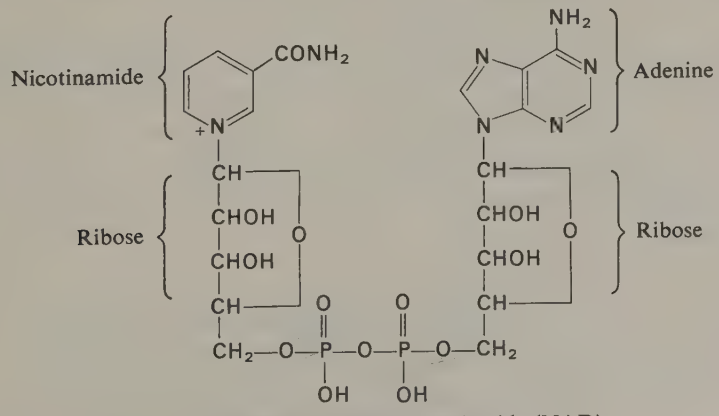


(36)

The immediate product of this condensation is a dihydropyridine derivative. The dehydrogenation (by oxidation) of this to the corresponding pyridine is accomplished with ease because of the great gain in stability that accompanies generation of the "aromatic" structure of the pyridine ring system.

35-12 Occurrence of pyridine derivatives in nature

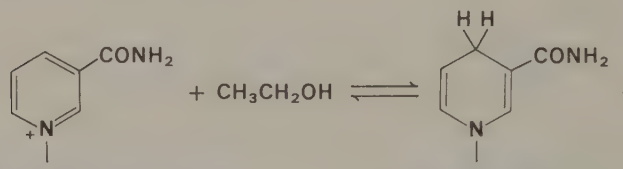
The pyridine ring, and its reduced (piperidine, dihydropyridine, and tetrahydropyridine) forms are of widespread natural occurrence, and are synthesized by plants, possibly by way of amino acids as precursors. Although the heterocyclic rings of pyridine derivatives are not synthesized by higher animals, several of them are of the greatest importance in the cellular economy of animal life.* Perhaps the most important pyridine derivatives are those which form the prosthetic groups of many enzymes whose function is the catalysis of oxidation reactions in the cells of both plants and animals. These are called NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate). NADP is a phosphate ester of NAD, and bears the additional phosphoric acid group on the adenine-linked ribose unit:



Nicotinamide adenine dinucleotide (NAD)

* And thus must be ingested by animals in their diet, in the form of vitamins.

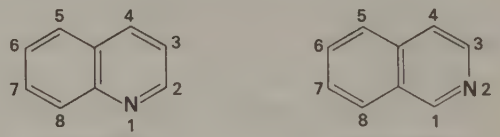
In combination with specific proteins, NAD and NADP form enzymes that participate in oxidation-reduction reactions in living cells. The NAD portion of the enzyme *alcohol dehydrogenase*, for example, accepts hydrogen from ethanol to form acetaldehyde and the reduced enzyme:



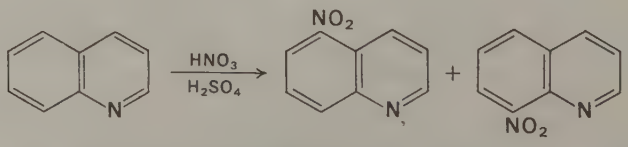
In coupled cellular reactions, NADH is reoxidized by transfer of its hydrogen to cooperating enzymes, and is transformed into NAD, which can then oxidize another molecule of substrate. The stereochemistry of this oxidation-reduction reaction has been discussed in Chapter 11.

35-13 Quinoline and isoquinoline

Quinoline and isoquinoline are the two possible *benzopyridines*:

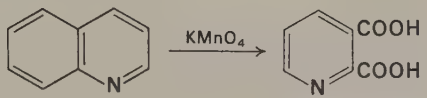


The properties of the heterocyclic ring of quinoline resemble those of pyridine: the 2 position is susceptible to nucleophilic attack, and 2-halogen substituents are readily displaced by nucleophilic reagents such as amines, alkoxides, or hydroxide ion. Electrophilic substitution can occur in either the hetero ring or the carbocyclic ring; and the ease and position of substitution is subject to considerable variation with changes in the kind of substitution reaction and the conditions of the reaction. For example, the nitration of quinoline in concentrated H_2SO_4 leads to substitution in the 5 and 8 positions.



A notable feature of the pyridine ring system is its stability to oxidation. Alkylpyridines are readily oxidized to pyridinecarboxylic acids as in the oxidation of nicotine

to nicotinic acid, which has been described. Quinoline is oxidized to pyridine-2,3-dicarboxylic acid, the benzene ring being destroyed:



Quinolinic acid
(pyridine-2,3-dicarboxylic acid)

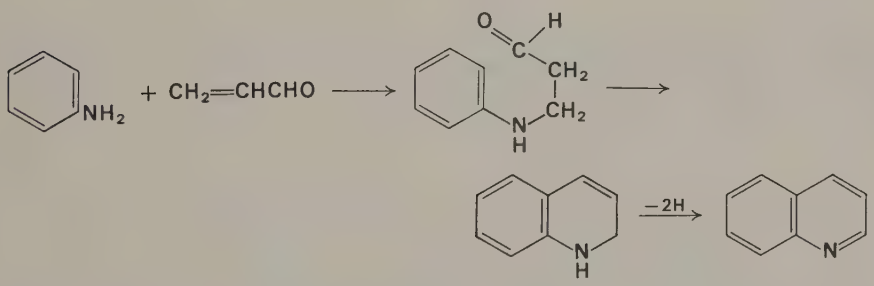
(39)

Exercise 4

When quinoline is nitrated with HNO_3 in (glacial) acetic acid solution, the product is almost exclusively 3-nitroquinoline. Can you suggest an explanation for this?

35-14 Synthesis of the quinoline ring system

In most syntheses of quinoline derivatives, the heterocyclic ring is formed by a ring closure, starting with a compound that already contains the carbocyclic (benzene) ring. One of the most versatile of the quinoline syntheses is the *Skraup synthesis*, in which an aromatic primary amine with a free *ortho* position is heated with glycerol, sulfuric acid, and an oxidizing agent, which may be nitrobenzene. For the synthesis of quinoline itself, the reaction proceeds as follows:

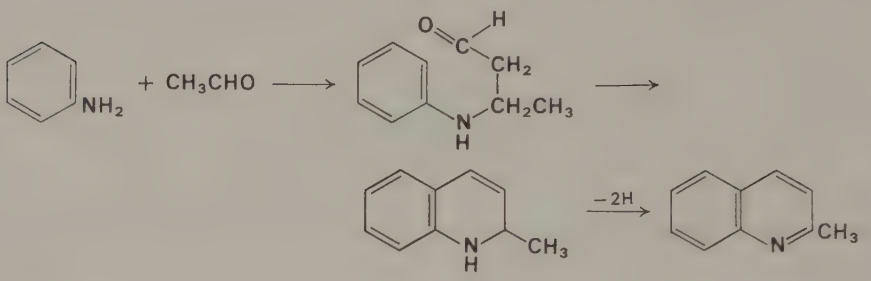


(40)

The acrolein that appears as the reactant in this formulation is derived from glycerol by dehydration in the course of the reaction. The final oxidation step is accomplished by nitrobenzene. When *m*-substituted anilines are used, ring closure can take place to give 5- and 7-substituted quinolines. Often both are obtained, but the 7-substituted quinoline is the chief, and often the exclusive, product.

A synthesis that resembles the Skraup synthesis is that in which an aromatic amine is condensed with an aliphatic aldehyde in the presence of a mineral acid. This

is called the *Döbner–von Miller* synthesis, which is illustrated by the preparation of quinaldine (2-methylquinoline):



(41)

The intermediate anilino compound may be regarded as having been formed by way of crotonaldehyde, which is formed by the aldol condensation of the acetaldehyde. In this process the final dehydrogenation occurs by the transfer of hydrogen to a hydrogen acceptor—perhaps the Schiff base formed from the starting amine and aldehyde.

Exercise 5

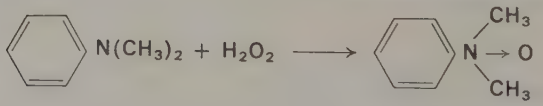
Outline the details of the steps in (41).

35-15 *N*-Oxides

The formation of amine oxides (Chapter 16) from tertiary amines has its counterpart in the oxidation of pyridine and quinoline to the *N*-oxides. The reagent usually employed is hydrogen peroxide in acetic acid solution:

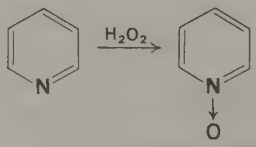
$$(CH_3)_3N + H_2O_2 \longrightarrow (CH_3)_3N \rightarrow O \qquad (42)$$

Trimethylamine oxide



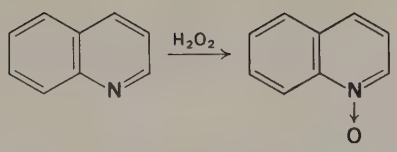
(43)

Dimethylaniline oxide



(44)

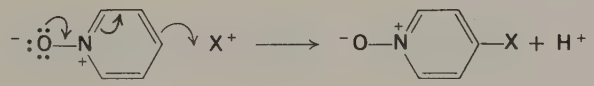
Pyridine *N*-oxide



(45)

Quinoline *N*-oxide

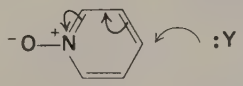
The *N*-oxidation of the heterocyclic nitrogen atom has an interesting effect upon the behavior of the ring toward substitution reagents. Pyridine *N*-oxide is more susceptible than pyridine to *both* nucleophilic *and* electrophilic substitution. Further, while pyridine undergoes substitution at the 3 position with electrophilic reagents, pyridine *N*-oxide reacts at the 4 position. The explanation for this is that the oxygen atom of the N—O grouping can supply electrons to the 4-position to accommodate the electrophilic demand:



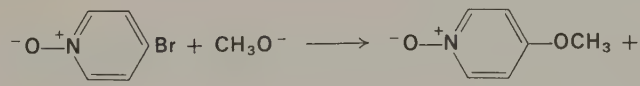
(46)

Pyridine *N*-oxide is readily nitrated to give 4-nitropyridine *N*-oxide in good yield.

The increased susceptibility of the 2 and 4 positions of pyridine *N*-oxide to nucleophilic attack is also readily understood. In this case, the positively charged nitrogen atom of the N—O grouping can accommodate the electrons supplied by the attacking nucleophile:



Hence, the ready replacement of the halogen atom from 4-bromopyridine *N*-oxide by a nucleophilic reagent takes place with greater ease than from 4-bromopyridine itself:



(47)

Since the oxygen atom of pyridine (and other heterocyclic) *N*-oxides can be readily removed by reduction with iron and acetic acid, *N*-oxidation can serve usefully as a device for the synthesis of 4-substituted pyridine derivatives.

35-16 Alkaloids

Many plants contain physiologically active basic compounds known as *alkaloids*, most of which are nitrogen heterocyclic compounds. Many are highly toxic, and a number of them are important medicinal agents. Such well known and widely used

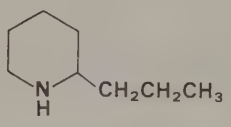
drugs as morphine, atropine, cocaine, strychnine, papaverine, curare, physostigmine (eserine), and numerous others are naturally occurring heterocyclic compounds. Some of these were introduced in Chapter 16.

The field of alkaloid chemistry is vast and complex, embracing many hundreds of compounds and a wide variety of structural classes. We can examine no more than a few representative examples of some of the principal groups.

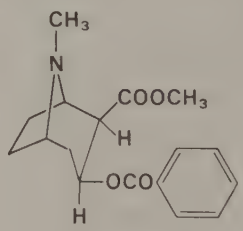
35-17 Alkaloids containing a pyridine or a reduced pyridine ring

The most widely distributed alkaloid is (−)-nicotine, found in plants of the genus *Nicotiana* (for example, tobacco). Nicotine is extremely lethal and in small doses effects first stimulation, then paralysis of the nervous ganglia. It has no useful clinical applications, but is used widely as an insecticide, for which it is produced in large amounts by the tobacco industry. Its structure is described in Section 40-6.

Other simple pyridine-derived alkaloids are coniine, the toxic principle of the water hemlock, *Conium maculatum*; atropine from *Atropa* species and other Solanaceae; and cocaine, a stimulant and local anesthetic, from the leaves of *Erythroxylon coca*:



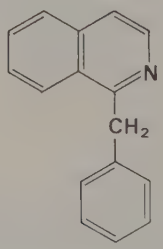
Coniine
(−)-2-*n*-propylpiperidine



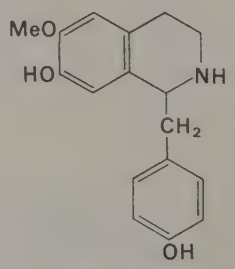
(−)-cocaine

35-18 Isoquinoline alkaloids

In a very large and diverse group of alkaloids, the compounds have structures based upon the ring system of isoquinoline. The most important and widespread of these are based upon 1-benzylisoquinoline:

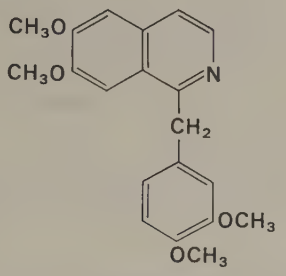


1-benzylisoquinoline

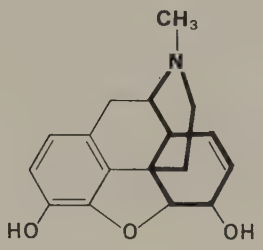


Coclaurine

A number of alkaloids related to one another in this way are found in the latex of the seed capsule of the opium poppy, *Papaver somniferum*; among them are morphine and papaverine:

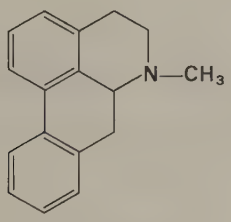


Papaverine

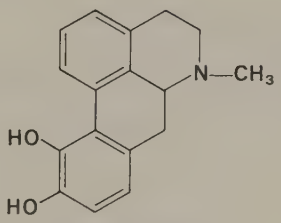


Morphine
(isoquinoline rings emphasized)

Apomorphine is a degradation product of morphine; it is a member of the "aporphine" group, many derivatives of which occur in nature:

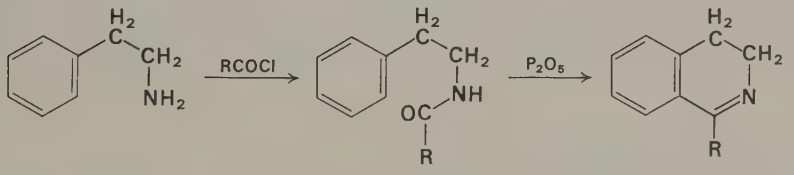


Aporphine



Apomorphine

Synthetic methods for the preparation of alkaloids of the benzylisoquinoline group are various because of the many forms in which the basic isoquinoline structure appears in the numerous alkaloids of this class. One of the routes to the isoquinoline ring system depends upon a ring closure of the following kind, called the *Bischler-Napieralski reaction*:



(48)

β-phenethylamine

1-(R)-3,4-dihydroisoquinoline

The ring-closure step is an acid-catalyzed electrophilic substitution into the aromatic ring and, as would be expected, is facilitated by electron-releasing (for example, CH_3O—) substituents in the aromatic nucleus.

Exercise 6

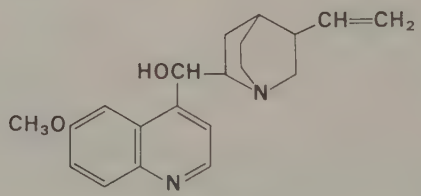
If the isoquinoline synthesis of the kind shown here is conducted with the use of 3,4-dimethoxyphenethylamine and R = 3,4-dimethoxybenzyl, the product is 3,4-dihydropapaverine, convertible to papaverine by dehydrogenation (heating with palladium or platinum black). Formulate these reactions.

Exercise 7

Can you suggest a possible course for the Bischler-Napieralski ring closure? Assume that it proceeds by way of the —C(OH)=N— tautomeric form of the amide, and that the ring-closure step is an electrophilic substitution into the aromatic ring. The reagent shown in (48) is phosphorus pentoxide, but $POCl_3$ can also be used.

35-19 Quinoline alkaloids

The quinoline nucleus does not occur widely in nature, but is the basic structural entity of the important alkaloid quinine:



Quinine

It is to be noted that quinine also possesses a quinuclidine ring as a part of its structure.

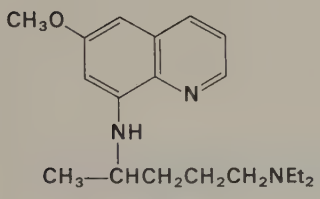
Quinine is of great practical as well as historical importance. For centuries it has been used to control the symptoms of malaria, one of the most widespread diseases of man. Quinine is being largely replaced by synthetic drugs.

35-20 Antimalarial drugs

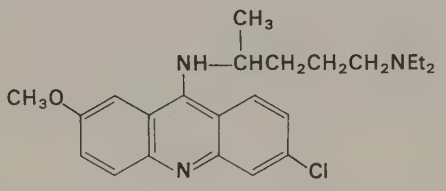
One of the serious military problems of World War II was the protection of fighting forces from the disabling consequences of malaria, a problem that was heightened by the fact that extensive operations were carried out in those areas of the world where the disease is prevalent. At the same time, supplies of quinine, the drug used for centuries

against malaria, were cut off by enemy control of quinine-producing areas, and so it became necessary to search for a substitute as effective as the natural drug. To this end an extensive program of research was undertaken by the allied nations, and thousands of synthetic compounds were prepared and tested against the malarial parasites (*Plasmodium* species).

One approach to the preparation of active antimalarial drugs was to synthesize quinoline derivatives with structural features resembling those of quinine but less complex in nature. Early studies on synthetic antimalarial drugs had led to the discovery in 1928 and 1933 of two clinically effective substances, Plasmoquin and Quinacrine (Atebrin):

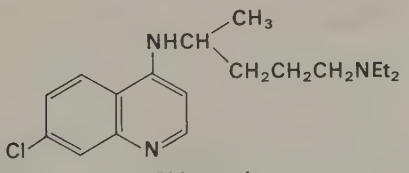


Plasmoquin



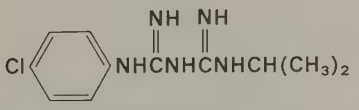
Quinacrine (Atebrin)

In 1943 Chloroquin was discovered and put into clinical use:



Chloroquin

It will be noted that the same or very similar structural features are found in the most effective antimalarial drugs: the quinoline nucleus, a methoxyl group in the 6 position (quinoline numbering), a chlorine atom in the 7 position, and a basic side chain. Quite a different drug, very effective and with a different mode of attack upon the malaria parasite, is Paludrin:



Paludrin

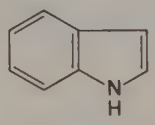
The development of *drug-resistant* microorganisms by adaptation, mutation, and natural selection presents a serious problem to modern medicine. Continued use of

many chemotherapeutic agents, particularly when they are used in less than optimal dosage, has in many instances induced the development of a strain of the micro-organism that is resistant to the drug.

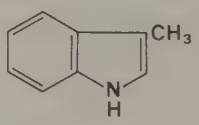
One example of drug resistance has been observed in the case of antimalarial drugs. In several parts of the world there are now strains of *Plasmodium falciparum* which are quite resistant to Chloroquin, the most generally used of the antimalarial drugs. These parasites are also resistant to other antimalarial drugs, and human malaria caused by these resistant strains presents a difficult clinical problem. The organic chemist has an important role to play in such circumstances, and has the responsibility to search for new drugs to which the parasite is susceptible. At present this goal is being pursued by a number of organic chemists engaged in the synthesis of novel chemical structures that possess antimalarial activity. That resistance to a new drug will develop in time is now to be anticipated; and so the synthesis and testing of new drugs is a never-ending task.

35-21 Indole

Indole, a benzopyrrole, is the structural basis for a wide variety of biologically important substances. Indole itself and its 3-methyl derivative, skatole, are found in feces:

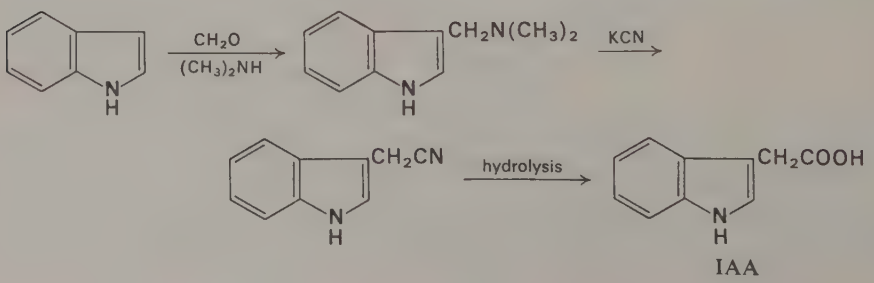


Indole



Skatole

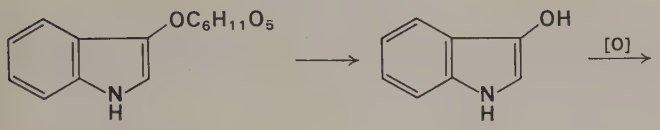
Indole is a very reactive nucleophile, and undergoes electrophilic substitution reactions with ease. Both the 2 and 3 positions are reactive, but unsubstituted indoles undergo substitution in the 3 position. Indole reacts with dimethylamine and formaldehyde in a Mannich reaction to give 3-dimethylaminomethylindole, *gramine*. Gramine undergoes ready nucleophilic displacement of the dimethylamino group; when it is treated with potassium cyanide the product is 3-indolylacetonitrile. Hydrolysis of the nitrile gives 3-indolylacetic acid (IAA), a natural plant-growth regulator (auxin):



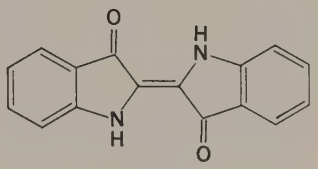
IAA

(49)

An important naturally occurring indole derivative is indican, the β-glucoside of 3-hydroxyindole, found in plants of the genus *Indigofera*. Acid or enzymatic hydrolysis of the glucoside yields glucose and 3-hydroxyindole, or indoxyl, the air oxidation of which yields the blue dye indigo:



Indican Indoxyl

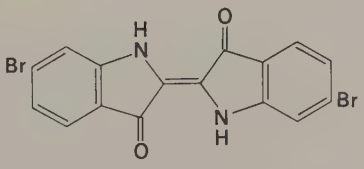


(50)

Indigo

Indigo, one of the oldest dyes used by man, was once a substance of great economic importance, and played a significant part in the development of organic chemistry in the latter half of the nineteenth century. The extended investigation of its structure by Baeyer resulted in many fundamental discoveries, and its synthesis and manufacture in Europe played an important role in the expansion of the chemical industry. The preparation of indigo from plant sources has been superseded by synthetic processes.

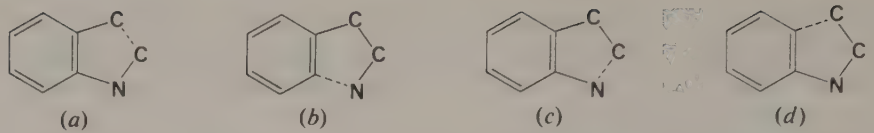
A violet dyestuff used in ancient times, 6,6′-dibromoindigo, is obtained from certain species of mollusc of the genus *Murex*. The dye, called Tyrian Purple, is not present in the animal, but is formed by a combination of oxidation and photochemical transformation of a colorless precursor that is obtained from a gland in the mollusc. The yield of Tyrian Purple is very small—about one milligram per gland—so the cost of producing it made it accessible only to the wealthy and titled; thus the phrase, "born to the purple."



Tyrian Purple

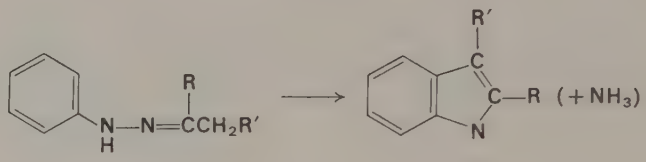
35-22 The Fischer indole synthesis

The synthesis of substituted indoles is usually accomplished by closure of the heterocyclic ring. In principle, this can be accomplished in any of four ways:



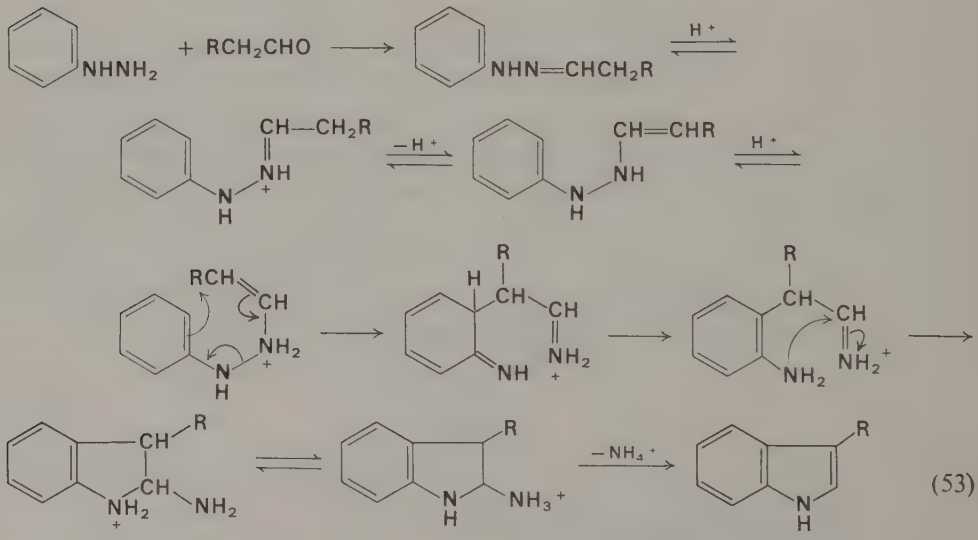
(51)

The last two of these processes, (*c*) and (*d*), lead to the formation of the heterocyclic ring in the *Fischer indole synthesis*, which is accomplished by the cyclization of an arylhydrazone with a strong hydrogen acid (for example, H_2SO_4) or Lewis acid ($ZnCl_2$). The overall reaction is the following:



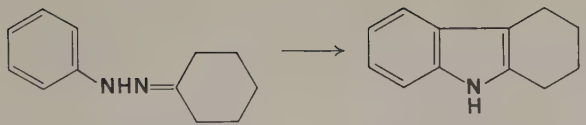
(52)

The course of this unusual reaction has been the subject of much study; an acceptable mechanism for it is described in Equations (53). It will be noted that the stages are such mechanistically unexceptional reactions as proton exchanges, tautomerization, electrophilic aromatic substitution, and addition of a nucleophile to an imino grouping. An aliphatic aldehyde is used in the example, but hydrazones of ketones can be used, as shown in (54), (55), and (56).



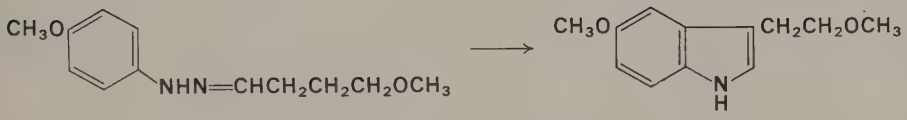
(53)

The Fischer indole synthesis is versatile, and can be used for the preparation of a wide variety of substituted indoles. Some examples are the following:

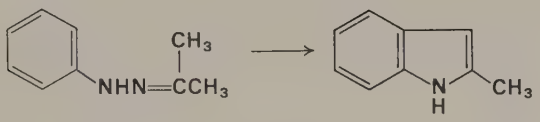


Cyclohexanone
phenyl hydrazone

(54)



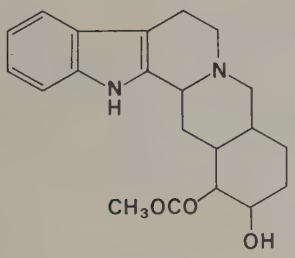
(55)



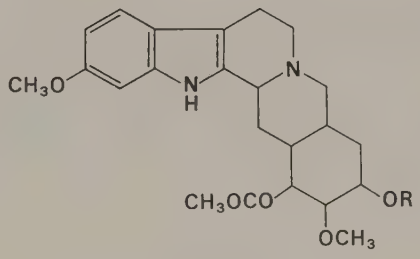
(56)

35-23 Indole alkaloids

Alkaloids based upon the *indole nucleus* range in complexity from the simple compound gramine to more complex alkaloids such as yohimbine, reserpine, and strychnine:

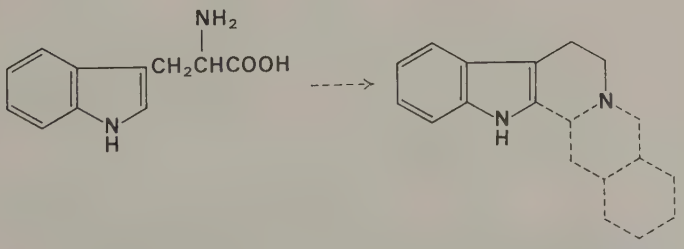


Yohimbine



Reserpine
(R = 3,4,5-trimethoxybenzoyl)

The indole alkaloids probably arise in the plant cell by biochemical transformations starting with the amino acid tryptophane:



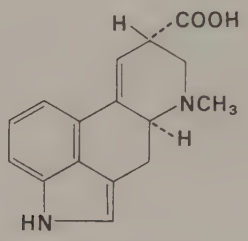
(57)

Tryptophane

Alkaloids of the yohimbine class

Here, the dotted lines represent additional fragments that make up the final alkaloid; the actual cellular reactions that occur between the starting material—tryptophane in this example—and the final alkaloid are still not known in all details.

A group of indole derivatives of great importance in medicine are derivatives of lysergic acid, which are known under the collective designation "ergot alkaloids" because of their occurrence in ergot, a fungus of cereal grains of the grass family (for example, rye). Lysergic acid has the structure



Lysergic acid

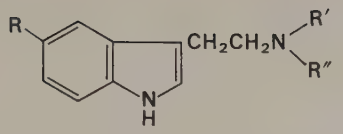
and occurs in nature as various amides formed between the acid and the amino group of either an amine or an amino acid. Ergometrine (ergonovine) is the amide of lysergic acid with L-(+)-2-amino-1-propanol. Ergonovine is used to treat migraine and to induce uterine contractions at childbirth.

The diethyl amide of lysergic acid, known as LSD, has the remarkable property of inducing a psychotic condition that resembles, but is not identical with, schizophrenia. It is the object of much investigation, not only because of the possibility that it may prove useful in psychiatric treatment, but because of abuses that have made it a serious socio-legal problem.

35-24 Hallucinogenic indole alkaloids

Besides LSD, a number of other indole derivatives are known to produce effects upon the central nervous system that give rise to disturbances of perception and behavior described as *hallucination*. Some of these are found in nature, and are the basis for the use of certain plant materials in rites and ceremonies in which altered states of awareness are induced in the participants.

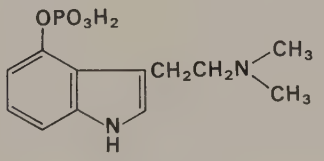
The South American plants *Piptadenia peregrina*, some *Virola* species, and *Acacia niopo* are used to prepare snuffs which, when inhaled, produce hallucinatory symptoms. These plants contain a number of closely related indole derivatives; among the physiologically most active are the following:



R = R′ = H, R″ = CH_3	*N*-methyltryptamine
R = H, R′ = R″ = CH_3	*N*,*N*-dimethyltryptamine
R = OH, R′ = R″ = CH_3	bufotenine

Dimethyltryptamine is reported to have several times the hallucinogenic activity of the well-known mescaline (peyote).

A Mexican species of mushroom, *Psilocybe mexicana*, is used by natives to produce a narcotic state characterized by hallucinations, colored visions, and behavioral disorientation. The active principle is *psilocybin*, the phosphate ester of 4-hydroxy-*N*,*N*-dimethyltryptamine:



Psilocybin

It is easily hydrolyzed to the hydroxy compound, *psilocin*, which is believed to be the active hallucinogen, formed *in vivo* by hydrolysis of the phosphate ester.

A number of other plants are used by native populations in various areas of the world for similar effects. Many (but not all) of these owe their activity to the presence of alkaloids containing the indole nucleus.

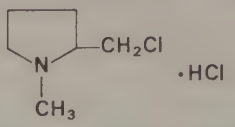
Problems

1. When 2,5-hexanedione (acetonylacetone) is treated with excess methylmagnesium bromide, and the reaction mixture decomposed with aqueous HCl, the product isolated is not the expected diol, but a compound $C_8H_{16}O$. Formulate this reaction.

2. Write the reaction showing the result of heating tetramethylethylene oxide with hot dilute H_2SO_4. The product has the composition $C_6H_{12}O$ (and thus is isomeric with the starting oxide).

3. What product would result from the reaction between *N*,*N*-dimethyl-β-chloroethylamine [$(CH_3)_2NCH_2CH_2Cl$] and dimethylamine?

4. When the hydrochloride of 2-chloromethyl-*N*-methylpyrrolidine



is treated with alkali, 3-chloro-*N*-methylpiperidine is formed. Formulate this change. (A cyclic imonium ion is an intermediate.)

5. Formulate the following reactions:
   (*a*) 2-bromopyridine + hot, alcoholic NaOEt →
   (*b*) 2-chloropyridine + NH_2NH_2 →
   (*c*) 2,3-dibromopyridine + methanolic NaOMe →
   (*d*) *N*-ethylpyridinium chloride + alkaline potassium ferricyanide →
   (*e*) quinoline + $NaNH_2$ →

6. Write the reactions involved in the synthesis of papaverine, starting with 3,4-dimethoxyphenylacetonitrile as the only organic compound.

7. A reagent used for the synthesis of α-amino acids is ethyl acetamidomalonate, $CH_3CONHCH(COOEt)_2$. For example, it can be alkylated with benzyl chloride to give a product that can be hydrolyzed and decarboxylated to give β-phenylalanine. Write the reactions that would be used in a synthesis of tryptophane, starting with indole and using ethyl acetamidomalonate in one of the steps.

36

Oxidation of organic compounds

Earlier in this book it was remarked that there are many satisfactory ways of presenting organic chemistry to the student: in terms of classes of compounds, functional-group behavior, types of reactions, and others. One type of reaction that is a pervasive part of the whole fabric of the subject is the oxidation of organic compounds. Although we have dealt earlier with oxidations of specific classes of compounds and functional groups, it is advantageous to iterate certain of these in order to emphasize the fundamental unity of what may appear to be many disparate types of oxidation reactions.

Oxidation is principally the loss or gain of electrons or hydrogen and oxygen atoms, often with concomitant breaking or forming of bonds. It is important that the student understand the fundamental nature of the oxidation process, so that he may understand oxidation reactions he has not previously encountered, be able to devise means of using oxidizing agents to accomplish novel transformations, and be able to devise new oxidizing reagents.

Among the most important oxidation reactions are those that occur in biological systems. It is worthwhile to discuss these in terms of the fundamental mechanisms of oxidation as the organic chemist views them, and thus to bring them, like many other cellular reactions, into the context of functional-group behavior. The biological oxidations treated in this chapter are some of those that can be discussed as *organic*

reactions, and not only in terms of the (sometimes less precise) concept of the overall transformation.

36-1 Introduction

All organic compounds are oxidizable, with varying degrees of ease and with the formation of a wide variety of types of oxidation products. The ultimate oxidation state of carbon is CO_2, and this complete oxidation is used in the determination of the elemental composition of a compound.

Planned and controlled oxidations of organic compounds are of almost limitless variety, and allow the alteration of functional groups, the partial degradation of compounds into smaller fragments, and the introduction of oxygen, all with the aim of preparing new organic compounds and determining structure.

36-2 Common oxidizing agents used in organic chemistry

Most of the oxidizing reagents used in organic chemistry are inorganic compounds in which a change from a higher to a lower valence occurs in the reaction. The number of known useful oxidizing agents is so large that only a few—the most generally useful—can be dealt with here. Table 36-1 lists the most commonly used ones, and the following sections will present examples of the use of some of them:

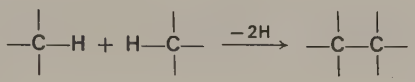
Table 36-1
Principal oxidizing agents used in organic chemistry

Oxidant	*Form used*	*Reduced form*	*Electron change*
Cr^{VI}	CrO_3, $K_2Cr_2O_7$	Cr^{III}	3
Mn^{VII}	$KMnO_4$	Mn^{IV} (MnO_2)	3
Mn^{VII}	$KMnO_4$	Mn^{II}	5
Mn^{IV}	MnO_2	Mn^{II}	2
Fe^{III}	$FeCl_3$, $K_3Fe(CN)_6$	Fe^{II}	1
Pb^{IV}	$Pb(OAc)_4$	Pb^{II}	2
I^{VII}	HIO_4	I^{V}	2
O_2	O_2	O^{--}	4
H_2O_2	H_2O_2	H_2O	2
RCO_3H	RCO_3H	RCO_2H	2
Cl, Br, I	Cl_2, Br_2, I_2	Cl^-, Br^-, I^-	2 (per X_2)
Se^{IV}	SeO_2	Se	4
Ag^+	Ag_2O	Ag^0	1
Cu^{++}	Cu^{++} salts	Cu^+	1

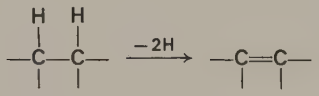
36-3 Types of oxidation reactions

In the majority of cases encountered in practice the oxidation of organic compounds occurs in one of the following ways.

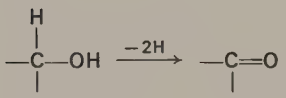
1. The removal of hydrogen to form a new bond between two atoms, or to convert a single bond into a double bond; for example:*



(1)



(2)



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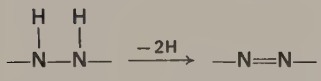

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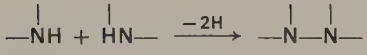
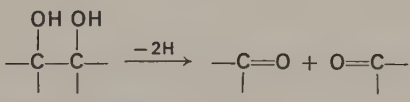


(5)

2. The removal of hydrogen followed by breaking of a bond between two (usually carbon) atoms:



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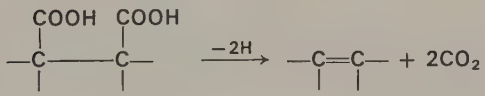
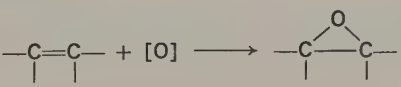


(7)

3. The addition of oxygen:



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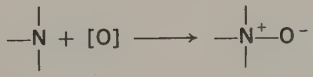
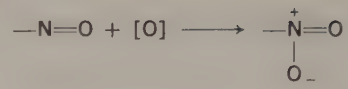


(9)

* The symbols $-2H$ and [O] are purely formal expressions and these equations are unbalanced and partial. The list of examples is not exhaustive but represents the most common types of such oxidations.



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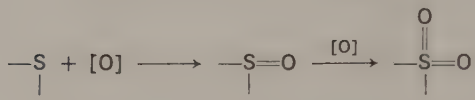
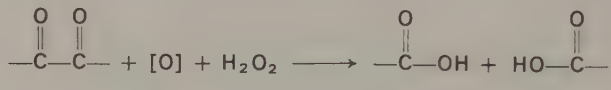


(11)

4. The addition of oxygen accompanied by the breaking of a bond:



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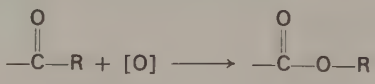

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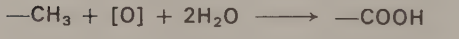

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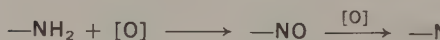

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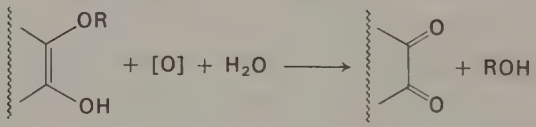
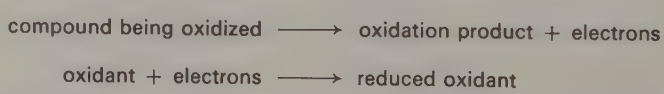


(16)

36-4 Oxidation-reduction equations

Although many oxidation reactions carried out in the laboratory do not require the use of carefully measured amounts of the oxidant, in some cases it is necessary to calculate the exact quantities needed. This calculation can be performed with a knowledge of (*a*) the total change in oxidation state of the reactants and (*b*) the identities of the final products. Balancing the equation for an oxidation reaction then permits a calculation of the amounts of reagents that will be needed.

There are numerous devices—most of them rather artificial—for balancing an oxidation-reduction equation. The following method, which depends essentially upon the formulation of the two half-reactions, is convenient:



(17)

To use this device, two "operators" are needed for balancing the half-reactions. These are H^+ and H_2O. A simple example will illustrate this: the oxidation of a secondary

alcohol to a ketone by means of CrO_3 (Cr^{6+}), the chromium being reduced to the chromic ion, Cr^{3+}; each reaction is balanced:

$$R_2CHOH \longrightarrow R_2C{=}O + 2H^+ + 2e \tag{18}$$

or

$$Cr^{VI} + 3e \longrightarrow Cr^{III}$$

$$CrO_3 + 6H^+ + 3e \longrightarrow Cr^{3+} + 3H_2O \tag{19}$$

The equations are then added, after adjusting them so that the electrons on both sides cancel out. In this example, the equations are adjusted to require $6e$ on each side:

$$3R_2CHOH \longrightarrow 3R_2C{=}O + 6H^+ + 6e \tag{20}$$

$$2Cr^{VI} + 6e \longrightarrow 2Cr^{III} \tag{21}$$

Sum:

$$3R_2CHOH + 2Cr^{VI} \longrightarrow 3R_2C{=}O + 6H^+ + 2Cr^{III} \tag{22}$$

Thus, two moles of CrO_3 are required to oxidize three moles of the alcohol.

In the oxidation reaction

$$RCH{=}CHR \xrightarrow{KMnO_4\ (Mn^{VII})} 2RCOOH + MnO_2\ (Mn^{IV}) \tag{23}$$

it is apparent that two oxygen atoms appear in each mole of the product (RCOOH) but are not contained in the original olefin. The half-reduction should provide for this by including H_2O in the equation, completing a material balance and a charge balance:

$$RCH{=}CHR + 4H_2O \longrightarrow 2RCOOH + 8H^+ + 8e \tag{24}$$

Since the oxidizing agent ($KMnO_4$) is reduced to MnO_2, the balanced half-reaction shows that a three-electron change occurs:

$$MnO_4^- + 4H^+ + 3e \longrightarrow MnO_2 + 2H_2O \tag{25}$$

Adjusting both half-reactions to an equal electron change, adding, and canceling:

$$3RCH{=}CHR + 12H_2O \longrightarrow 6RCOOH + 24H^+ + 24e \tag{26}$$

$$8MnO_4^- + 32H^+ + 24e \longrightarrow 8MnO_2 + 16H_2O \tag{27}$$

Sum:

$$3RCH{=}CHR + 8MnO_4^- + 8H^+ \longrightarrow 6RCOOH + 8MnO_2 + 4H_2O \tag{28}$$

Although this final equation is not yet complete, it does provide the information that three moles of the olefin require eight moles of $KMnO_4$ for oxidation to six moles

of RCOOH. If a complete equation is desired, the last step is to add to both sides of the equation $8K^+$ and $8OH^-$, giving

$$3RCH{=}CHR + 8KMnO_4 + 4H_2O \longrightarrow 6RCOOH + 8MnO_2 + 8KOH \qquad (29)$$

Exercise 1

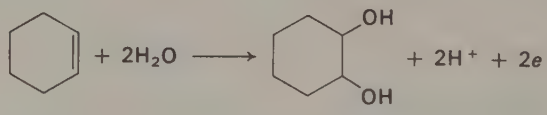
Carry out a material balance for each element in this final equation to show that it is a complete expression. (The group R may be considered as a unit.)

Exercise 2

Derive the complete balanced equation for the oxidation of RCH=CHR to 2RCOOH, using CrO_3 in aqueous H_2SO_4, given that $Cr_2(SO_4)_3$ is formed.

Additional half-reactions showing the electron changes for some organic oxidations are the following:

$$CH_3CH_2CH_2COOH + 4H_2O \longrightarrow CH_3COOH + 2CO_2 + 12H^+ + 12e \qquad (30)$$



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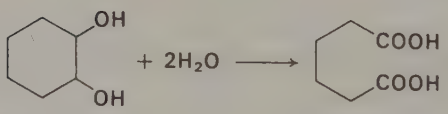
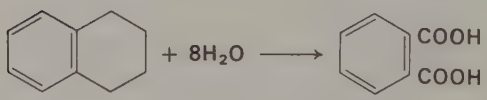


(32)



(33)

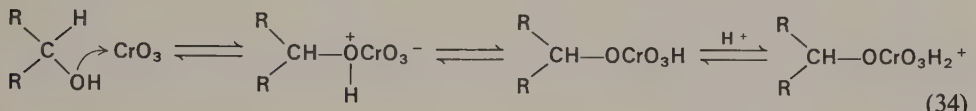
Exercise 3

Show (*a*) how many moles of CrO_3 are needed for (30) and (32); (*b*) how many moles of $KMnO_4$ are needed for (31) and (33), assuming that Cr^{3+} and MnO_2, respectively, are produced.

36-5 Chromic acid oxidations

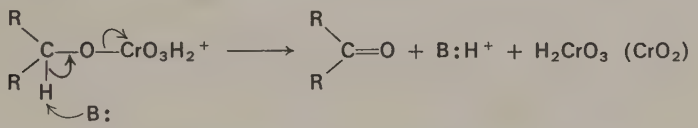
Chromic acid (chromium trioxide, CrO_3) is a versatile oxidizing agent, capable of bringing about a variety of oxidative changes in organic compounds. Its most common use is the oxidation of secondary alcohols to ketones. The details of this reaction have been revealed by study of its kinetics, and can be expressed by the following mechanism. The several stages are shown as separate steps for clarity of exposition.

Step 1: Nucleophilic attack of the OH group upon CrO_3 with formation of a chromic ester:



(34)

Step 2: Removal of a proton from carbon, perhaps by one of the oxygen atoms of the $—CrO_3H_2^+$ group, or perhaps by an external nucleophile (for example, the solvent medium). The latter course is conceptually adequate for our purpose, and can be represented as follows, with B: representing the proton-accepting agent:



(35)

It can be seen that H_2CrO_3 represents Cr^{IV}. The eventual formation of Cr^{III} can be accounted for by the electron transfer

$$Cr^{IV} + Cr^{VI} \longrightarrow 2Cr^{V} \tag{36}$$

and then the oxidation of another mole of R_2CHOH

$$2R_2CHOH + 2Cr^{V} \longrightarrow 2Cr^{III} + 2R_2C{=}O + 4H^+ \tag{37}$$

The sum of all of these equations implies, as described earlier, that three moles of R_2CHOH require two moles of CrO_3 for oxidation to the ketone.

Oxidation of an aldehyde to a carboxylic acid follows a similar course. In the formulation of the reaction it is convenient to regard the aldehyde as acting in the hydrated form, $RCH(OH)_2$.

Chromium trioxide can be used under a variety of experimental conditions: in water, aqueous acetic acid, acetone, or pyridine solution. The reagent commonly known as *Jones' reagent* is a solution of CrO_3 in aqueous sulfuric acid, the concentration

being adjusted so that a measured amount of the reagent contains a standardized amount of oxidant.

The oxidation of secondary alcohols to ketones is a general reaction applicable to a wide range of compounds. With suitable control of conditions (temperature, solvent, and amount of oxidant) the oxidation can be made selective, leaving other oxidizable functions (for example, C=C) unaffected.

Tertiary alcohols are relatively stable to oxidation by chromic acid. When sufficiently vigorous conditions are used oxidation does occur, but with degradation of the molecule into smaller fragments. The oxidation of primary alcohols to aldehydes occurs by the mechanism discussed above, with the formation of the aldehyde. This reaction is not generally useful in aqueous media, however, because of the ease with which the aldehyde is further oxidized to the carboxylic acid. It can be applied successfully if a means can be found to remove the aldehyde from the reaction mixture as soon as it is formed. For example, the oxidation of 1-propanol to propionaldehyde can be accomplished by carrying out the reaction at a temperature above the boiling point of the aldehyde, which distills from the reaction mixture as it is formed, and is carried to a condenser and then to a receiving flask. The complex formed between CrO_3 and pyridine can be used in non-aqueous solvents; under these conditions it is capable of oxidizing primary alcohols to aldehydes without further oxidizing the aldehydes.

Exercise 4

Show the organic product formed by the (two-electron) chromic acid oxidation of the following compounds: (*a*) 2-butanol, (*b*) cholestan-3β-ol, (*c*) 4,4-dimethyl-2-pentanol, (*d*) cyclopentanol, (*e*) menthol.

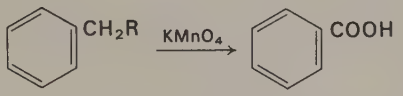
Exercise 5

Calculate the amount of CrO_3, in grams, that must be present in 100 ml of a CrO_3-H_2O-H_2SO_4 solution so that 1 ml of solution will oxidize 100 mg of isopropyl alcohol to acetone.

36-6 Potassium permanganate oxidations

Potassium permanganate, $KMnO_4$, is a versatile and widely used oxidizing agent. It is ordinarily used in neutral or alkaline solution, in which case the MnO_4^- is reduced to MnO_2. Potassium permanganate finds its most frequent use in

(*a*) The oxidation of carbon-linked substituents on aromatic rings to give carboxylic acids:



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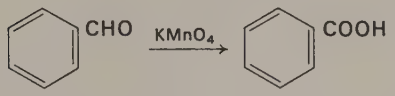
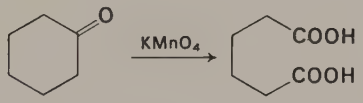


(39)

(*b*) The oxidation of ketones to carboxylic acids and of cyclic ketones to dicarboxylic acids:

$$RCH_2COCH_2R' \xrightarrow{KMnO_4} RCOOH + R'CH_2COOH + R'COOH + RCH_2COOH \quad (40)$$



(41)

The first of these reactions (40) is often impracticable; when R and R′ are not the same, a mixture of products may be formed that cannot be separated easily.

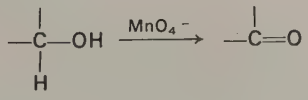
(*c*) The hydroxylation of carbon-carbon double bonds with the formation of 1,2-glycols:

$$RCH{=}CHR' \xrightarrow{KMnO_4} \underset{OH}{RCH}\!-\!\underset{OH}{CHR'} \quad (42)$$

(*d*) Numerous other oxidations of a wide variety of types, not easily categorized into discrete classes. The general statement can be made that most organic compounds containing functional groups are oxidizable with $KMnO_4$, but many of these reactions are not of predictable generality.

36-7 Permanganate oxidation of alcohols and aldehydes

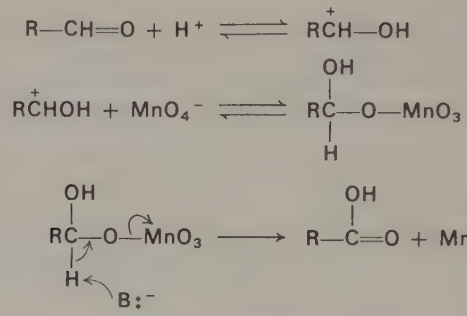
The oxidation



(43)

appears to be mechanistically rather complex, but probably follows a course similar to

that for CrO_3 oxidation. The oxidation of —CHO to —COOH by $KMnO_4$ has been formulated in the following way:

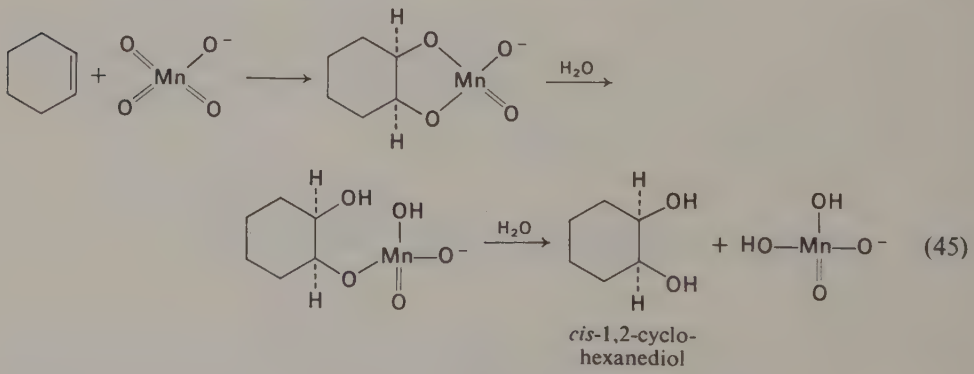


(44)

When ^{18}O-labeled $KMnO_4$ is used, ^{18}O is found in the carboxylic acid, as required by this mechanism.

36-8 *Cis*-hydroxylation of the carbon-carbon double bond

Potassium permanganate. The oxidation of the carbon-carbon double bond by $KMnO_4$ under mild and controlled conditions (dilute aqueous $KMnO_4$ at about 0–5°) proceeds as shown in the following equations. It is a characteristic of this reaction that the two —OH groups are added from the same side of the double bond in an overall *cis*-addition. Cyclohexene, for instance, gives *cis*-1,2-cyclohexanediol. The reason for this is that the attack of MnO_4^- upon the double bond proceeds by way of the formation of a cyclic ester, hydrolysis of which occurs with breaking of the Mn—O bonds:

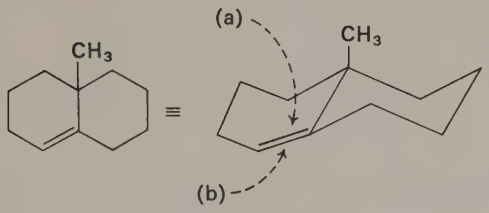


(45)

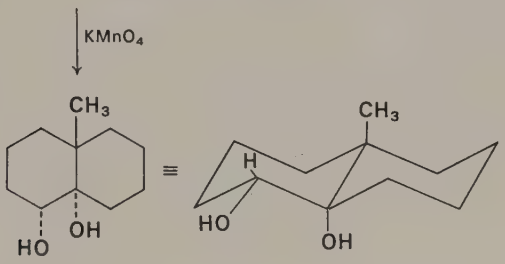
cis-1,2-cyclohexanediol

Note that $H_2MnO_4^- \equiv MnO_4^{3-} \equiv Mn^{V}$. Thus, $Mn^{VII}O_4^- + 2e \rightarrow Mn^{V}O_4^{3-}$ overall. Further disproportionations between intermediate oxidation states of manganese result finally in the formation of $Mn^{IV}O_2$.

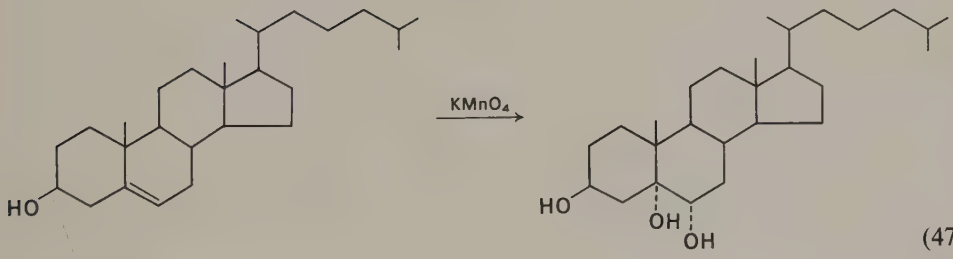
Since MnO_4^- is a bulky, space-filling ion, its approach to the double bond is influenced by the steric environment, and stereoselective oxidation can often be achieved. Two illustrative examples are the following:



Approach of MnO_4^- in direction (*a*) is impeded by the axial —CH_3 group. Approach in direction (*b*) is favored.



(46)

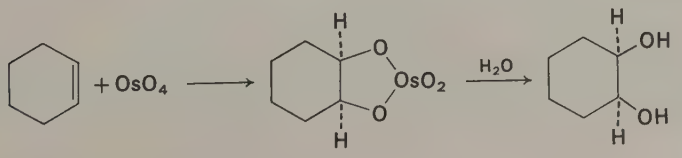


(47)

Cholesterol Cholestan-3β5α6α-triol

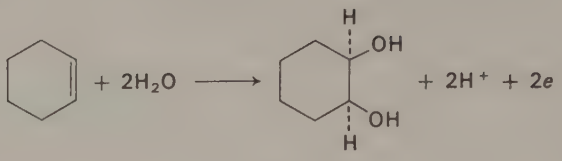
Evidence supporting the mechanism described for the permanganate hydroxylation reaction is given by the observation that when ^{18}O-labeled $KMnO_4$ is used, the oxygen atoms of the glycol are also ^{18}O-labeled.

Osmium tetroxide. Another reagent that hydroxylates an olefinic double bond with the same overall result, and by a mechanism comparable to $KMnO_4$ hydroxylation, is osmium tetroxide, OsO_4. The formation of an intermediate cyclic ester proceeds as shown below. This ester is often isolated prior to its hydrolysis to the glycol:



(48)

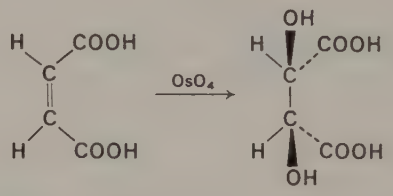
Note that $H_2OsO_4 \equiv OsO_3 \equiv Os^{VI}$. Thus, the overall change is a two-electron oxidation-reduction:



(49)

$$OsO_4 + 2e + 2H^+ \longrightarrow OsO_3 + H_2O \qquad (50)$$

The following examples illustrate some practical applications of osmium tetroxide oxidation:*



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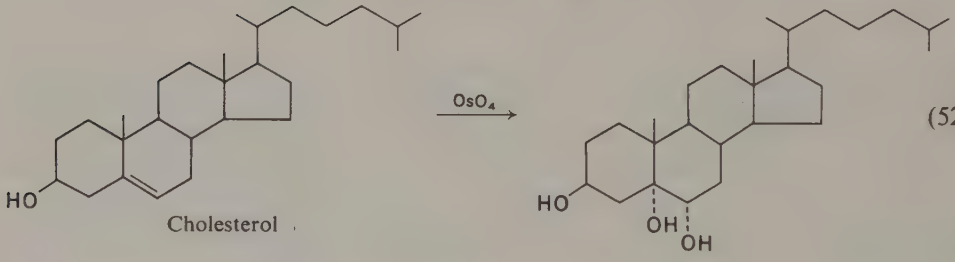
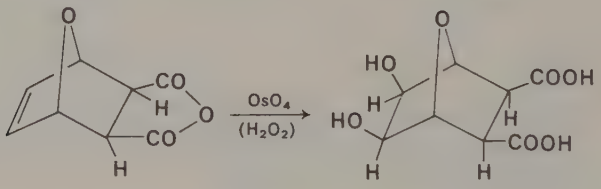


Cholesterol

(52)



(53)

36-9 Epoxidation of carbon-carbon double bonds. *Trans*-hydroxylation

Epoxides (systematic name, *oxiranes*) are three-membered-ring compounds of which the following are typical examples:

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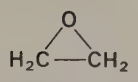
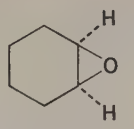
* The intermediate cyclic osmic esters are omitted from these equations. In practice the osmic ester is cleaved, with concomitant oxidation or reduction of the Os^{VI}. In some experimental procedures the OsO_4 is used in small (catalytic) amount, for it is regenerated by the oxidizing agent (for example, H_2O_2).



Ethylene oxide
(oxirane)

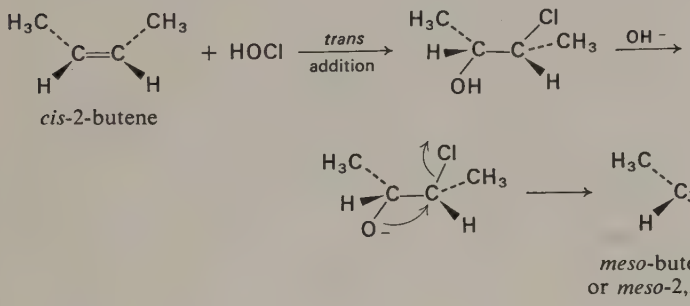


Cyclohexene
oxide

Epoxides can be prepared in several ways:

1. Ethylene oxide is made industrially by the direct reaction of ethylene with oxygen. This is not a general method and has little application to other compounds.

2. The intramolecular displacement of halogen or other displaceable group (for example, a sulfonic acid ester) by an adjacent hydroxyl group is a general and widely employed procedure. The required 1-hydroxy-2-chloro compound, for instance, can be prepared by the addition of HOCl to an olefinic double bond. The following example shows the reaction along with the details of the stereochemistry:



cis-2-butene

meso-butene-2,3-oxide
or *meso*-2,3-epoxybutane

(54)

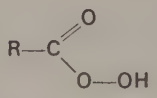
Exercise 6

Formulate the addition of HOCl to *trans*-2-butene and the formation of the epoxide. Show all of the stereochemistry involved. In what terms would you describe the stereochemistry of the final product (the epoxide)?

The most general method for the epoxidation of the carbon-carbon double bond is by the use of a peroxycarboxylic acid, RCO_3H. Peroxy acids can be prepared in several ways, the simplest being the equilibrium reaction between a carboxylic acid and hydrogen peroxide

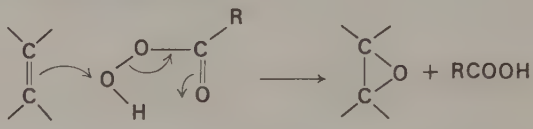
$$RCOOH + H_2O_2 \rightleftharpoons RCOO_2H + H_2O \qquad (55)$$

Peroxy acids are acyl derivatives of hydrogen peroxide and can be represented by the structure



(56)

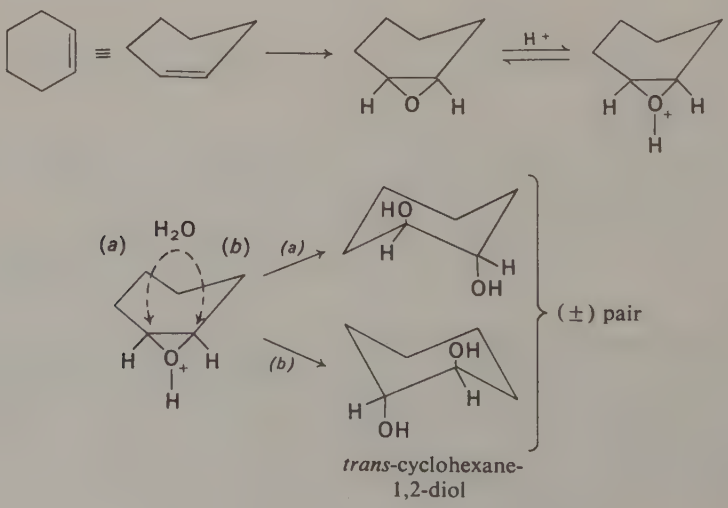
The most generally useful property of peroxy acids is their ability to donate an oxygen atom to a nucleophilic reagent. In epoxide formation, the carbon-carbon double bond of the olefin acts as the nucleophile:



(57)

Carbon-carbon double bonds attached to electron-withdrawing substituents, as in α,β-unsaturated carbonyl compounds, are poor nucleophiles and react very slowly or not at all. For normal double bonds, as in alkenes, cyclohexene, and so on, the reaction proceeds readily to give good yields of the epoxides.

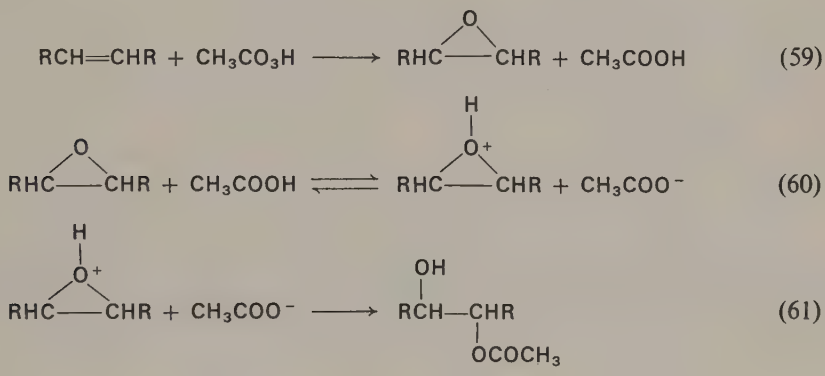
Although the three-membered epoxide ring is readily formed and epoxides are stable and isolable compounds, the angle strain in the small ring is such that epoxides are susceptible to ring-opening, most readily by acid-catalyzed processes, but also by nucleophilic attack under basic conditions. The hydrolysis of epoxides by dilute aqueous mineral acid proceeds by nucleophilic attack by H_2O upon the protonated epoxide. The hydrolysis of cyclohexene oxide, in which the stereochemistry is readily apparent, will illustrate:



(58)

It will be seen from this example that the overall result of the reaction sequence, olefin → epoxide → glycol, is the *trans* addition of the two hydroxyl groups. This is in contrast to $KMnO_4$ or OsO_4 hydroxylation, in which the overall addition is *cis*. The formation of the *trans*-glycol from the epoxide in this way necessarily involves inversion of configuration at the carbon atom from which the C—O bond is displaced by attack of the nucleophile, thus accounting for the formation of *trans*-cyclohexane-1,2-diol from cyclohexene oxide, in which the oxide ring fusion is necessarily *cis*.

When the epoxidation reaction is carried out in acetic or formic acid (that is, with $CH_3COOH + H_2O_2$ or $HCOOH + H_2O_2$), the epoxide is formed at once, and opens by attack of the solvent acid:



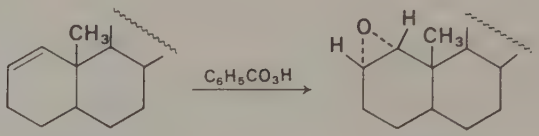
The product is the monoacetate (or monoformate) of the glycol; it can be converted into the glycol by saponification.

If the olefin/peroxy-acid reaction mixture is buffered (for example, with Na_2HPO_3 or $NaHCO_3$), protonation is inhibited and the epoxide can be isolated.

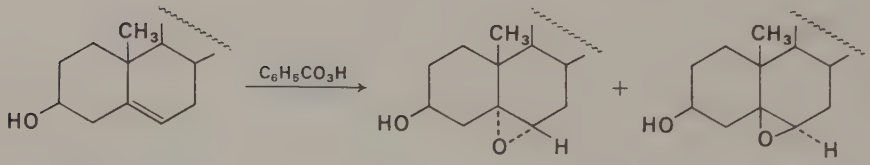
36-10 Stereochemical aspects of epoxidation with peroxy acids

It will be recalled (Section 36-8) that when potassium permanganate is used to hydroxylate a double bond in an unsymmetrical environment, nearby groups may influence by steric interference the direction of approach to the double bond, so that attack does not occur equally at both faces of the molecule. Similar effects are observed in epoxidation with peroxy acids. For instance, cholest-1-ene gives principally the α-epoxide with perbenzoic acid, and cholesterol (cholest-4-ene-3β-ol) principally (but not

exclusively) the α-oxide; in each of these cases the methyl group at C-10 shields the β face of the molecule:

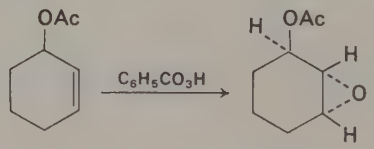


A/B rings of cholest-1-ene (Mostly) (62)

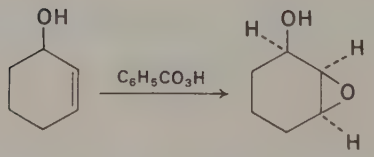


A/B rings of cholesterol α-oxide (mostly) β-oxide (63)

Steric influences can be overcome by other structural factors. Although 3-acetoxycyclohexene is epoxidized from the side opposite to the —OAc group, 3-hydroxycyclohexene gives the epoxide in which the oxide ring and the —OH group are *cis*:



(64)

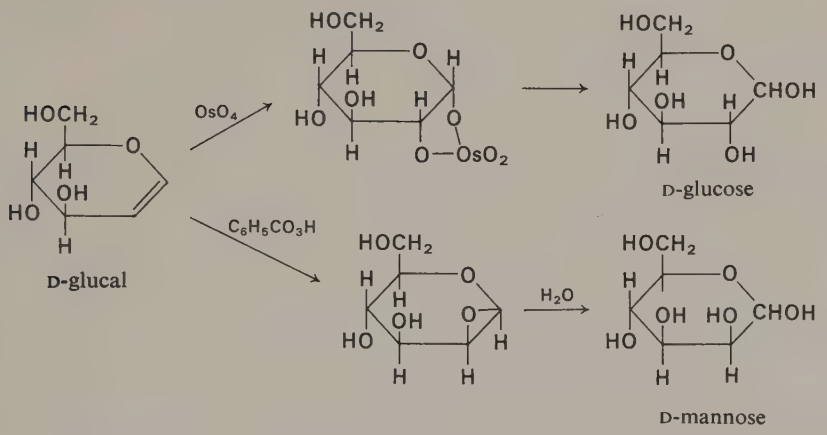


(65)

It is probable that in the attack of the peroxy acid upon the cyclohexenol, hydrogen bonding between the —OH group and the peroxy acid directs the attack and governs the stereochemical result.

Similar results are observed in the epoxidation of certain sugar derivatives. Glycals, which have structures typified by D-glucal (a D-glucose derivative), upon epoxidation followed by hydrolytic epoxide ring opening give sugars epimeric at C-2, depending upon whether the free hydroxy compound or its acetate is used. The reaction with osmium tetraoxide is also shown in the following equations; it will be seen that in this case the stereochemistry of OsO_4 epoxidation is governed by the steric influence of

the adjacent hydroxyl group (at C-3) and hydrogen bonding does not appear to control the stereochemical result:



(66)

Exercise 7

Perbenzoic acid oxidation of D-glucal *triacetate* yields, after a final saponification step, D-glucose. Formulate the reactions, and explain why the product is not the same as that obtained by perbenzoic acid oxidation of D-glucal itself.

Exercise 8

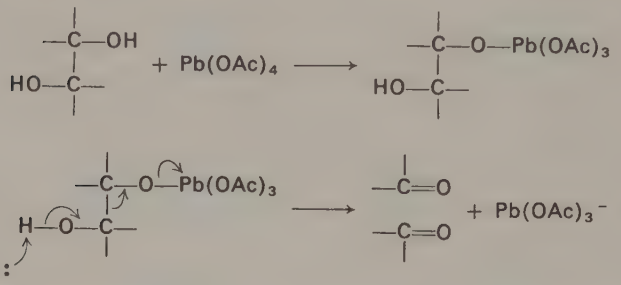
Write the steps involved in the acid-catalyzed hydrolysis of the epoxy ether RHC(O)CH—OR′.

36-11 Periodic acid and lead tetraacetate oxidations

The oxidative cleavage of 1,2-diols by periodic acid has been described in Chapter 13. This oxidation can also be carried out with *lead tetraacetate*, $Pb(OAc)_4$; both of these reagents are useful for a number of oxidations of other kinds. Lead tetraacetate is prepared by dissolving red lead oxide, Pb_3O_4, in a mixture of acetic acid and acetic anhydride; it crystallizes from the solution on cooling. Lead tetraacetate is a versatile oxidizing agent, and only a few of its many reactions are considered here.

The cleavage of 1,2-diols by lead tetraacetate (hereinafter referred to as LTA) proceeds in a manner that resembles the periodic acid reaction, differing in mechanistic

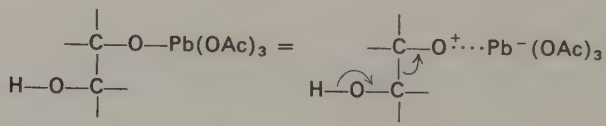
detail but producing the same overall result. The reaction of LTA with a glycol is regarded as proceeding through the formation of an intermediate ester:



(67)

The resemblance of this reaction to the CrO_3 oxidation of an alcohol (Section 36-5) is to be noted.

The tendency of Pb^{IV} (in LTA) to reduce its valency to the Pb^{II} state by the displacement shown in the above equation produces an electron deficiency on oxygen in the O—Pb bond. A simplified expression (in which the concerted character of the reaction is implicit) is

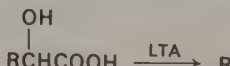


(68)

Indeed it is convenient, although often artificial, to formulate many of the reactions of LTA as proceeding by way of the removal of two electrons to produce an $—O^+$ intermediate.

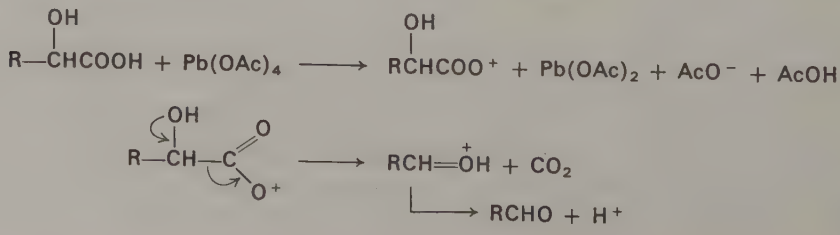
36-12 Oxidative decarboxylation with lead tetraacetate

A useful reaction of LTA is the oxidative decarboxylation of α-hydroxy acids:



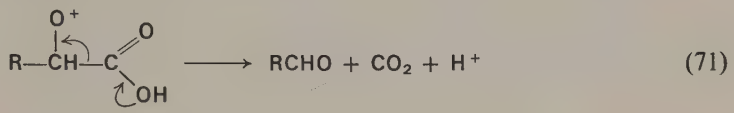
(69)

A simple and adequate representation of this reaction, using the conceptual device of assuming an intermediate $—O^+$ species, is the following:



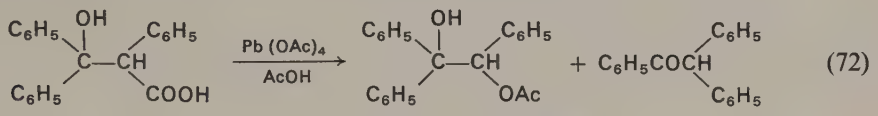
(70)

It will also be seen that the reaction could equally well be formulated as proceeding through the electron-deficient hydroxyl oxygen atom, with an identical outcome:



(71)

Evidence that it is indeed the —COO^+ pathway and not the —$\overset{|}{C}H—O^+$ pathway that is taken is found in the results of the following experiment:

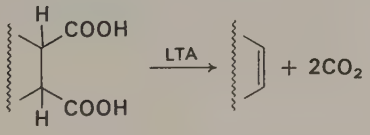


(72)

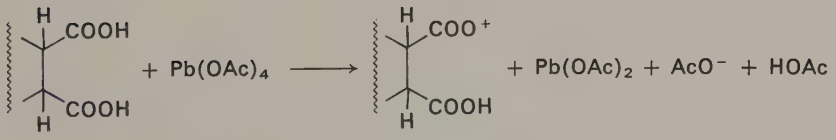
Exercise 9

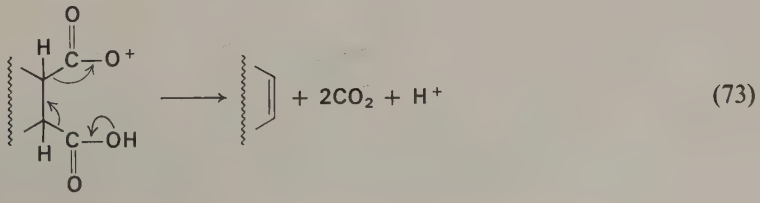
How does the observed result of the LTA oxidation of 2,3,3-triphenyl-3-hydroxypropanoic acid support the mechanistic course proceeding by way of the —COO^+ pathway over that proceeding by the $(C_6H_5)_2C—O^+$ route?

An oxidative decarboxylation reaction of another kind can be readily understood by the application of the same concept, the generation of a —COO^+ intermediate:



via





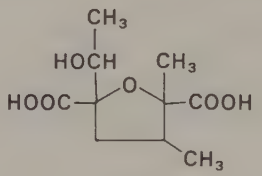
(73)

Exercise 10

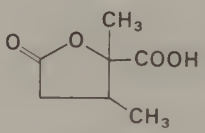
Oxidation of $HOOCCH_2COOEt$ with lead tetraacetate in acetic acid yields CH_3COOCH_2COOEt (ethyl acetoxyacetate). Show a possible course for this transformation.

Exercise 11

Oxidation of compound A with lead tetraacetate gives a number of products, including CO_2, acetaldehyde, 3-methyl-4-ketopentanoic acid, and the lactone B. Show how these products are formed by formulating the detailed sequence of events.



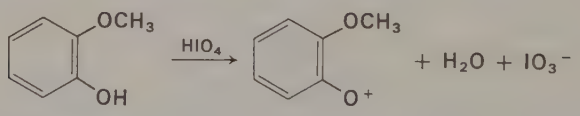
A



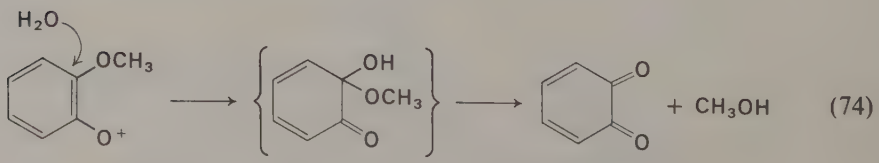
B

36-13 Oxidation of phenols by periodic acid

The oxidation of guaiacol (*o*-methoxyphenol) with aqueous periodic acid yields *o*-benzoquinone. Oxidation of *p*-benzyloxyphenol in the same way yields *p*-benzoquinone and benzyl alcohol. Both of these reactions are readily accounted for by a common mechanism, the essential feature of which is the generation of electron deficiency on the oxygen atom of the phenolic —OH group:



Guaiacol

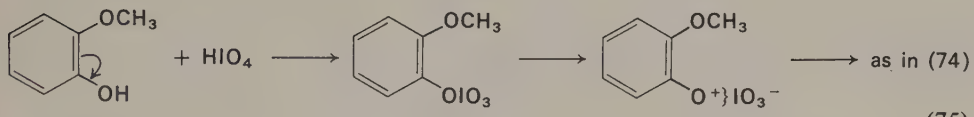


(74)

o-benzoquinone

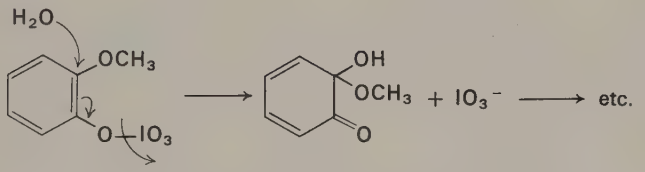
It is not certain whether the loss of two electrons from the phenolic oxygen atom

is a discrete step, or whether a concerted process occurs, in which the nucleophilic attack (of methanol) displaces the IO_3^- ion:



Guaiacol (75)

or



(76)

Exercise 12

Write the balanced oxidation-reduction half-reaction for the oxidation of guaiacol with periodic acid.

Exercise 13

Show the course of the HIO_4 oxidation of (*a*) *p*-benzyloxyphenol to give *p*-benzoquinone and benzyl alcohol; (*b*) 4-hydroxydiphenyl ether to give *p*-benzoquinone and phenol.

Exercise 14

Periodic acid oxidation of *o*-hydroxybenzyl alcohol gives a neutral compound (not a quinone) of the composition $C_7H_6O_2$. What is its structure, and how is it formed?

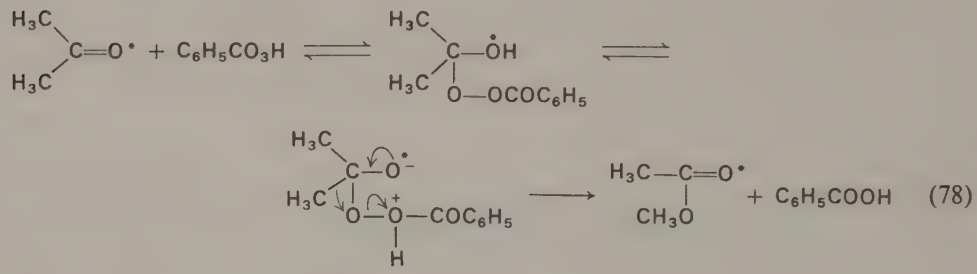
36-14 Oxidation of ketones with peroxy acids. The Baeyer-Villiger reaction

The reaction of a peroxy acid with a ketone leads to the formation of an ester by a process that appears to be the simple insertion of an oxygen atom:

$$RCOR + R'CO_3H \longrightarrow RCO{-}OR + R'CO_2H \qquad (77)$$

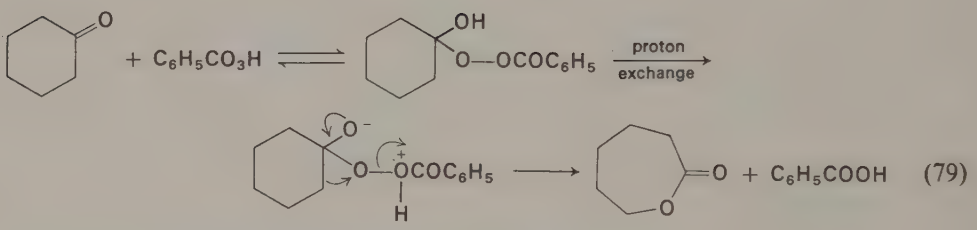
This reaction, known as the *Baeyer-Villiger reaction* (Chapter 34) proceeds by way of a carbonyl addition reaction, followed by a rearrangement initiated by the generation of electron-deficient oxygen. Using acetone and peroxybenzoic acid as reagents, the

course of the reaction can be represented as (the oxygen atom is starred simply for identification):



(78)

Cyclic ketones give lactones:

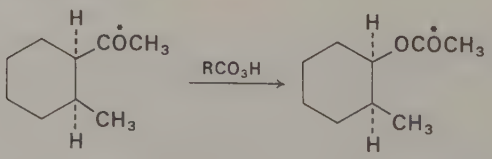


(79)

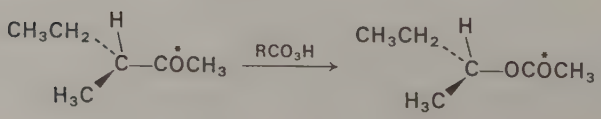
An important feature of the reaction is its *intramolecular* character: the migrating group does not become free, but migrates in a transition state in which the new C—O bond forms as the C—C bond is broken. This accounts for two aspects of the reaction: (1) If the migrating group is asymmetric, its configuration remains the same; and (2) large-ring ketones are oxidized to lactones. If the reaction followed a course such as

$$\text{ketone} \longrightarrow \text{hydroxy acid} \longrightarrow \text{lactone}$$

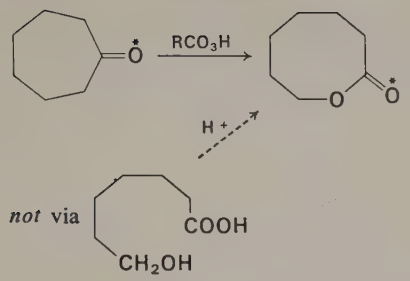
cyclic ketones larger than cyclohexanone would not be expected to form lactones, for the formation of lactones of seven or more ring elements by ring closure would not occur under the conditions of the reaction.



(80)



(81)



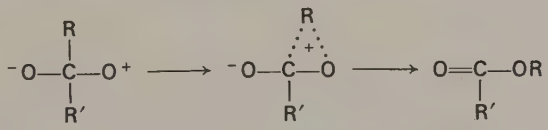
(82)

The mechanism shown implies that the carbonyl group of the original ketone (the starred oxygen atom in the above equations) becomes the carbonyl group of the resulting ester or lactone. That this is the case has been demonstrated by experiments with ^{18}O-labeled reagents.

When an unsymmetrical ketone RCOR′ is oxidized either of the two R groups can migrate; when these groups are nearly alike in character a mixture of products will be obtained. In general the order of migratory aptitude is

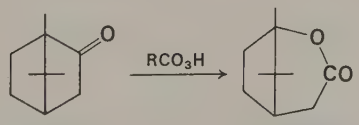
t-alkyl > *sec*-alkyl > benzyl or phenyl > *pri*-alkyl > methyl

This order reflects the capacity for the migrating group to accommodate a positive charge in the transition state for rearrangment:



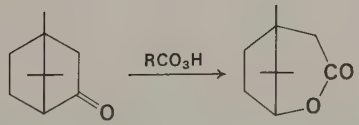
(83)

The following reactions have been observed experimentally:



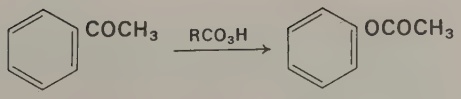
Camphor — Principal product

(84)



Epicamphor

(85)



Phenyl acetate

(86)

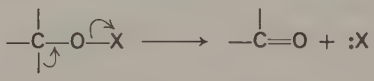
The last of the above examples illustrates one of the important applications of the Baeyer-Villiger reaction: the conversion of an acetophenone into the corresponding phenyl acetate, which can be saponified to give the phenol. Thus, the general transformation

$$ArCOCH_3 \longrightarrow ArOH \tag{87}$$

can be accomplished. Since acetophenone derivatives are readily accessible by Friedel-Crafts acylation, this provides a convenient synthesis of phenols.

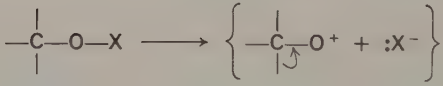
36-15 A general concept of oxidation reactions

A wide variety of oxidation reactions, at first sight disparate in kind, can be rationalized by the central concept expressed in the following general equation:



(88)

or the formal



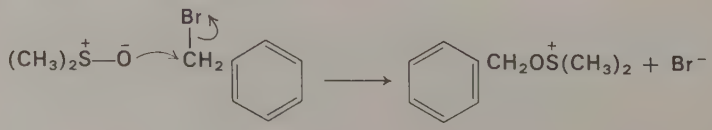
(89)

The departure of X with the pair of electrons of the O—X bond represents the two-electron transfer to X. That the loss of :X may be concerted with —C(=O)— bond formation rather than passing through a discrete $—O^+$ stage does not affect this understanding of the overall process.

Two methods of alcohol oxidation that do not involve the reduction of a metal atom are consistent with this general concept. In one, dimethylsulfoxide [$(CH_3)_2S{=}O$, DMSO] is the oxidant and is converted into dimethylsulfide; the half-reaction for the reduction of DMSO is

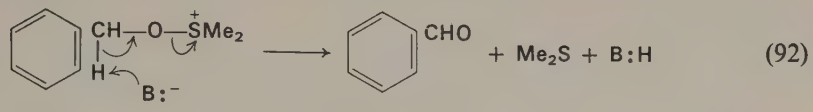
$$(CH_3)_2SO + 2H^+ + 2e \longrightarrow (CH_3)_2S + H_2O \tag{90}$$

The initial step in this procedure is the use of DMSO as the nucleophile in a displacement reaction of the following kind:



(91)

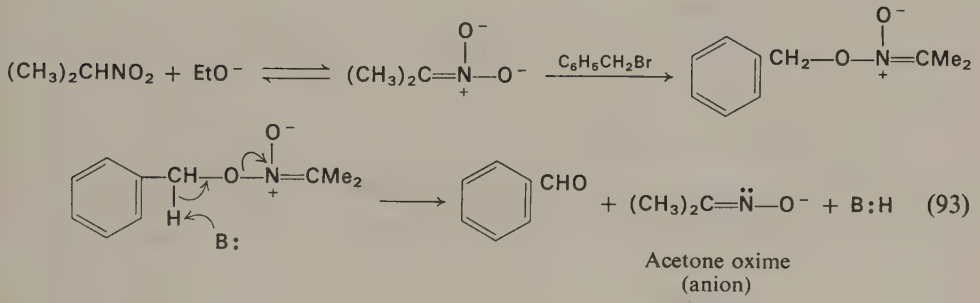
Removal of a proton and elimination of $(CH_3)_2S$ completes the process:*



(92)

There are a variety of methods for converting the $-\overset{|}{\underset{|}{C}}-OH$ group of the alcohol to the $-\overset{|}{\underset{|}{C}}-O\overset{+}{S}Me_2$ intermediate, and of effecting proton removal in the last step, but the overall reactions are all describable in the same terms.

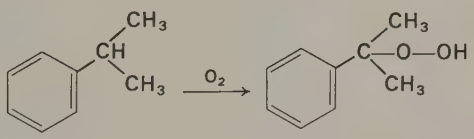
Another reaction, which appears quite unlike the above but bears an intimate mechanistic relationship to it, is the following:



(93)

It can be seen that this reaction involves the overall reduction of the nitro group, $-NO_2$, to the nitroso group, —NO. Note that acetone oxime can be written as the tautomeric structure $(CH_3)_2CHNO$.

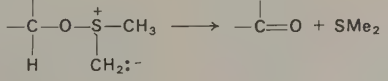
The decomposition of cumene hydroperoxide, described in an earlier chapter, is repeated here to emphasize its relationship to the foregoing reactions:

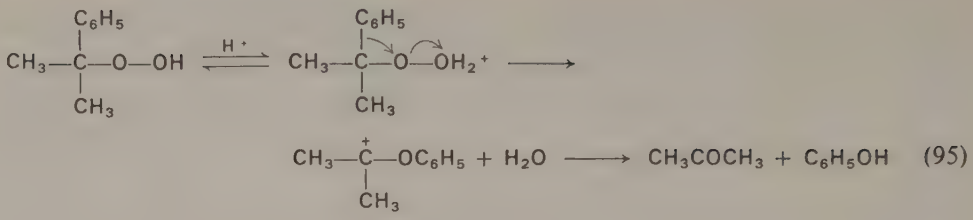


Cumene Cumene hydroperoxide

(94)

* Evidence has been obtained that sulfur ylid formation may occur as an intermediate step, by proton removal from an *S*-methyl group:



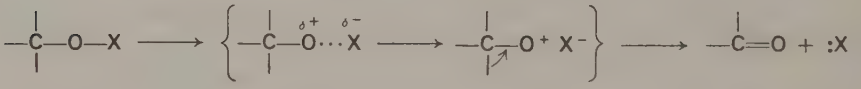


(95)

36-16 Oxidation as an elimination reaction

The general expression (88)–(89) given in Section 36-15 can now be reviewed in terms of the substituents X as they have appeared in the oxidation reactions so far discussed. It will be recognized that the overall process is an *elimination reaction*, as shown in (94) and Table 36-2.

Table 36-2
Oxidizing agents in the general expression



Oxidizing reagent	O—X	:X
CrO_3	$O—CrO_3H_2^+$	H_2CrO_3
$KMnO_4$	$O—MnO_3$	MnO_3^-
HIO_4	$O—IO_3$	IO_3^-
Me_2SO	$O—\overset{+}{S}Me_2$	Me_2S
$Pb(OAc)_4$	$O—Pb(OAc)_3$	$Pb(OAc)_2 + OAc^-$
O_2	$O—OH_2^+$	H_2O
$(CH_3)_2CHNO_2$	$O—\overset{+}{N}(O^-)=CMe_2$	$Me_2C=\ddot{N}—O^-$
Br_2	O—Br	Br^-
HNO_3	$O—NO_2$	NO_2^-
RCO_3H	$O—\overset{+}{O}(H)COR$	RCO_2H

Exercise 15

The following reactions have been observed. Account for each by writing a reasonable mechanism (the equations given below are not balanced).

(*a*) $C_6H_5NH_2 + RCO_3H \longrightarrow C_6H_5NO_2$

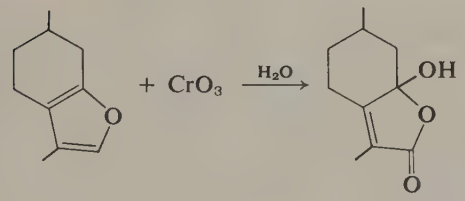
(*b*) $RHC(O)CHR + Me_2SO \longrightarrow RCH(OH)COR + Me_2S$

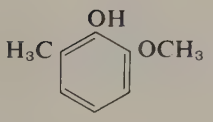
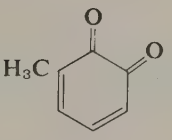
(*c*) $CH_3C(CN)=CHCH_3 + KMnO_4 \longrightarrow CH_3COCHOHCH_3 + HCN$

(*d*) $HO-C(C_6H_5)(C_6H_5)-COOH + CrO_3 \longrightarrow C_6H_5COC_6H_5 + CO_2$

(*e*) $C_6H_5CH(OH)C(CH_3)_3 + CrO_3 \xrightarrow{H_2O} C_6H_5CHO + (CH_3)_3COH$

(*f*) $C_6H_5COC(OH)(CH_2Br)C_6H_5 + CrO_3 \xrightarrow{H_2O} C_6H_5COCH_2Br + C_6H_5COOH$

(*g*)  $+ CrO_3 \xrightarrow{H_2O}$

(*h*)  $+ HIO_4 \xrightarrow{H_2O}$  $+ CH_3OH$

36-17 Other oxidation reactions

Oxidation reactions include so vast a range of types and mechanisms that the preceding sections have given only a selection of some of the most generally used. Precise mechanistic details of many, while they can be interpreted with reasonable assurance, have not been established with certainty. What has been said should, however, provide

the student with an understanding of the basic principles and enable him to interpret rationally oxidation reactions of many kinds.

Additional oxidation reactions have been dealt with in other chapters: ozonolysis of olefinic compounds, biological oxidative dealkylation, oxidation of aromatic side chains, and others. A subject that has been touched upon but not yet examined in detail is the oxidation that occurs in living cells. Since biological oxidation reactions are comprehensible in terms of the principles discussed in this chapter, and because they are of central importance in the metabolism of living organisms, they deserve further study, and are the subject of the following sections.

36-18 Biological oxidation

Biological oxidation reactions involve the transfer of electrons, the introduction of oxygen into organic molecules, and the removal of hydrogen. There are many oxidative degradation reactions in which complex molecules are transformed into simpler ones, and oxidative coupling reactions in which complex molecules are constructed.

The summary following shows, without mechanistic detail, some representative biological oxidation reactions; the succeeding discussion selects some of these for close examination.

1. Dehydrogenation-hydrogenation:

$$CH_3CH(OH)COOH \rightleftharpoons CH_3COCOOH \quad (96)$$

$$HOOCCH_2CH_2COOH \rightleftharpoons HOOCH{=}CHCOOH \quad (97)$$

$$RCH_2CH_2COOH \rightleftharpoons RCH{=}CHCOOH \quad (98)$$

$$CH_3(CH_2)_7CH_2CH_2(CH_2)_7COOH \rightleftharpoons CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH \quad (99)$$

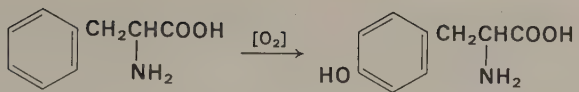
$$RCH_2CH(NH_2)COOH \rightleftharpoons RCH_2C(=NH)COOH \quad (100)$$

2. Introduction of oxygen:

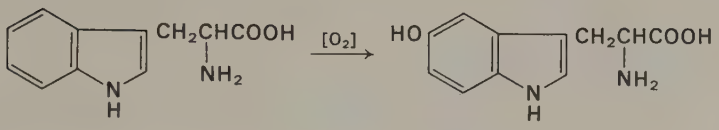
$$RCH{=}CR_2 \longrightarrow RCH\text{—}CR_2 \quad (101)$$

(with O bridging the two carbons)

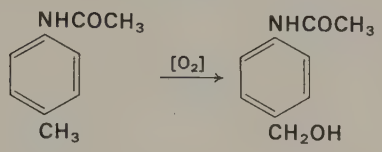
This is often followed by ring opening (to a glycol), rearrangement (to a ketone), or attack of a carbon-carbon double bond (usually with cyclization).



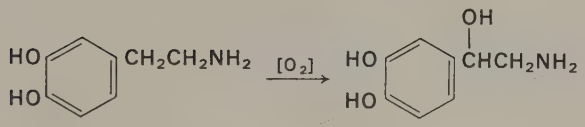
(102)



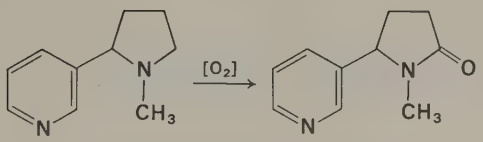
(103)



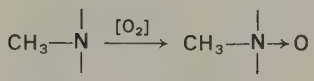
(104)



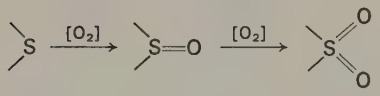
(105)



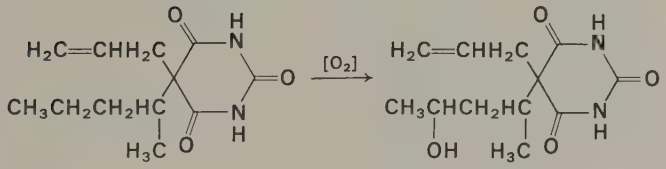
(106)



(107)

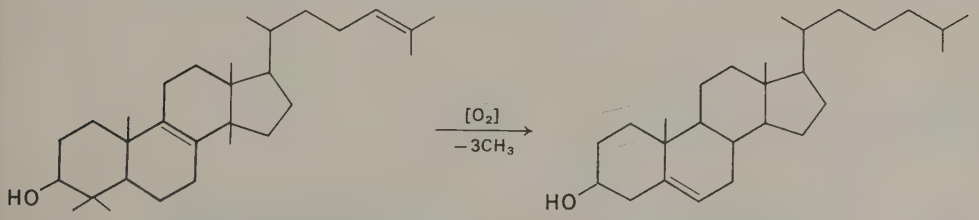


(108)



(109)

3. Oxidation with loss of the oxidized group:



Lanosterol Cholesterol (110)

The intimate mechanisms (at the bond-breaking and bond-forming level) of many of these reactions are not understood in complete detail. In most cases the enzymes or enzyme systems are known and characterized, and the coenzymes (prosthetic groups) have been identified, but in many cases it is only the overall transformation that can be formulated in precise structural terms.

Certain theories have been proposed for some of these reactions, but for the most part remain to be proved in detail. Let us consider the general reaction for introduction of oxygen. This can be formulated

$$S + NADH + H^+ + O_2 \longrightarrow SO + NAD^+ + H_2O \qquad (111)$$

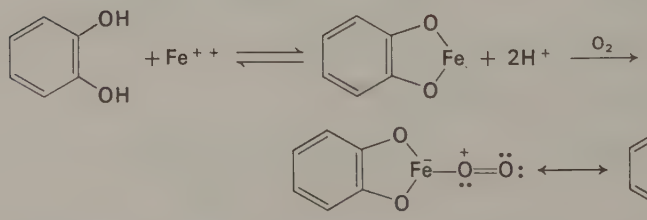
where S is the substrate being oxidized and SO its oxygenated (for example, epoxidized or hydroxylated) product. Experiments with labeled reactants have shown that the oxygen atom of SO derives from molecular oxygen:

$$S + NADH + H^+ + {}^{18}O_2 \longrightarrow S{}^{18}O + NAD^+ + H_2{}^{18}O \qquad (112)$$

What is the mechanism by which the oxygen molecule is separated into the constituent atoms? What is the nature of the reaction step or steps in which the O═O bond is broken?

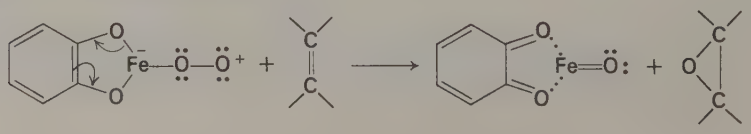
Studies on non-enzymatic model systems have led to the proposal that the transfer of oxygen takes place within a complex composed of a metal ion, an enediol (such as 1,2-dihydroxybenzene), and oxygen. The actual transfer involves the separation of an O—O bond, with $\ddot{\underset{\cdot\cdot}{O}}:$ being furnished to a nucleophile (for example, a carbon-carbon double bond). It will be recognized that the (hypothetical) electron-deficient oxygen atom would be a strongly electrophilic species. The complete process can be formulated as follows, using epoxidation as an example, with iron as the metal:

(*a*) Formation of an oxygenated complex



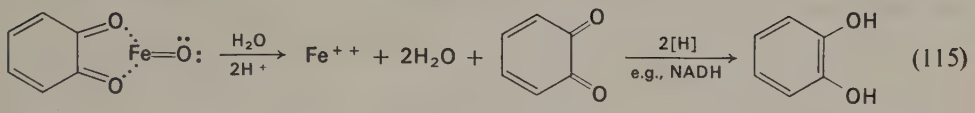
(113)

(*b*) Transfer of O to a nucleophile



(114)

(*c*) Regeneration of the original enediol



(115)

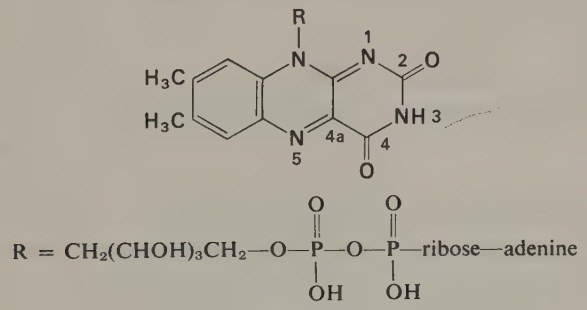
The role of the NAD^+-NADH hydrogen-transfer system is therefore to reduce the *o*-quinonoid product back to the original 1,2-dihydroxy compound, with no overall change in the oxidation state of Fe^{++}. This concept provides an attractive hypothesis into which many oxygenase reactions can be rationalized, but it should be borne in mind that it has not been established as the true biological process.

The α,β-dehydrogenation of fatty acids as the first step in their metabolic degradation to acetyl CoA involves the enzymatic reaction

$$RCH_2CH_2COSCoA \xrightarrow{FAD} RCH{=}CHCOSCoA + \text{reduced FAD} \qquad (116)$$

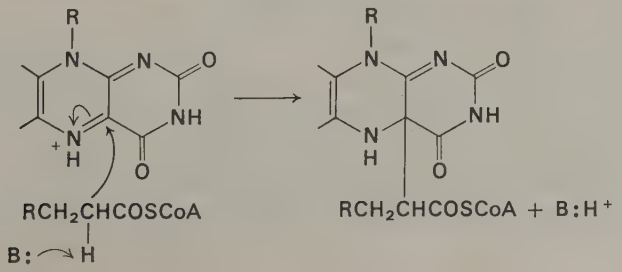
This and related reactions require the —SCoA acyl derivative; they do not occur with the free acid. Since the —SCoA grouping is not altered in the reaction, it can be suggested that the role of the —COSCoA function is to activate the α hydrogen atom of $RCH_2CH_2COSCoA$; that is, to make possible the formation of the α-carbanion.

FAD, flavin adenine dinucleotide, has the structure



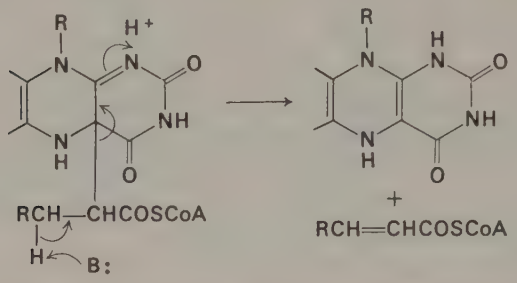
(117)

It will be observed that the $-\overset{5}{N}{=}\overset{4a}{C}-$ grouping is that of a Schiff base so that (particularly in its protonated form) it could undergo addition of the anionic α carbon atom of $RCH_2CH_2COSCoA$ in a reaction resembling the initial step of an aldol-like (or Claisen-like) condensation. Using only the relevant portion of FAD, and omitting intermediate ionic steps, this can be formulated



(118)

Formation of the α,β double bond can now proceed by acid-base catalysis in a conventional manner:



(Reduced FAD) (119)

(Dehydrogenated product)

This hypothesis can be applied to the dehydrogenation by FAD enzymes of other systems of the general type

$$-\overset{|}{C}H-YH \xrightarrow{FAD} -\overset{|}{C}=Y + FADH \qquad (120)$$

where Y represents a nucleophilic atom capable of attacking the protonated FAD at the 4a position as in the above equations.

Exercise 16

How could the formation of an α-keto acid from an α-amino acid be formulated, using the above as a model of the dehydrogenation step?

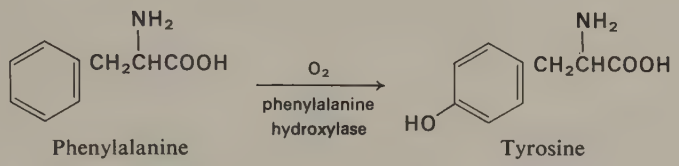
It is beyond the scope of this treatment to describe the details of the various enzymes that are known to catalyze reactions of the kinds alluded to above. It is important to note, however, that large groups of enzymes of disparate biological function often contain a common prosthetic group (for example, NAD or FAD), and to recognize the unique mechanistic function of the prosthetic group as distinct from the catalytic role of the total enzyme system.

36-19 Biological hydroxylation of aromatic compounds

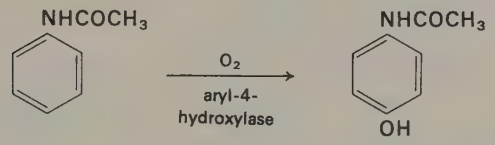
The widespread occurrence and metabolic importance of phenolic compounds in both animals and plant materials has led to extensive studies of their biosynthetic origins. Natural phenols can be classed broadly in two groups: (1) those in which the phenolic hydroxyl groups represent oxygen present at early, pre-aromatic stages of synthesis; and (2) those in which oxygen has been introduced into an aromatic substrate.

In the latter case, oxygen is introduced from *molecular oxygen* in an enzymatically catalyzed process. The enzymes are called mono-oxygenases or, more simply, hydroxy-

lases. Two relatively simple examples of the reaction are the hydroxylation of phenylalanine to tyrosine, a process of central importance in aromatic amino acid (and thus, protein) synthesis; and the hydroxylation of a "foreign" compound, acetanilide, to *p*-hydroxyacetanilide.



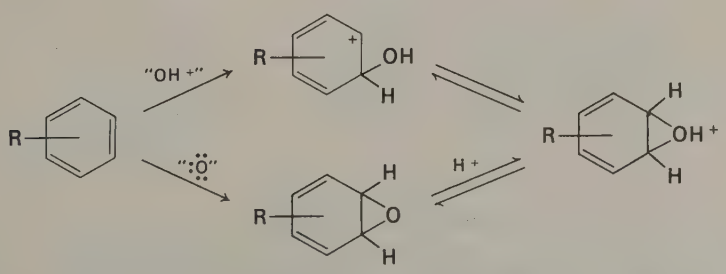
Phenylalanine Tyrosine (121)



p-hydroxyacetanilide (*p*-acetaminophenol) (122)

The detailed mechanisms of these oxidation reactions with respect to the precise role of the enzyme and the actual bond-making processes at the molecular level are not known with certainty. That they are not the same for all aromatic hydroxylation reactions is indicated by the fact that the enzyme prosthetic groups are not the same in every case. Some enzymes are metal-containing (copper, iron), others do not appear to contain metals.

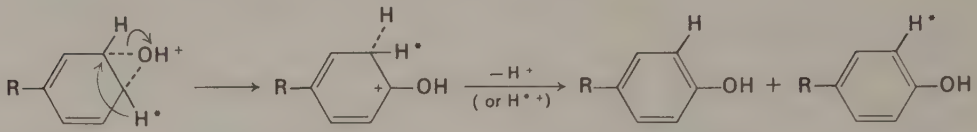
It is probable, however, that a step common to many aromatic hydroxylation reactions is the donation of electron-deficient oxygen to the ring. This can be viewed as taking place by direct electrophilic substitution by attack of the (hypothetical) equivalent of HO^+; or by the formation of an intermediate unstable epoxide. The latter course has been demonstrated by the identification of a 1,2-dihydroxy-1,2-dihydroaromatic compound as the intermediate in the enzymatic oxygenation of naphthalene. It will be observed that the electrophilic introduction of HO^+ and epoxidation followed by protonation are essentially equivalent:



(123)

Either of these intermediate steps can accommodate an interesting observation

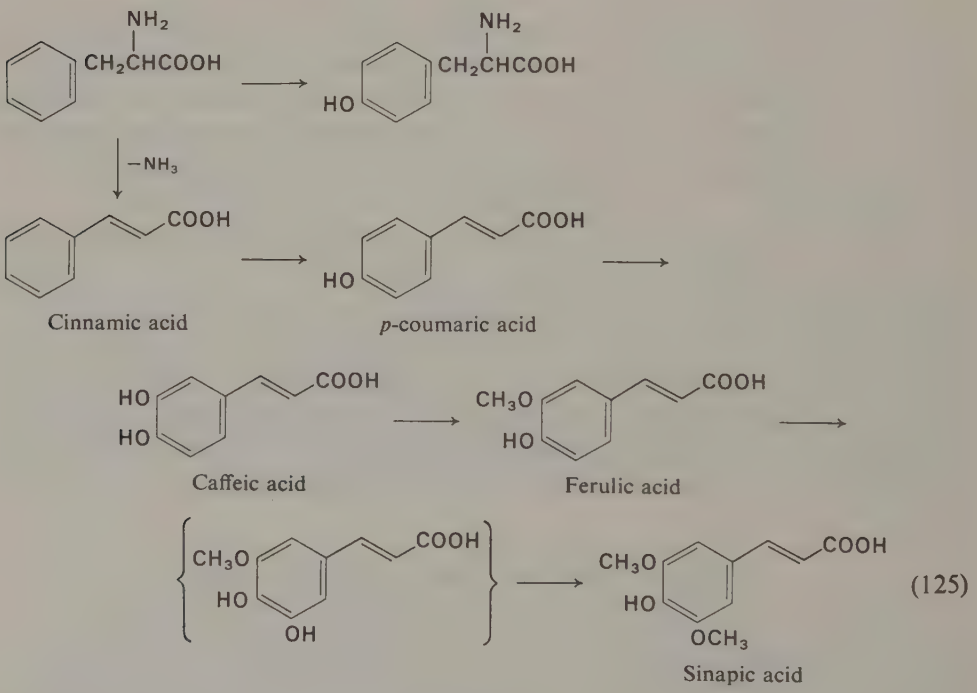
that has been made in studies of the hydroxylation reaction. This is the so called "NIH shift":*



(124)

When the starred hydrogen atom (H*) is labeled—for example, when it is tritium or deuterium—it can be found in the position adjacent to that at which hydroxylation occurs; that is, when the labeled hydrogen is originally *para*, and hydroxylation is *para*, labeled hydrogen is found in the *meta* position.

Successive hydroxylations can occur, leading from *p*-hydroxy to 3,4-dihydroxy and 3,4,5-trihydroxy compounds. Experiments in which isotopically labeled compounds were administered to living plants have demonstrated that the following transformations occur *in vivo*:†

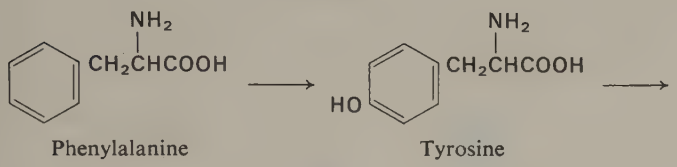


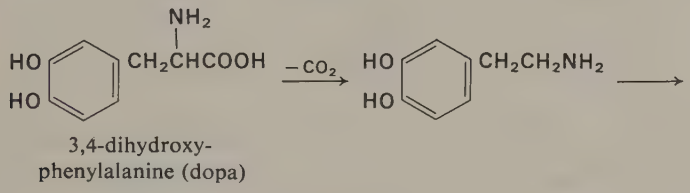
(125)

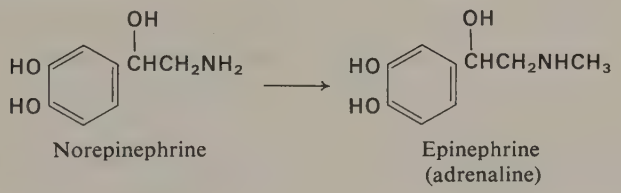
* This shift was first observed in studies carried out at the National Institutes of Health (NIH).

† The loss of ammonia and the *O*-methylation of aromatic hydroxyl groups at intermediate stages of this synthetic series are concomitant processes not directly related to the hydroxylation reaction itself.

The biosynthesis of the important hormones norepinephrine and epinephrine follows a related course (and includes an additional step of hydroxylation of the $-CH_2-$ group of the side chain):







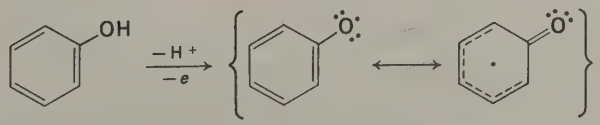
(126)

36-20 Phenol oxidative coupling reactions

One of the most widely occurring oxidation reactions of nature, and one that can be carried out in the laboratory with unexceptional reagents, is the overall two-electron oxidation reaction in which two phenolic compounds are coupled by carbon-carbon or carbon-oxygen bonds.

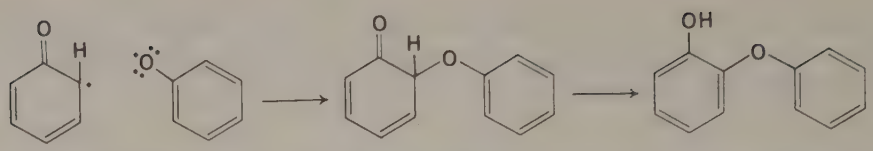
These reactions can be interpreted in either of two ways; but it is still not established which of the two mechanisms to be described is the correct one (or whether both are valid, depending upon the particular circumstances of the reaction).

1. The one-electron (radical) mechanism. In this mechanism each of the two phenolic nuclei suffers a one-electron oxidation, followed by a coupling of the resultant free radicals. Using phenol itself as the example, the reaction is pictured as follows:



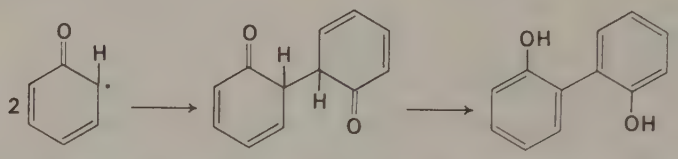
(127)

Phenoxyl radical



(128)

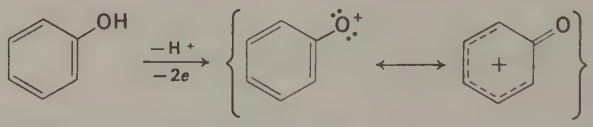
A step corresponding to (128), but in which *para* coupling (C—O bond formation) takes place, is equally valid:



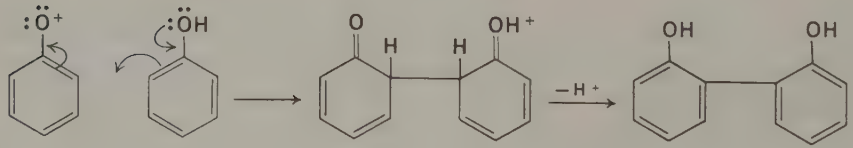
(129)

Electron spin resonance (ESR) measurements have shown that free aroxyl radicals (Ar—$\ddot{\underset{\cdot\cdot}{O}}$:) are indeed formed in phenol oxidations by one-electron oxidants such as ferric ions. Such measurements do not, however, establish that the aroxyl radicals immediately couple, rather than losing a second electron to produce a positively charged "-onium" species. The latter course is illustrated by mechanism 2.

2. The two-electron (per molecule) mechanism. In this process, the removal of two electrons from one phenol molecule generates the electrophilic *phenoxonium* ion. This then attacks a neutral phenol molecule by an electrophilic substitution mechanism:

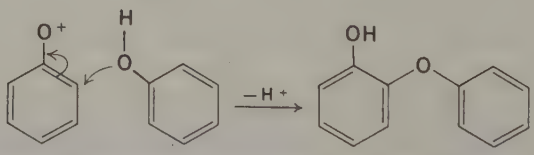


(130)



(131)

or



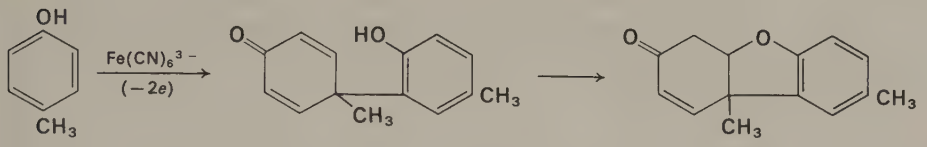
(132)

Again, coupling at the *para* position [step (132)] is equally valid.

Since it is apparent that either mechanism 1 or mechanism 2 is a satisfactory formulation of the coupling process (so far as the overall reaction is concerned, they are equivalent) and since there is no firm experimental evidence for the correctness of one over the other, the examples to be presented will be couched in terms of mechanism 2. The two-electron mechanism provides for the direct application of the princi-

ples of electrophilic aromatic substitution; and a reaction written in terms of mechanism 2 can, if desired, be readily reformulated in terms of mechanism 1.*

Let us examine a specific example of this oxidative coupling reaction. The oxidation of *p*-cresol with potassium ferricyanide yields the coupled product known as *Pummerer's ketone*:



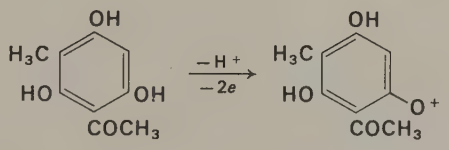
Pummerer's ketone

(133)

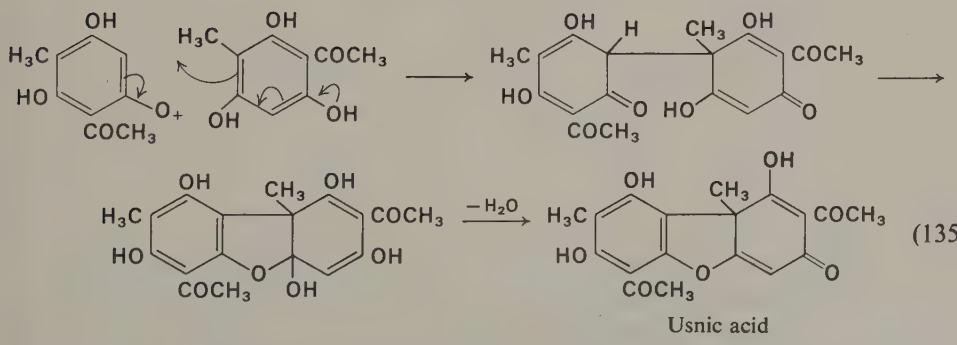
Exercise 17

Formulate the reaction leading to Pummerer's ketone by both the one-electron (mechanism 1) and the two-electron (mechanism 2) route.

The reaction leading to the formation of Pummerer's ketone is the simple prototype of an oxidative phenol coupling reaction by which *usnic acid*, a constituent of certain lichens, is formed in nature. The reaction is formulated according to mechanism 2:



(134)



(135)

Usnic acid

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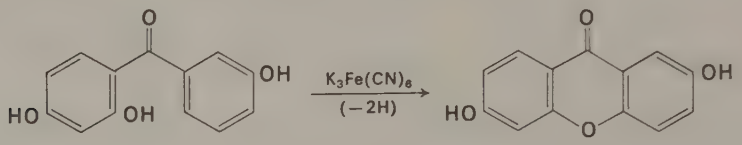
* Although it could be argued in favor of the one-electron mechanism that the reactions are often carried out with the aid of one-electron oxidants (for example, ferric salts, as in $Fe^{3+} \rightarrow Fe^{2+}$), such one-electron oxidizing agents are also widely used to perform oxidations involving an overall two-electron change in which radical mechanisms are not invoked.

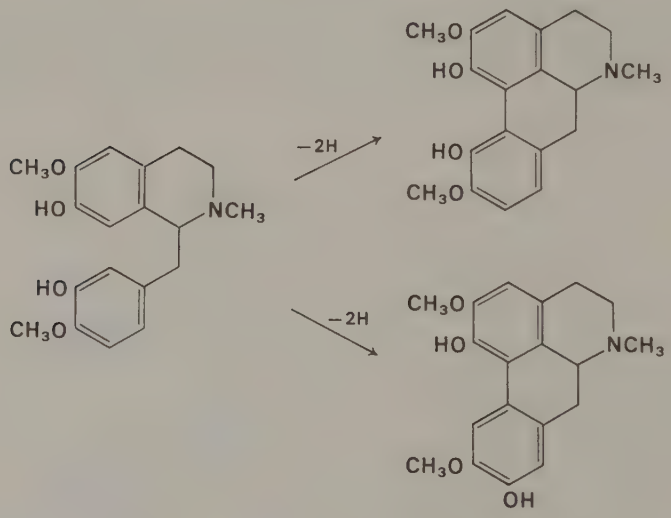
It is apparent that usnic acid ($C_{18}H_{16}O_7$) is an oxidative dimer of 3-methyl-2,4,6-trihydroxyacetophenone; namely, $2C_9H_{10}O_4 - 2H - H_2O = C_{18}H_{16}O_7$. The acidic character of usnic acid is due to the fact that it is a triketone [in the right-hand ring as shown in (135)] containing the structural unit $CH(CO)_3$ [written in (135) in the enolic form, in which the —OH group is acidic].

Intramolecular oxidative phenol coupling reactions are common in nature. A simple example that proceeds readily *in vitro*, and may be considered the prototype of many naturally occurring processes, is the following:



(136)

Oxidative coupling, with the formation of a carbon-carbon bond, occurs in the natural syntheses of *aporphine* alkaloids from 1-benzyltetrahydroisoquinolines. In the following example, note that the coupling may proceed either in the *ortho* or the *para* manner, to give aporphines with different patterns of substitution:



(137)

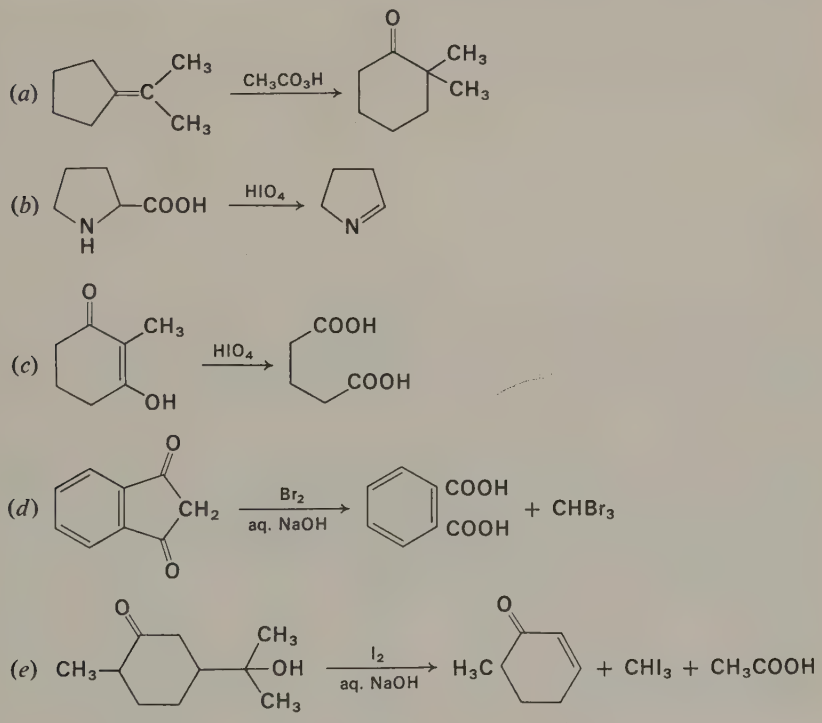
Although many reactions such as those described in the foregoing discussion have been carried out in the laboratory with a variety of oxidizing agents, the natural processes are, of course, enzymatically catalyzed by biological oxidizing systems, often of an unknown kind. The biological oxidants may in some (or all?) cases be enzymes containing metals that act as electron-transfer systems similar to the ferric-ferrous system used in *in vitro* experiments.

Exercise 18

Formulate the ring closure reactions of (136) and (137) by both the aroxyl radical (mechanism 1) and the aroxonium ion (mechanism 2) route.

Problems

1. Suggest reasonable mechanisms for the following oxidative transformations:



37

Biological compounds. Primary and secondary metabolism

The cells of living organisms of all kinds, from single-celled protozoa to the multicelled higher organisms, are the sites of an intense synthetic activity in which organic compounds are made, transformed, and degraded, perform essential roles in growth and reproduction, and contribute in innumerable ways to the survival and evolution of species. Many of these compounds are of rather simple constitution and are common to living cells of all kinds: they are the stuff of life itself, and cannot be used to distinguish, say, a plant from an animal, or a frog from an elephant. It is true that if we examine the fine structure of certain protein molecules we can distinguish not only phyla but often even species or individuals; yet the gross structures of these protein molecules, their component parts, and the manner in which they are synthesized are essentially the same.

We have already studied some compounds of biological importance; for example, the carbohydrates, the fats, and fatty acids. In this chapter we shall examine other organic compounds that make up the living cell, and inquire into how their structures have been established and how they are synthesized. Our concern here, as in other parts of this book that deal with biological substances, will be how the organic chemist attacks the questions of their constitution. What may be called the *biochemistry* of these compounds depends for its study upon their *organic chemistry*. Our emphasis will be upon their chemical properties as revealed by the nature of their functionality and their molecular structure. It will be observed that nearly all of the chemistry of the functional groups of these compounds has already been encountered

in earlier chapters, and that the study of biologically important compounds is for the most part the application of familiar principles of organic reactions in a special context. This chapter, then, deals with a realm that is both organic chemistry and biochemistry, at the interface between these two areas of study.

37-1 Primary and secondary metabolites

The cells of living organisms are the scene of an incredibly varied chemical activity. Chemical compounds as simple as carbon dioxide and acetic acid and as complex as high-molecular-weight proteins are synthesized, degraded, and used as the starting materials for intricate syntheses. While most of these reactions are under the control of catalytic enzyme systems, nearly all of them can be looked at in a more abstract way; namely, in terms of the organic molecules that act as substrates and whose reactions can be studied in terms of the basic mechanistic principles underlying organic reactions of all kinds.

The chemical compounds found in living organisms may be broadly grouped into two main classes:

1. *Primary metabolites* include those compounds that are found in living matter of all kinds—microorganisms, algae, fungi, plants, and invertebrate and vertebrate animals. Since the basic structure of the living cell comprises proteins and nucleic acids, the most universal of primary metabolites are the twenty-odd amino acids of which proteins are constructed and the few purines, pyrimidines, and five-carbon sugars that make up the nucleic acids.

In addition to these, the simple and familiar six-carbon atom sugars, the low-molecular-weight carboxylic acids formed in carbohydrate metabolism, and the fatty acids are universal participants in all cellular metabolism. These compounds constitute the basic chemical machinery by which living things operate. They are called primary metabolites because they do not differ among organisms, but underlie the chemical activities of life of all kinds.

2. *Secondary metabolites* (Chapter 38) are usually more complex in structure and are for the most part characteristic of particular kinds of organisms, or of specific phyla, genera, or species of plants and animals.

There is of course not always a clear dividing line between primary and secondary metabolites. Chlorophyll, for instance, is a universal constituent of higher plants, and so possesses the quality of ubiquity that characterizes primary metabolites. Yet its absence from bacteria, fungi, and animals sets it apart from such compounds as the amino acids and sugars that all cells contain.

In general, it can be said that the "natural products" whose study has traditionally been the domain of the organic chemist represent what are ordinarily regarded as

secondary metabolites. Plant and animal pigments, unusual sugars, alkaloids, terpenes, many steroids, phenolic glycosides, and a host of compounds of unique and unusual structures reflect the genetic individuality of genera, species, and individuals. It would be a mistake, however, to say that all secondary metabolites are unique and unusual organic compounds of complex structures. So simple a compound as methane is the product of some microbiological degradation processes; ethylene is not only a product of cellular metabolism of many fruits, but is also involved in the regulation of their respiration; simple esters of low-molecular-weight alcohols and acids are common constituents of the fragrant volatile principles of flowers and fruits; and many simple benzene derivatives abound in nature.

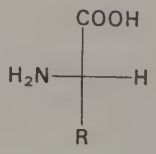
While the study of the chemical behavior of secondary metabolites is ordinarily regarded as falling within the area known as organic chemistry, and the study of their biosynthesis, metabolic function, and physiological significance in the area known as biochemistry, it must be recognized that there can be no discontinuity between these two areas and that there is a large region in which "organic" and "biological" chemistry are indistinguishable. It behooves the student of biological science, therefore, to regard organic chemistry in all of its aspects as an indispensable foundation for the study of life processes.

There are a number of compound classes whose importance is so great that they deserve special consideration. *Proteins* are the universal constituents of all living matter, from viruses to man, and thus have been the subject of special study. Since proteins (which include such specialized compounds as enzymes, antibodies, and certain hormones) are made up of combinations of some twenty-odd *α-amino acids*, these too deserve particular attention.

37-2 Amino acids

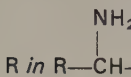
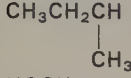
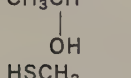
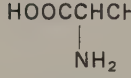
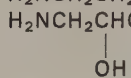
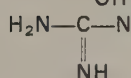
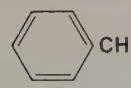
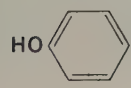
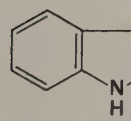
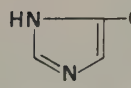
Hydrolysis of proteins, which are linear polyamides called *polypeptides*, yields a mixture of about 20 amino acids. Not every protein contains all of the known amino acids. Some proteins contain very high proportions of certain ones, and other proteins are deficient in some amino acids. For example, silk fibroin contains 44% glycine and 2% glutamic acid; egg albumin contains 3% glycine and 17% glutamic acid; and gelatin contains 26% glycine and 11% glutamic acid.

Nearly all of the amino acids found in proteins are α-amino acids of the general structure and stereochemistry

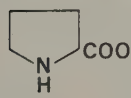
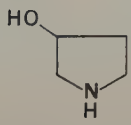


(1)

Table 37-1
The common amino acids derived from proteins

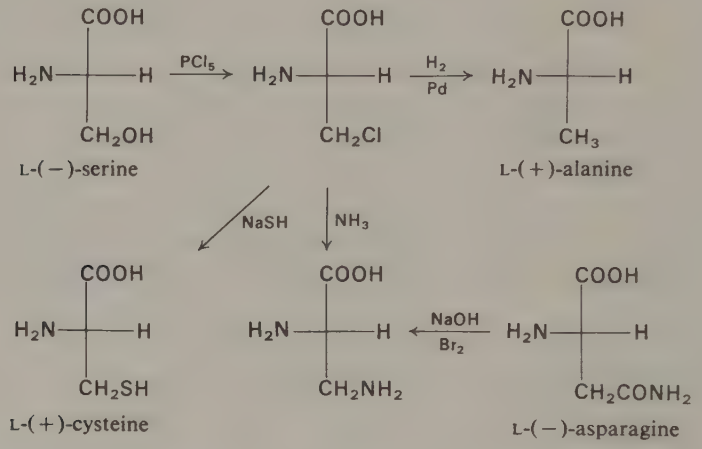
R *in* 	*Name of amino acid*
H	glycine
CH_3	alanine
$(CH_3)_2CH$	valine
$(CH_3)_2CHCH_2$	leucine
	isoleucine
$HOCH_2$	serine
	threonine
$HSCH_2$	cysteine
	cystine
$CH_3SCH_2CH_2$	methionine
$HOOCCH_2$	aspartic acid
H_2NCOCH_2	asparagine (the amide of aspartic acid)
$HOOCCH_2CH_2$	glutamic acid
$H_2NCOCH_2CH_2$	glutamine (the amide of glutamic acid)
$H_2NCH_2CH_2CH_2CH_2$	lysine
	hydroxylysine
	arginine
	phenylalanine
	tyrosine
	tryptophane
	histidine

In addition to these:

	proline
	hydroxyproline

With the exception of glycine (R = H), all of the amino acids derived from proteins are optically active; they belong to the L series and most have the S configuration. Table 37-1 shows the structures of the common protein-derived α-amino acids, all of which are commonly referred to by non-systematic names.

The configurational relationships of the natural amino acids have been established by interconversions that relate them finally to L-glyceraldehyde. An example of a series of interconversions that shows the stereochemical relationships among several amino acids is the following:



(2)

It will be seen that, as in the case of sugars, the configurational designation (L or D) bears no relationship to the sign of the optical rotation.

D Amino acids are also known in nature, but not as constituents of normal proteins. A number of them are found in certain polypeptide antibiotics and as elements of cell-wall constituents of bacteria. The antibiotic Gramicidin-S, for instance, is a polypeptide consisting of ten amino acid units, one of which is D-phenylalanine; the other nine are L amino acids.

37-3 Chemical properties of amino acids*

Amino acids show the chemical behavior that would be expected from the presence of the amino and carboxyl groups. They can be *N*-acylated, *N*-alkylated, esterified, and reduced to amino alcohols (with lithium aluminum hydrides)—all unexceptional reactions that have been discussed in detail earlier. But certain aspects of the chemical behavior of amino acids have special importance.

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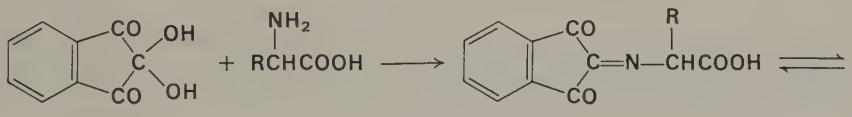
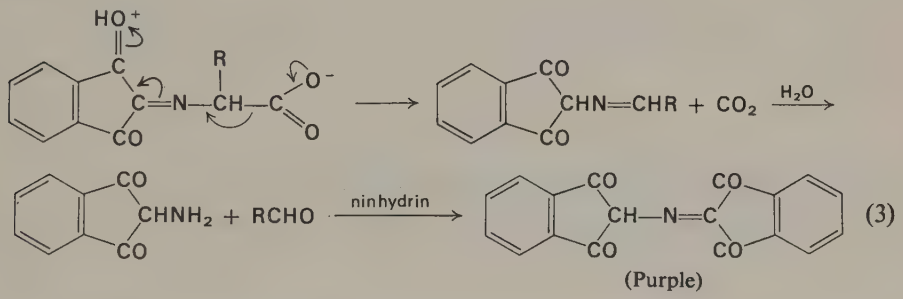
* Unless specifically indicated to the contrary, the term "amino acids" will refer to the α-amino acids.

The ninhydrin reaction. The reaction of amino acids with triketohydrindene hydrate (ninhydrin) is of special importance for the qualitative detection and quantitative estimation of amino acids. It depends upon the oxidation of the amino acid to the corresponding aldehyde, followed by the formation of a deeply colored condensation product; these reactions are shown in the following scheme:



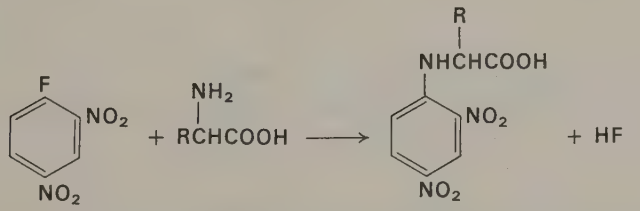
Ninhydrin



(3)

The ninhydrin reaction is widely used to disclose the location of amino acids on paper and thin-layer chromatograms. The chromatogram is sprayed with a solution of ninhydrin and then heated; amino acids are revealed by the appearance of red to violet spots.

Reaction with 2,4-dinitrofluorobenzene. The ready nucleophilic displacement of fluorine by attack of bases upon 2,4-dinitrofluorobenzene is exemplified in the following reaction with an amino acid:

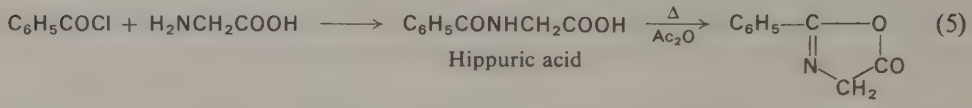


(4)

The *N*-dinitrophenyl derivatives are stable to acidic hydrolysis. They are valuable for identification, and play a special role in the determination of protein structure (Section 37-7).

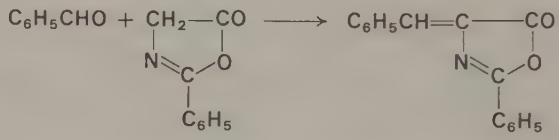
Reactions in which —NH_2 and —COOH take part to form cyclic compounds. *N*-Acylation of α-amino acids by a variety of reagents leads to compounds that are capable of undergoing subsequent rection leading to ring closure.

A useful application of this reaction is the preparation and cyclization of *N*-benzoylglycine (hippuric acid):



(5)

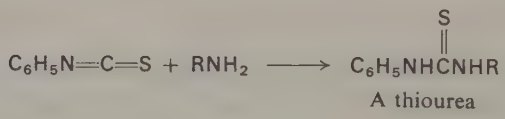
The oxazolone (usually called an *azlactone*) possesses the special property that the —CH_2— group is sufficiently active to be condensed with an aldehyde in an aldol-like reaction:



(6)

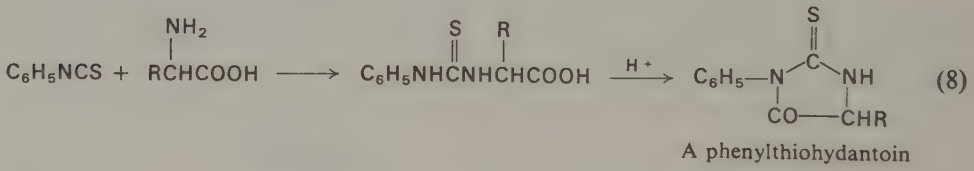
Further reference to this condensation will be made in Section 37-5.

The reaction of amines with phenyl isothiocyanate is a general reaction:



(7)

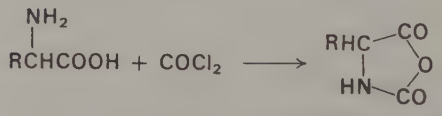
Formation of the corresponding derivative of an amino acid occurs in the same way, but the thiourea so formed can be cyclized by treatment with acids:



(8)

This reaction can also be used in the analysis of polypeptide structure (see Section 37-7).

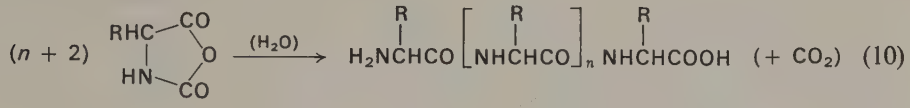
Leuchs anhydrides. An interesting and useful amino acid derivative is formed by the reaction of an amino acid with phosgene:



An oxazolidinedione
(a Leuchs anhydride)

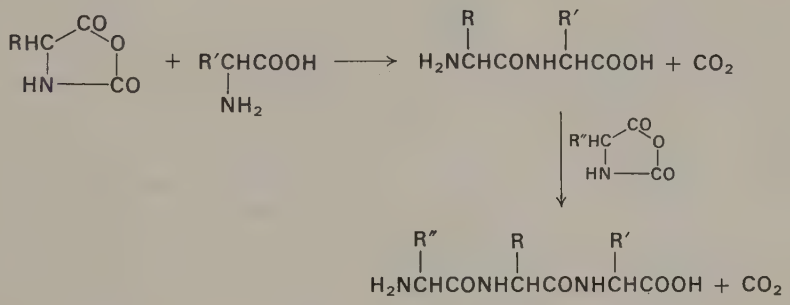
(9)

When a Leuchs anhydride is heated with a trace of water, it polymerizes to form a long-chain polypeptide:



The polypeptides formed in this way are of course composed of only one amino acid monomer, and thus differ from natural polypeptides, which are composed of many different amino acid units.

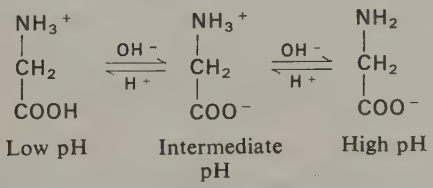
Reaction of a Leuchs anhydride with a second amino acid can lead to dipeptide formation; reaction of this dipeptide with another Leuchs anhydride can give a tripeptide; and so on:



This method of polypeptide synthesis is frequently used but has practical limitations, one of which is the contamination of the desired polypeptide by polymers of the anhydrides.

37-4 Physical properties of amino acids

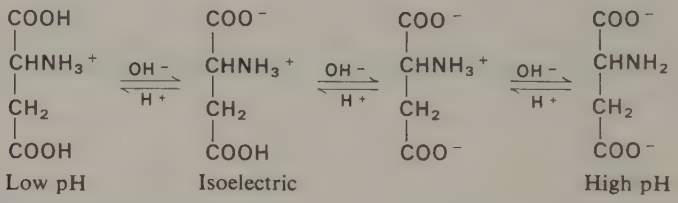
Amino acids are both amines and carboxylic acids, and thus can undergo acid-base proton-transfer reactions of two kinds. For example, consider glycine:



The intermediate species has no net charge; it is called a *zwitterion*, and the pH at which its concentration is maximum is called the *isoelectric point* (pI). Amino acids that contain no additional acidic or basic functions have isoelectric points in the

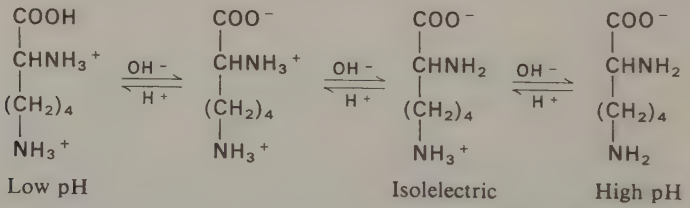
region of pH 5–7. In aqueous solution they exist in the zwitterionic form. For this reason, most amino acids are salt-like, in that they are soluble in water, insoluble in non-polar solvents such as benzene and ether, have relatively high melting points, and are quite involatile.

Some amino acids possess a second —COOH group (glutamic acid, aspartic acid) or a second basic function (—NH_2 in lysine, —C(=NH)NH_2 in arginine). These have isoelectric points below or above those of simple amino acids. Aspartic acid shows the following proton-transfer equilibria:



(13)

Lysine behaves as follows:



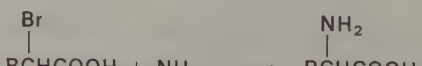
(14)

The pI values for alanine, aspartic acid, and lysine are 6.00, 2.77, and 9.74.

37-5 Synthesis of amino acids

Amino acids, some of which are commercially valuable as dietary additives, can be prepared by various synthetic procedures, as well as by isolation from certain natural sources. L-Glutamic acid is obtained from soybeans, and L-cystine from animal hair. However, most amino acids are prepared synthetically. A wide variety of synthetic methods have been developed; some of those more often employed are the following.

Reactions of amines with α-halogen acids. Reaction of an α-bromocarboxylic acid with ammonia results in direct displacement of —Br by —NH_2:

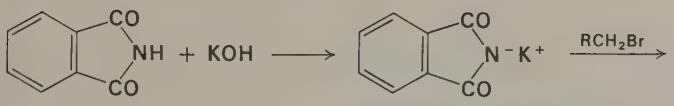


(15)

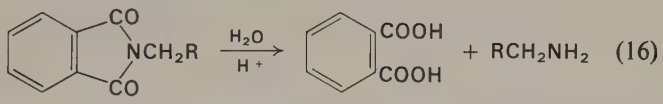
Exercise 1

Undesired by-products may also be formed in this reaction. What are they, and how would you select experimental conditions to minimize them?

A variant of this procedure in which secondary and tertiary by-products are not formed is the *Gabriel synthesis*. This method is a general one for the preparation of primary amines and can be formulated by the general expression



Potassium phthalimide



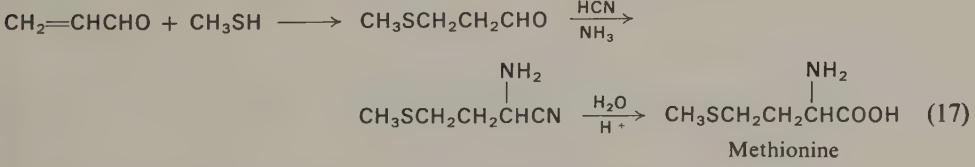
(16)

When the halide is an α-bromo acid, the product is the corresponding amino acid.

Exercise 2

Write the equations for the Gabriel synthesis of (*a*) 2-aminobutane, (*b*) glycine, (*c*) phenylalanine, and (*d*) benzylamine.

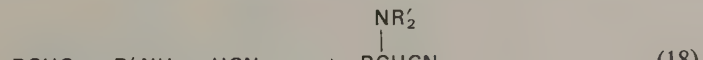
The Strecker synthesis. The addition of HCN and ammonia to an aldehyde yields an α-amino nitrile, acid-catalyzed hydrolysis of which gives the α-amino acid. This method is employed in the synthesis of nutritionally important *methionine*:



Methionine

(17)

Substituted amines may be used in the same way:

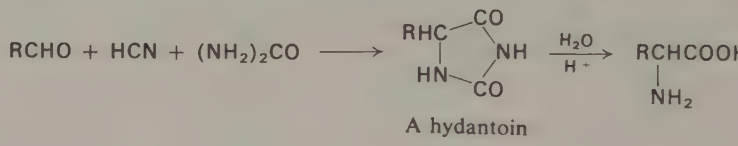


(18)

Exercise 3

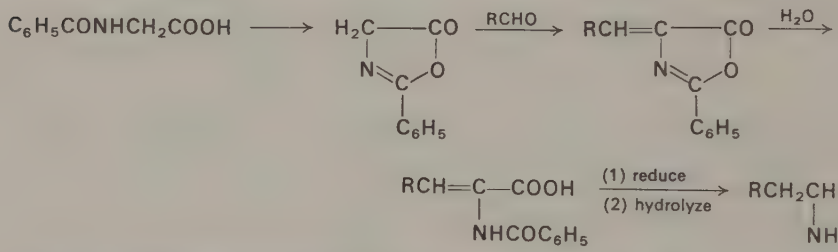
Write a reasonable mechanism for the reaction of an aldehyde with HCN and dimethylamine to give an α-dimethylamino nitrile.

A modification of the Strecker synthesis yields an intermediate *hydantoin*, hydrolysis of which gives the amino acid:



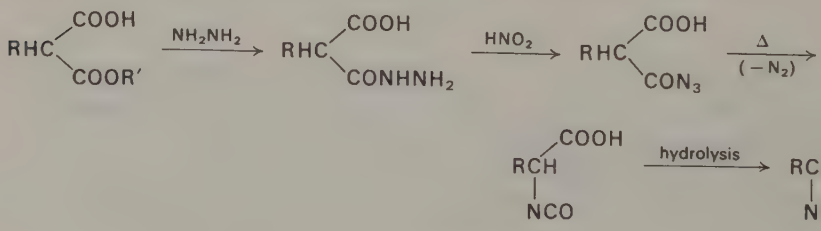
A hydantoin (19)

The Erlenmeyer (azlactone) synthesis.

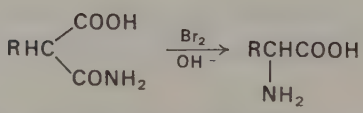


(20)

Curtius, Hofmann, and Schmidt reactions. The Curtius (21) and Hofmann (22) rearrangements (Chapter 34) involve the overall transformation $RCOOH \rightarrow RNH_2$. When applied to 1,1-dicarboxylic acids, they lead to α-amino acids:

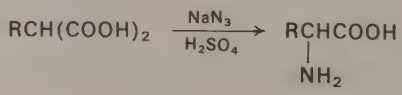


(21)

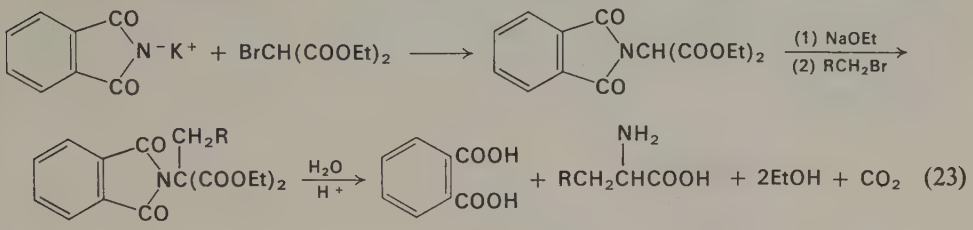


(22)

The Schmidt reaction can also be used; it proceeds as follows:



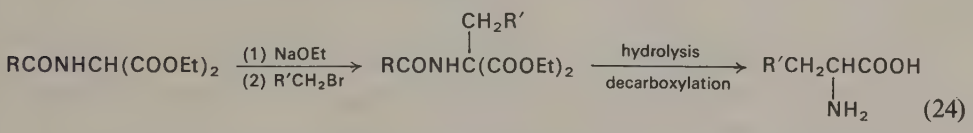
Alkylation of α-aminomalonic acid derivatives. The reaction of potassium phthalimide and a bromomalonic ester yields an *N*-substituted malonic ester that still contains an active α hydrogen atom, and that can therefore be alkylated in the usual way:



(23)

The most common manner of applying this synthetic principle is with an α-acetamidomalonic ester, $CH_3CONHCH(COOR)_2$, which is prepared by the reduction of a nitromalonic ester and acetylation of the resulting α-amino ester. Other α-acylaminomalonic esters (for example, *N*-benzoylamino, *N*-formylamino) are also used.

The general procedure is as follows:

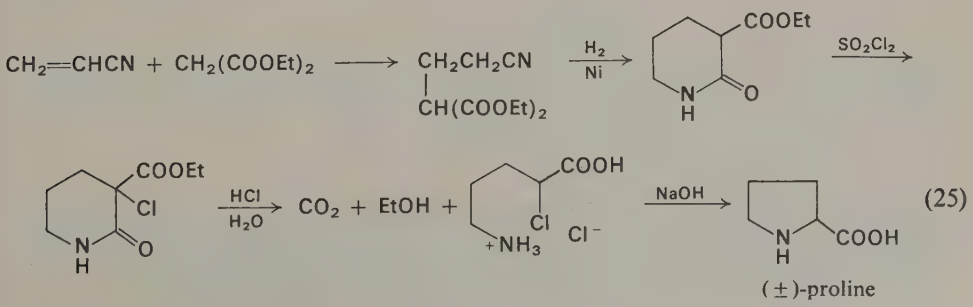


(24)

Exercise 4

By each of the synthetic methods described above, show how you could synthesize the following amino acids, using any starting materials that you regard as reasonably available: (*a*) tyrosine, (*b*) leucine, (*c*) ethionine ($EtSCH_2CH_2CH(NH_2)COOH$), (*d*) glycine, (*e*) *N*,*N*-dimethylglycine, (*f*) phenylalanine, (*g*) valine.

Miscellaneous methods. Numerous other procedures, some of general application, others of a unique character, are available for amino acid synthesis. An example of a special synthesis is that of proline:

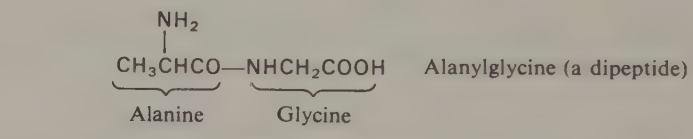


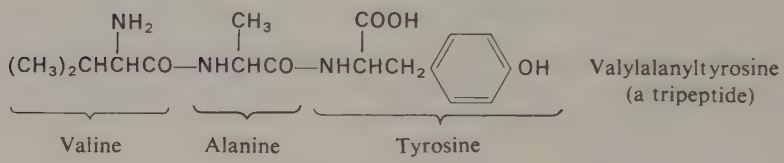
(25)

(±)-proline

37-6 Polypeptides and proteins

The *peptide* linkage is formed by joining the amino group of one amino acid with the carboxyl group of another; it is an *amide* linkage. Since amino acids are bifunctional, they may be joined to each other in chains consisting of two, three, four, or many peptide units. Compounds of this kind are called dipeptides, tripeptides, tetrapeptides, and polypeptides:



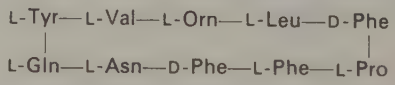


Proteins are polypeptides consisting of many amino acids joined in this way. Their molecular weights range from a few thousand to several million. There is no sharp division between proteins and polypeptides of lower molecular weights.

Nature affords many polypeptides of intermediate molecular weight; that is, containing about ten to forty amino acid units. Many of these have important physiological functions, ranging from the regulation of blood pressure to oxytocic and antibacterial activities. A representative polypeptide in this group is the nonapeptide *bradykinin*, a hypotensive agent:*

Arg—Pro—Pro—Gly—Phe—Ser—Pro—Phe—Arg

The antibacterial agent *tyrocidin* is a cyclic decapeptide of the following structure:†



The adrenocorticotrophic hormone (ACTH) that stimulates the metabolic activity of the adrenal cortex is a polypeptide consisting of thirty-nine amino acids.

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* Polypeptide structures are conveniently represented with abbreviations of the names of the constituent amino acid units: alanine = Ala, leucine = Leu, tyrosine = Tyr, and so on. For a list of these see L. Stryer, *Biochemistry*, p. 17, W. H. Freeman and Company, San Francisco, 1975.

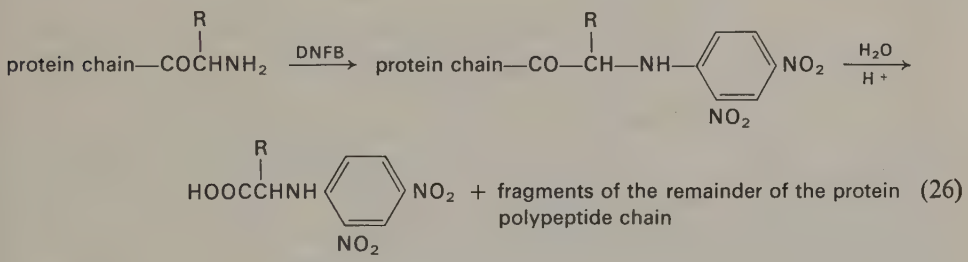
† "Orn" represents the amino acid *ornithine*, $H_2N(CH_2)_3CH(NH_2)COOH$.

37-7 The structure of polypeptides

Complete hydrolysis of a polypeptide into its constituent amino acids is the first step in establishing its structure. This procedure is ordinarily coupled with the quantitative determination of the individual amino acids. This is best accomplished by chromatographic separation of the amino acids on an ion-exchange column and measurement of the intensity of color produced by treating each fraction with ninhydrin. Alternatively, the amino acid mixture may be separated by two-dimensional paper or thin-layer chromatography, and the individual spots eluted and measured by the use of a color-forming reagent.

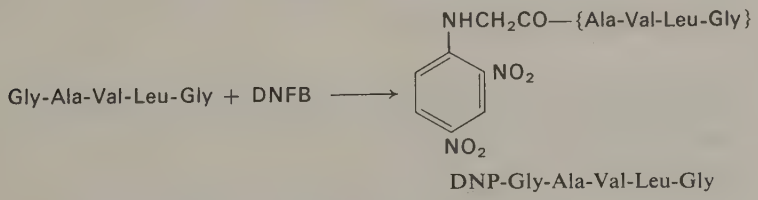
Of course, such analyses do not reveal the more important feature of polypeptide structure—*the sequence of amino acids* in the polypeptide chain. The determination of sequence is very simple in principle: the amino acids are removed and identified one at a time. This can be done in practice, but a modified procedure can also be employed.

2,4-Dinitrofluorobenzene (DNFB) reacts with compounds containing amino groups in the manner described in Chapter 30. When DNFB reacts with the amino group at the end of a polypeptide chain, and the resulting derivative is hydrolyzed, the DNP (dinitrophenyl) derivative of the terminal amino acid is formed and can be isolated:



(26)

Partial hydrolysis leads to di-, tri-, and larger peptides attached to the dinitrophenyl group, each of which defines a small portion of the whole polypeptide chain. For example, consider the pentapeptide glycyl-alanyl-valyl-leucyl-glycine:



DNP-Gly-Ala-Val-Leu-Gly

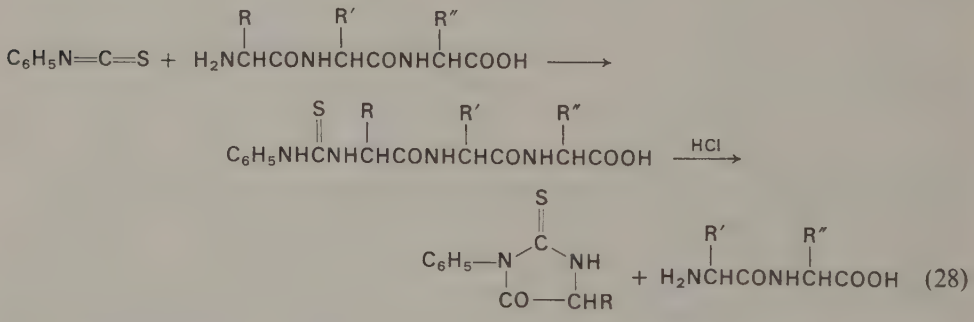
(27)

Partial hydrolysis of the DNFB derivative will give DNP-Gly, DNP-Gly-Ala, DNP-Gly-Ala-Val, and so on, as well as Ala-Val, Val-Leu, Val-Leu-Gly, and so on. DNP-Gly-Ala-Val can be identified by hydrolysis, giving DNP-Gly and DNP-Gly-Ala, as

well as Ala-Val.* Treatment of the intermediate fragments with DNFB yields further information. In this way, the complete structure of the polypeptide can be worked out.

As the size of the polypeptide increases, a great deal more effort is required to work out the complete sequence of its amino acids, but numerous large polypeptides have indeed been "sequenced" in this way. One of the earliest successes was the complete structural analysis of insulin, the antidiabetic hormone. Insulin is a "small" protein of molecular weight about 6,000. It consists of two separate polypeptide chains joined by disulfide (—S—S—) linkages. Sanger's application of the DNFB method enabled him to work out the complete structure. One of the two chains has the composition Gly-Ile-Val-Glu-Gln-Cys-Cys-Ala-Ser-Val-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Asn.

Degradation of a polypeptide by removal of the amino acids one by one is also practicable. In one such method (Edman degradation procedure) the amino-containing terminus of the polypeptide reacts with phenylisothiocyanate. The procedure is illustrated here with a tripeptide:



(28)

The phenylthiohydantoin containing the terminal amino acid unit (R) can be isolated and identified, and the remaining polypeptide (in this example, a dipeptide) treated again with phenylisothiocyanate to remove the second amino acid (R′), and so on. By this procedure one can work down the chain, identifying the amino acids one by one.

Other methods of polypeptide degradation are known.

Exercise 5

Another reagent that can be used to remove amino acids one by one is potassium cyanate, KNCO. Formulate the process by which this degradation can be accomplished.

---

* In practice, many DNP derivatives of di- and tripeptides can be prepared separately and used as reference compounds to identify the hydrolytic fragments by direct comparison.

One of the practical requirements for sequence analysis of very large polypeptides (that is, proteins) is that they must first be divided into units of manageable size, for end-group analysis of a polypeptide of 100 or more amino acids is technically difficult. Enzymes are known that can cleave polypeptide chains at specific locations to yield fragments of relatively small size (for example, five units of 20 amino acids each from an original chain of 100). The details of these procedures are too specialized for discussion here.

37-8 Synthesis of polypeptides

It is one of the goals of the chemist to reproduce synthetically the complex compounds that make up the living cell. The smaller molecules of the primary metabolites (sugars, amino acids, carboxylic acids, and so on) and most of the known compounds of secondary metabolism (terpenes, steroids, alkaloids, phenolic compounds) can be more or less readily synthesized. The proteins (including enzymes), nucleic acids, and other "biopolymers" present more formidable problems to the synthetic chemist.

Polypeptides of intermediate size (for example, bradykinin, Section 37-6) can be synthesized with relative ease, but the greater the number and variety of the amino acid units the greater the synthetic difficulties. Some success has been achieved; for example, the enzyme ribonuclease has been prepared synthetically. It is a single-chain polypeptide of 124 amino acids.

It is proper to ask why the synthesis of a polypeptide is important when its structure can be established by the degradation procedures described above. The simplest answer is that a synthesis by unambiguous procedures provides final confirmation of a structure arrived at by other means. But of equal importance is the fact that when synthetic procedures have been developed it becomes possible to prepare molecules with controlled departures from the structure of the natural compound, thus providing an opportunity for examining the relationship between structure and biological activity. For example, suppose a biologically active polypeptide has a sequence of amino acids A-B-C-D-E-F-G-H. Synthesis of polypeptides with altered sequences (for example, A-B-D-C-E-F-G), or with the substitution of a different amino acid for one or more of the normal ones, provides a means for probing the structural requirements for activity and eventually for gaining insight into the structure of the substrate with which the polypeptide interacts.

The strategy of polypeptide synthesis is simple in principle. It consists of the following steps:

1. Blocking the $—NH_2$, —COOH, and other groups that are not to take part in the reaction.
2. Causing an $—NH_2$ group and an "activated" —COOH group to react to form the new peptide bond, —CO—NH—.

3. Removing one of the original blocking groups, thus freeing an $—NH_2$ or —COOH group to form the next peptide bond.

4. All of these steps must be performed by means that do not cause racemization.

The tactics of polypeptide synthesis have attained a high degree of versatility, both in the variety of "blocking" groups that have been developed and in the methods for forming the peptide bond.

Amino blocking groups. The blocking group must fit the following requirements: it must lower the nucleophilic reactivity of the $—NH_2$ group; it must not be lost during the peptide-forming step; and it must be readily removable. Some *N*-protecting groups with these qualities are the following:

1. $C_6H_5CH_2OCOCl$ (benzyl chlorocarbonate) reacts with amino groups to form *N*-benzyloxycarbonyl derivatives:

$$C_6H_5CH_2OCOCl + H_2NCHCOOH \longrightarrow C_6H_5CH_2OCONHCHCOOH \qquad (29)$$

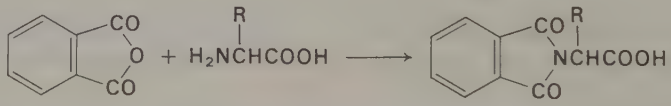
The $C_6H_5CH_2OCO—$ group is readily removed by acid hydrolysis, by catalytic hydrogenolysis, or by reduction with sodium in liquid ammonia.

2. $(CH_3)_3COCOCl$ (*t*-butyl chlorocarbonate) acylates amino groups to form *N*-butoxycarbonyl derivatives:

$$(CH_3)_3COCOCl + H_2NCHCOOH \longrightarrow (CH_3)_3COCONHCHCOOH \qquad (30)$$

The *t*-butoxycarbonyl group is resistant to hydrogenolysis and to hydrolysis under basic conditions but is very sensitive to acidic hydrolysis.

3. Phthalic anhydride can be used to convert amino acids into *N*-phthaloyl derivatives:

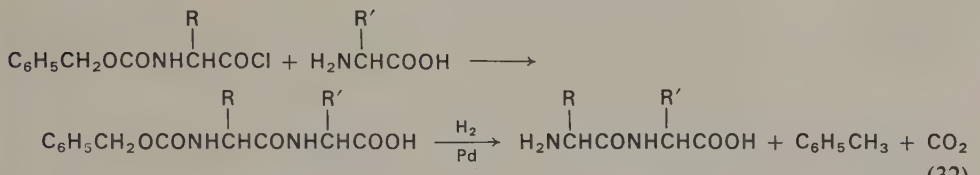


(31)

Removal of the phthaloyl group can be accomplished with hydrazine, forming phthalhydrazide and liberating the amino group.

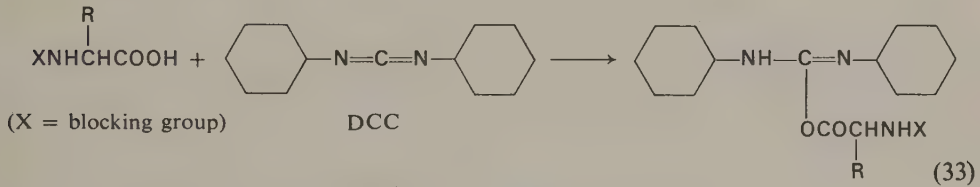
Carboxyl activation. In order to link the carboxyl group of the blocked (*N*-substituted) amino acid to the free $—NH_2$ group of the second amino acid, the carboxyl group must be converted into an active acylating entity. The simplest and most

direct way to do this is to convert it into the acyl halide, as in the following synthesis of a dipeptide:



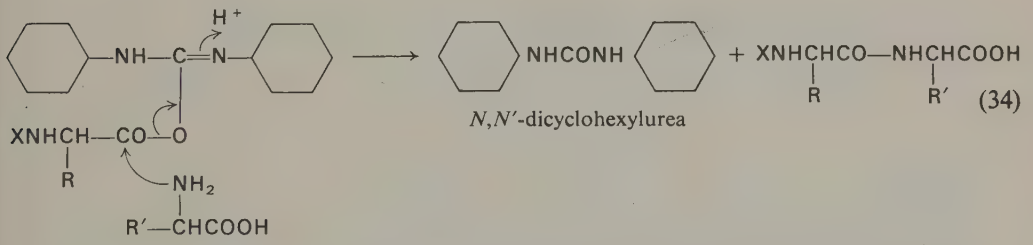
(32)

Other methods of carboxyl group activation are used. A useful reagent that allows activation of the carboxyl group without the necessity for isolating the intermediate is *N,N'*-dicyclohexylcarbodiimide (DCC); this reacts with an *N*-protected amino acid in the following way:



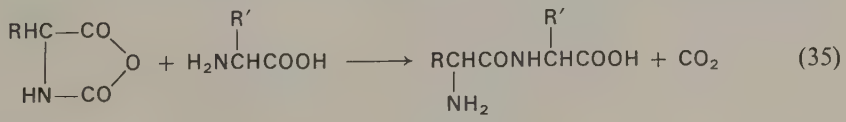
(33)

The second step is the reaction with a second amino acid:



(34)

N-Carboxyanhydrides of amino acids (Section 37-3) react with amino acids to form dipeptides (or with dipeptides to form tripeptides, and so on):



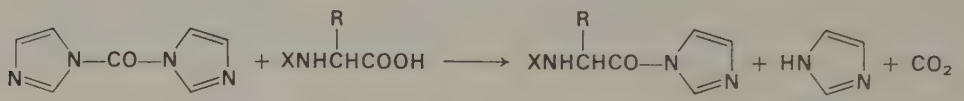
(35)

Addition of another carboxyanhydride to the dipeptide gives a tripeptide, and the process can be repeated to build up a chain of peptide units. Although it suffers from the possibility of self-polymerization of the carboxyanhydride, this method has been used with much success in polypeptide synthesis.

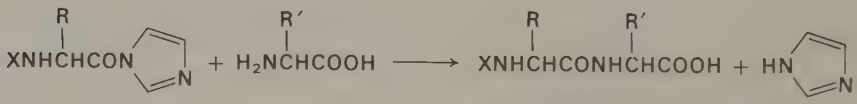
A highly reactive derivative of a carboxylic acid is formed by the use of the reagent *N,N'*-carbonyldiimidazole, which is prepared by the reaction of imidazole with phosgene:

(36)

The reaction with the carboxylic acid group of an *N*-protected amino acid and the subsequent *N*-acylation of a second amino acid proceed as follows:



(X = blocking group) (37)



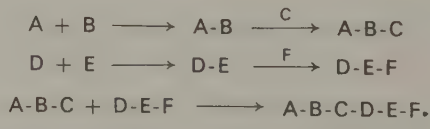
(38)

Exercise 6

Formulate a plausible mechanism for the formation of an *N*-acylimidazole by the reaction of a carboxylic acid with *N,N'*-carbonyldiimidazole.

It will be seen that by treatment of the dipeptide with *N,N'*-carbonyldiimidazole, and then with a third amino acid, a tripeptide is formed, and so on.

All of these methods are effective for the synthesis of polypeptides of a limited number of amino acid units, but the manipulative difficulties associated with isolation, purification, and characterization of products increase as the polypeptide chain grows longer. A modified procedure is to prepare the required number of small polypeptides, and join them to produce the final product:



(39)

This procedure has been used successfully, for example, in the synthesis of oxytocin and ribonuclease.

37-9 Solid-state peptide synthesis

In a recently developed method of peptide synthesis, one end of a growing polypeptide chain is kept attached to a solid support, from which the product is detached as a final step. A typical procedure is to employ a polymer containing $—CH_2Cl$ groups, to which the first *N*-protected amino acid is attached through ester linkage. Removal of the *N*-protecting group, reaction with a second amino acid (with the use of dicyclohexylcarbodiimide, DCC), and so on, builds up the polypeptide, which is at length cleaved from the polymeric support and recovered from solution:

$$\text{polymer—CH}_2\text{Cl} + \text{XNHCHCOO}^- \longrightarrow \text{polymer—CH}_2\text{OCOCHNHX} + \text{Cl}^- \longrightarrow$$

$$\text{polymer—CH}_2\text{OCOCHNH}_2 \xrightarrow[\text{DCC}]{\text{XNHCHCOOH}}$$

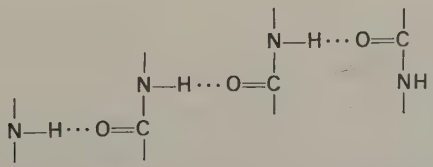
$$\text{polymer—CH}_2\text{OCOCHNHCOCHNHX} \longrightarrow \text{and so on} \qquad (40)$$

37-10 Secondary and tertiary structures of proteins

The description of a protein as a linear polypeptide is correct only in that the constituent amino acids are joined as links in a chain. The actual proteins are seldom long, thin chains, but are more often coiled or folded to give helical or compact, often globular, molecules. The binding forces that give rise to the unique conformations characteristic of individual proteins are of several kinds:

(*a*) ***Disulfide linkages.*** Oxidative coupling of two —SH groups to form an —S—S— bond can join two portions of a protein chain, to form a loop or ring; or can join two polypeptide chains together. Cysteine residues ($\cdots$NHCH(CH_2SH)CO$\cdots$) provide the means for such coupling.

(*b*) ***Hydrogen bonds.*** The presence of the recurring —NHCO— unit along the linear polypeptide chain provides for a structural organization common to the majority of proteins:



(41)

Parts of the same chain, or parts of separate chains

The most distinctive structural consequence of hydrogen bonding between peptide units is the coiling of the chain into a helix, the "turns" of which are joined by N—H···O=C bonds.

(*c*) ***Dipolar interactions*** between charged substituents. Ionized amino and carboxyl groups, suitably disposed along the polypeptide chain, can give rise to electrostatic bonding between different segments of one protein chain, or between two separate chains.

(*d*) ***Hydrophobic (van der Waals) attraction*** between closely contiguous "fatty" substituents (for example, hydrocarbon side chains).

The *secondary* and *tertiary* structure of a protein are the consequences of the operation of these various binding forces; depending upon the amino acid composition, the overall shape of the protein molecule may range from a nearly linear chain to a tightly coiled bundle. Structural proteins (silk, fibroin, keratin) possess more or less extended structures; metabolically functional proteins (hemoglobin, lysozyme) are complex folded molecules. Some proteins are aggregates of individual polypeptide subunits linked together by the kinds of binding forces mentioned above. Hemoglobin, for example, is a complex consisting of four distinct subunits folded and combined into a compact bundle. Each subunit contains the oxygen-carrying heme group. Proteins consisting of complexes of separate polypeptides are said to possess a *quaternary structure*.

37-11 Protein structure and catalysis

It can now be recognized that the *active site* of a protein—that portion of the molecule at which the substrate undergoes chemical change—is determined by the secondary and tertiary structure of the polypeptide chain. By suitable coiling and folding of the chain, the requisite groupings are disposed in such a way as to provide a constellation of exposed groups that are so disposed as to permit a substrate molecule to achieve optimal "fit" at the catalytic site (often called the "active site"). When an enzyme prosthetic group is involved in the chemical reaction, it too will be so positioned with respect to the substrate as to permit electron or group transfer to occur.

The detailed structure (that is, arrangement of functional groups) of the active sites of some enzymes have been revealed, in most cases by X-ray diffraction methods, and progress in studies of this kind is continuing.

37-12 Prosthetic groups

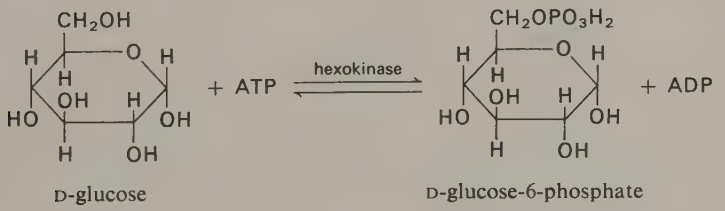
The activity of many, but not all, enzymes is dependent upon relatively small, non-protein, organic compounds. An enzyme of this kind is thus composed of a specific

protein molecule combined with the smaller *prosthetic group*, or *cofactor*. As has been said in other contexts in this book, the chemical change catalyzed by the protein may often be formulated in terms of the prosthetic group and the substrate alone, without explicit structural formulation of the protein component.

The prosthetic groups whose roles are best understood include those that are described in detail elsewhere in the text. These are (*a*) nicotinamide, as part of the hydrogen-transfer enzymes NAD and NADP; (*b*) thiamin pyrophosphate, as part of cocarboxylases and transketolases; (*c*) riboflavin, as part of the flavin-adenine-dinucleotide (FAD); (*d*) pyridoxal phosphate, in transamination reactions; (*e*) adenosine triphosphate (ATP), a prosthetic group involved in a great many enzymatic reactions; (*f*) coenzyme A. Certain other prosthetic groups are alluded to in other sections.

37-13 Glycolysis and the citric acid cycle

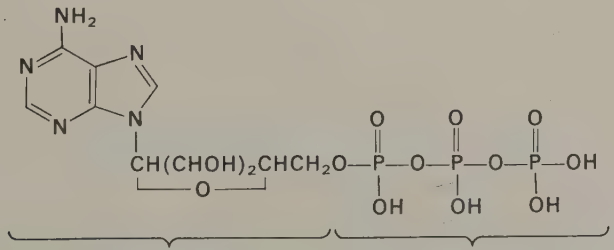
The utilization of glucose for the energetic and synthetic requirements of living organisms starts with the formation of the 6-phosphate ester



(42)

D-glucose D-glucose-6-phosphate

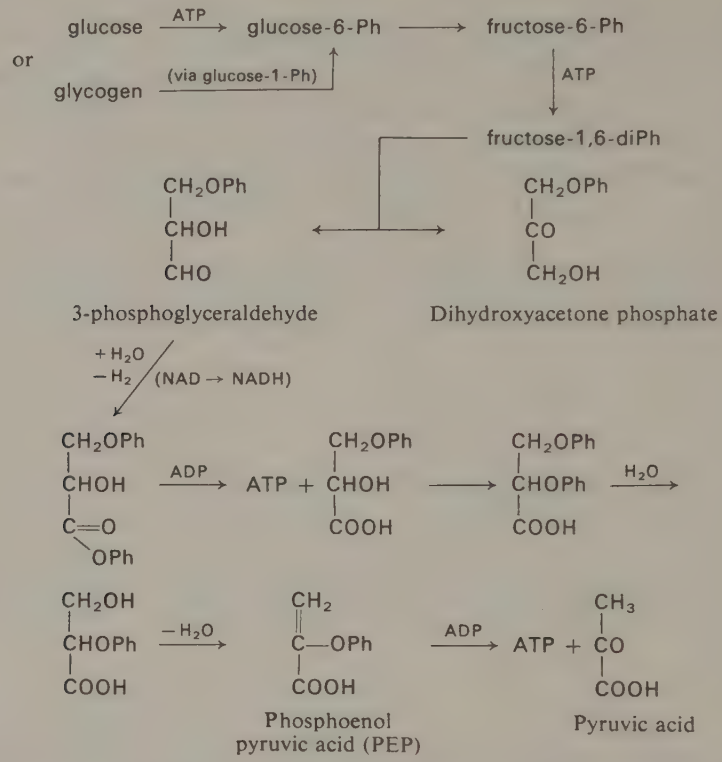
by the phosphorylating agent adenosine triphosphate (ATP):



(43)

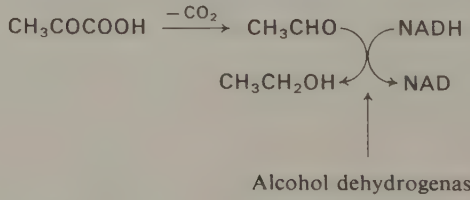
ATP

Subsequent reactions are as follows:*



(44)

Pyruvic acid occupies a central role in glucose breakdown. In some organisms (for example, yeast under anaerobic conditions) the pyruvic acid is decarboxylated to acetaldehyde and the latter reduced to ethanol by an enzyme whose cofactor is reduced NAD:



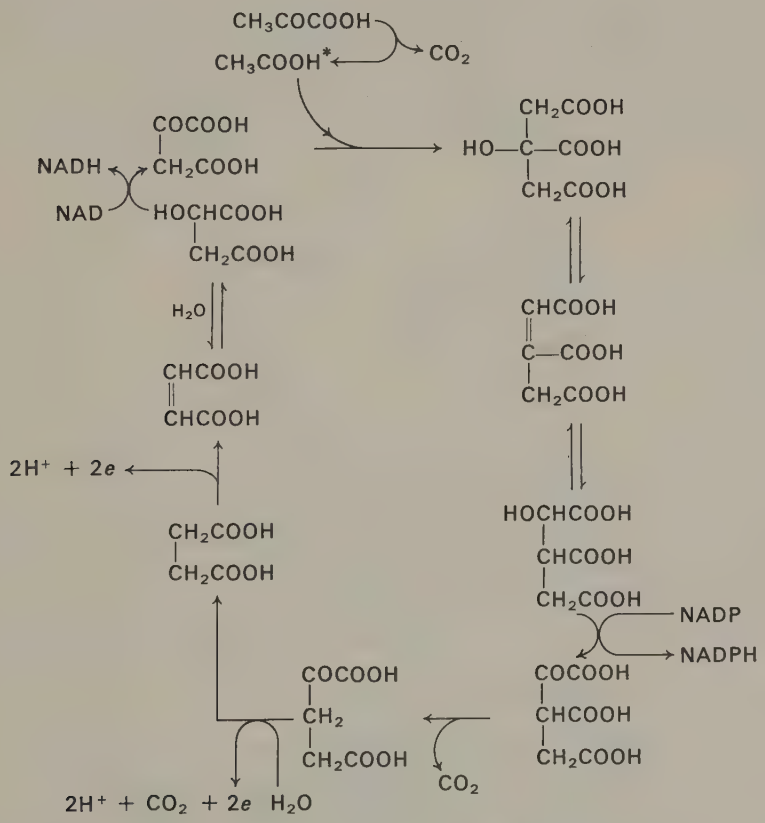
(45)

* —Ph will be used to represent the —$\overset{\overset{O}{\|}}{P}(OH)_2$ grouping. Moreover, although at physiological pH values acidic hydroxyl groups are ionized, the group will ordinarily be written for convenience as the undissociated structure.

In the glycolysis that occurs in muscle under anaerobic conditions, pyruvic acid is reduced to lactic acid.

Under aerobic conditions the degradation proceeds in another way, leading to the oxidation of pyruvic acid and its transformation into fats, amino acids, and other end products of cellular synthetic reactions. The manner in which the transformation of pyruvic acid takes place has been studied in great detail by numerous workers, who have contributed many details to what was first proposed by Krebs as the *citric acid cycle*. Krebs suggested a scheme whereby pyruvic acid is continuously fed into a cyclic process, the products of which are carbon dioxide and water, and the intermediates of which are used for the elaboration of the complex end products of primary and secondary metabolism (Chapters 38 and 39).

The citric acid cycle may be represented as follows:



(46)

Various substances found in the citric acid cycle are of importance in the metabolism

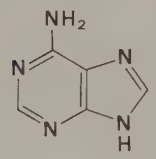
* As acetyl coenzyme A. See Section 23-27.

of amino acids, fats, steroids, and, in plants, of terpenes, alkaloids, and other secondary plant substances.

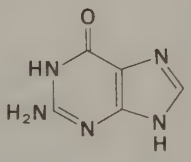
Further discussion of the biosyntheses in which these low-molecular-weight compounds are utilized will be found in the following chapter.

37-14 Nucleic acids

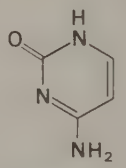
The nucleus of the cell is differentiated from the nonnuclear material chemically as well as structurally. The principal constituent of the nucleus is the chromosomal material that comprises the genetic units of heredity. This genetic material is found to be nucleoprotein in nature. *Nucleoproteins* are combinations of protein with *nucleic acids*, which are complex substances comparable to proteins in molecular weight and consisting of three chief constituents: sugar, purine or pyrimidine bases, and phosphoric acid units. The chromosomal nucleic acids contain deoxyribose as the sugar, in combination with four heterocyclic units: adenine, guanine, cytosine, and thymine.*



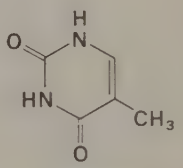
Adenine



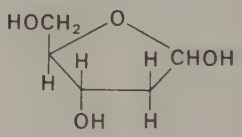
Guanine



Cytosine



Thymine



2-deoxy-D-ribose

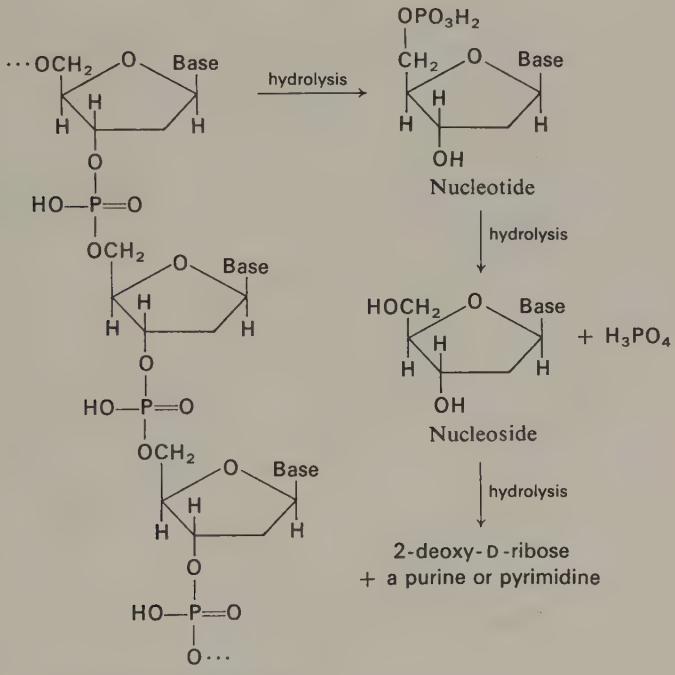
Hydrolysis of a nucleic acid proceeds in steps:

nucleic acid ⟶ nucleotides
nucleotide ⟶ nucleoside + phosphoric acid
nucleoside ⟶ purine or pyrimidine + sugar

* Small amounts of other bases are found in some deoxyribonucleic acid (DNA) samples, but these are variable and often of unknown significance.

37-15 Structure of nucleic acids

The complete structures of nucleic acids are known with less certainty than those of proteins (about which exact information is only beginning to be obtained). A schematic description of a nucleic acid structure may be given as follows:*



(47)

Deoxyribonucleic acid (DNA)

The exact sequence of the purine and pyrimidine bases in many nucleic acids is not yet known. It is clear that an enormous number of different nucleic acids can be constructed by altering the sequence of the four bases in a polynucleotide chain of, say, 100 units. Indeed, it is believed that in this possibility for variation in structure lies the ultimate explanation for the fact that the genetic material can contain so great a number of individual hereditary determinants (genes), each of them consisting of combinations of a few common building units.

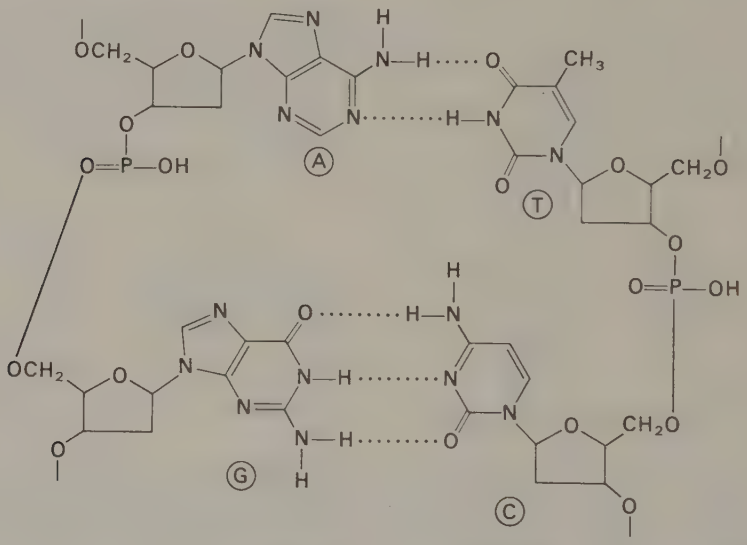
37-16 The structure of deoxyribonucleic acids and the replication of genetic material

The replication of living cells is accomplished with the reproduction of the nuclear material; this is to say that the genetic information contained in the chromosomes is

* Deoxyribose is characteristic of nuclear deoxyribonucleic acids; ribonucleic acids (RNA), in which the sugar is ribose, are also known.

passed on from cell to cell as the organism grows by cell divisions and cellular differentiation. It must be concluded that there exists a mechanism by which the synthesis of nucleic acid is controlled in such a way that the sequence of purine and pyrimidine bases characterizing a given molecule of DNA is identical in the two daughter cells formed by cell division.

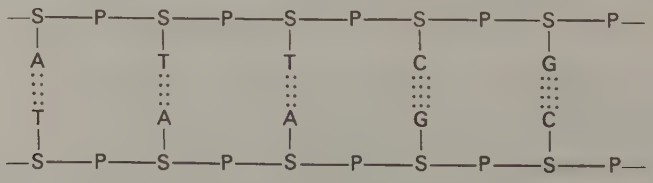
A model of the DNA molecule was proposed by Watson and Crick in 1953 that provides a satisfactory answer to the problem of how such replication is carried out. The essential idea of the Watson-Crick model is that the molecule consists of two separate chains of polynucleotide material intertwined with each other in the form of a double helix. The separate chains are held together by hydrogen bonds between the purine and pyrimidine groups, which are always paired in such a way that *adenine is bonded to thymine, and guanine to cystosine*:



(48)

Ⓐ = adenine Ⓖ = guanine Ⓣ = thymine Ⓒ = cytosine

A DNA molecule can be represented schematically in the following way:



(S = sugar; P = phosphate)

The two polynucleotide chains are intertwined in the double helix shown in Figure 37-1.

Figure 37-1 shows two things: (1) the structure of the nucleic acid molecule (the lower part of the figure) and (2) the process by which the molecule is duplicated. The formation of the new molecule consists of the synthesis of two new polynucleotide chains in such a way that the sequence of purine and pyrimidine residues is directed by the necessity for each base to pair with its complementary base; thus each new

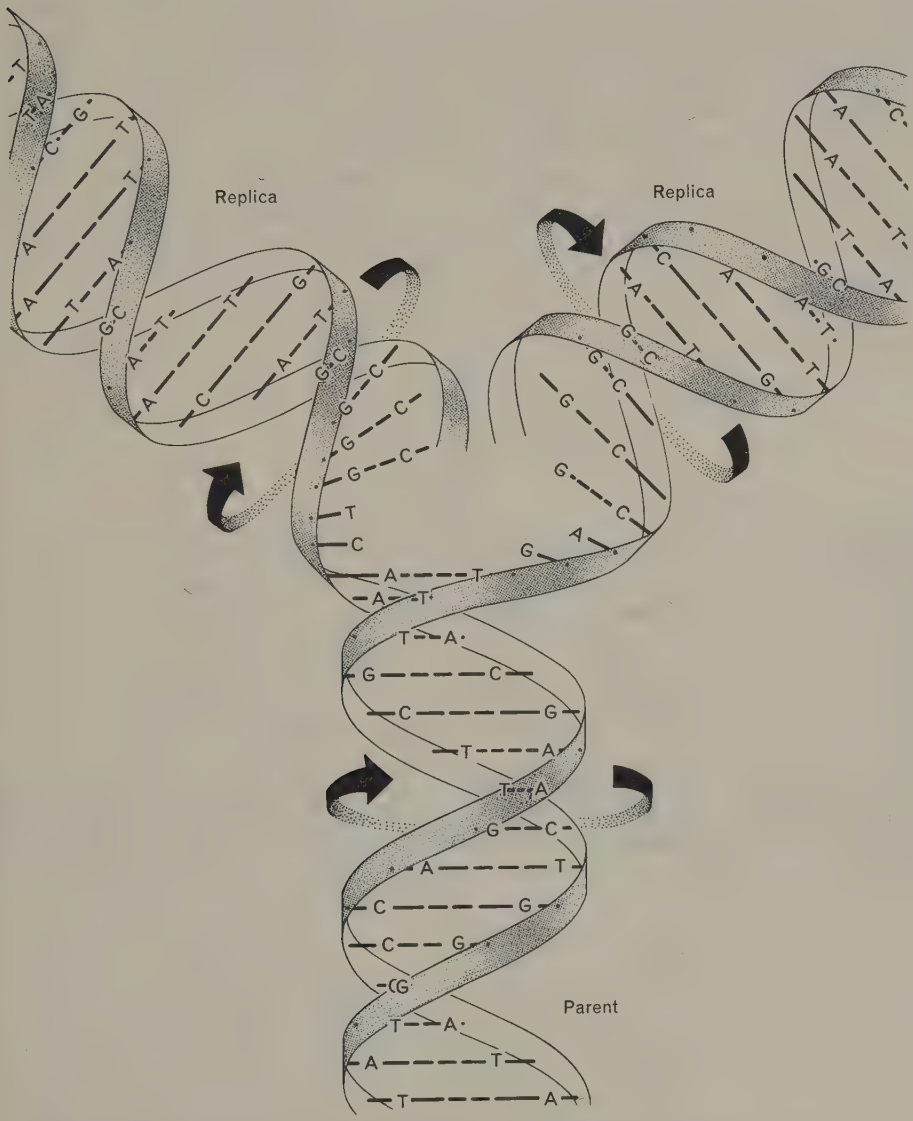
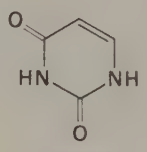


Figure 37-1
The replication of DNA, according to Watson and Crick. (From Gunther S. Stent, *Molecular Biology of Bacterial Viruses*, W. H. Freeman and Company, San Francisco, 1963.

strand is coded by one strand of the original chain, the individual nucleotides being selected so that A pairs with T, T with A, C with G, and G with C. Consequently, each original double helix gives rise to two new double helices, each identical and each containing one half of the original DNA molecule.

The genetic information in the chromosomal DNA is expressed as products of cellular chemical activity. This metabolic activity is controlled by specific enzymes, of which living cells may contain many thousands, depending upon the complexity of the organism in which they are found. These enzymes are proteins; they are synthesized in the cell under the control of the nuclear DNA by a process closely parallel to that by which the duplication of the DNA itself takes place.

Enzyme synthesis takes place under the direct influence of ribonucleic acids (RNA), the structures of which are determined by the code contained in the DNA molecule. RNA, containing ribose instead of deoxyribose and uracil in place of thymine,



Uracil

is a polynucleotide whose synthesis occurs at the DNA molecule in such a way that the sequence of the four bases adenine, uracil, cytosine, and guanine corresponds directly to the base sequence in that part of the DNA molecule that serves as the template for its formation. Thus, the RNA molecules contain copies of the genetic information carried by the DNA, so that the enzymes whose syntheses they direct are specifically related to the genetic characteristics of the organism.*

* The details of the manner in which protein synthesis is controlled by RNA are beyond the scope of this text. Excellent descriptions of these important processes are to be found in the articles in *The Living Cell: Readings from Scientific American* (W. H. Freeman and Company, San Francisco, 1965), and in modern textbooks of biochemistry.

38

Secondary metabolites I: Terpenes

The world abounds in natural organic compounds of nearly every conceivable structural class, the study of which is one of the most fascinating and fruitful areas of study open to the organic chemist. The cells of living organisms—plants, fungi, bacteria, lichens, and insects and other animals—are the sites of intricate and complex synthetic activities that result in the formation of many varieties of compounds, many of great practical importance to mankind.

It is within the plant kingdom and particularly in the higher, green plants that we find the broadest spectrum of synthetic capabilities. Synthesis in plants is the more striking because the starting materials are simple substances—water, carbon dioxide, nitrogen (both elemental and as inorganic salts), and phosphorus and sulfur compounds. From these are elaborated organic compounds ranging in complexity from simple carboxylic acids, low-molecular-weight aliphatic compounds, and even simple hydrocarbons, to polynuclear aromatic compounds, sterols, and alkaloids. Only a few of these can be considered in detail within the limits of a general textbook, and only the broad outlines of the synthetic processes that lead to their formation can be

presented. It is the purpose of this chapter to describe some of the main features of synthesis in living organisms (biosynthesis), and to show how a few universally distributed starting materials and reaction types lead to so diverse an array of products.

38-1 Naturally occurring compounds

The primary synthetic process of nature is photosynthesis, by which green plants utilize the energy of sunlight to incorporate the carbon of carbon dioxide into carbohydrates. The further metabolic alteration of sugars leads to the formation of a pool of simple organic compounds, many of them low-molecular-weight carboxylic acids, amino acids, and aromatic compounds, which by specific, genetically controlled, enzymatically catalyzed organic reactions give rise to the complex compounds in which the plant kingdom abounds. These reactions, which utilize a pool of available starting materials that are quite universal in their distribution, but which lead to compounds that are often unique to one plant or one plant family, are referred to as the *secondary metabolism* of plants; the products of secondary metabolism are called *natural products*.

Three major groups of organic compounds constitute the bulk of the compounds produced by the secondary metabolism of plants:

1. *Terpenes, steroids, and carotenoids.* These are the products of reactions in which the primary reactant is acetic acid (as acetyl coenzyme A); this is converted to a primary five-carbon-atom building unit, from which the more elaborate final products are formed.

2. *Compounds containing aromatic—usually phenolic—groups in simple benzenoid, naphthalene-derived, or anthracene-derived structures.* These, too, are the result of the combination of two-carbon-atom units, namely, acetic acid as acetyl coenzyme A.

Another group of aromatic compounds, which are not built up from acetic acid units but by the combination of a four-carbon-atom sugar with a derivative of pyruvic acid, is widely distributed in nature. It might be classified separately from the acetate-derived aromatic compounds, but since compounds of this group often contain structural features that are derived in part from acetyl coenzyme A and in part from the carbohydrate pathway, it will be convenient to discuss all of the aromatic compounds under the single rubric.

3. *Alkaloids.* Although this is a class of compounds of widely various structural types, a very large proportion of them are formed in nature by transformations that

start with simple amino acids. A brief introduction to the biosynthesis of alkaloids is to be found in Chapter 35.

38-2 Terpenoids, steroids, and carotenoids. Biosynthetic origins

An important class of natural products, widely distributed in both plant and animal organisms and deriving from a common precursor, are the *terpenoid*, *steroid*, and *carotenoid* compounds. They are most advantageously described in terms of the synthetic pathways by which they are formed in the living organism, for it is known that despite the wide structural diversity in these three classes of compounds all of them arise by successive combination of simple five-carbon-atom units to give C_{10}, C_{15}, C_{20}, C_{30}, and C_{40} compounds. Further alterations of these by ring-closures, introduction of oxygen, loss of one or more carbon atoms, and occasional skeletal rearrangements give the final, naturally occurring products.

The compound at the head of the synthetic sequence is *mevalonic acid*, formed in the following way from acetyl coenzyme A. Each of the steps shown is enzyme-mediated, but it will be apparent that the chemical reactions are not themselves exceptional; they include aldol-like condensations, reductions, dehydrations, and so on, which, though catalyzed by specific enzymes, are mechanistically straightforward:

$$2CH_3CO{-}SCoA \longrightarrow CH_3COCH_2CO{-}SCoA + CoASH \qquad (1)$$

$$CH_3COCH_2CO{-}SCoA + CH_3CO{-}SCoA \longrightarrow CH_3{-}\overset{\displaystyle OH}{\overset{|}{C}}(CH_2CO{-}SCoA){-}CH_2CO{-}SCoA \qquad (2)$$

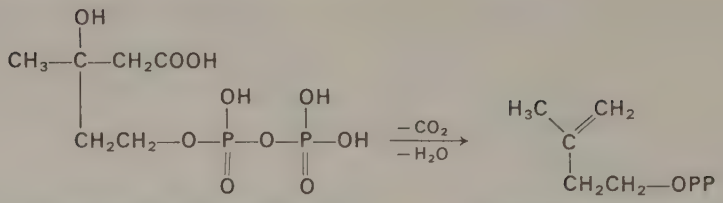
$$CH_3{-}\overset{\displaystyle OH}{\overset{|}{C}}(CH_2CO{-}SCoA){-}CH_2CO{-}SCoA \longrightarrow CH_3{-}\overset{\displaystyle OH}{\overset{|}{C}}(CH_2CH_2OH){-}CH_2COOH \qquad (3)$$

Mevalonic acid (MVA)

The steps shown are: (1) a Claisen-like condensation leading to an acetoacetic CoA ester; (2) an aldol-like condensation of the CH_3— of acetyl CoA with the carbonyl group of acetoacetyl CoA; and (3) a reduction of —CH_2CO—SCoA to —CH_2CH_2OH, with hydrolysis of the other —CH_2CO—SCoA to the acid, —CH_2COOH.

Mevalonic acid is transformed by reaction with ATP into MVA pyrophosphate, and this, by loss of H_2O and CO_2, yields the fundamental C_5 building unit *isopentyl pyrophosphate*. This is isomerized by an enzyme-mediated prototropy into γ,γ-dimethylallyl pyrophosphate:*

* The symbol —OPP will be used for the pyrophosphate grouping.



(4)

Mevalonic acid pyrophosphate — Isopentenyl pyrophosphate

(5)

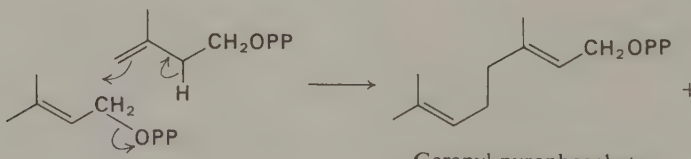
γ,γ-dimethylallyl pyrophosphate
(3-methyl-2-butenyl pyrophosphate)

38-3 The pentenyl pyrophosphates

The two five-carbon-atom pyrophosphates are structurally capable of undergoing polymerization into C_{10}, C_{15}, C_{20}, and larger compounds.

The unique reactivity of γ,γ-dimethylallyl pyrophosphate is due to two features of its structure: (1) the excellent leaving-group capability of the pyrophosphate anion (since pyrophosphoric acid is a strong acid) and (2) the high degree of stabilization of the dimethylallyl cation. These properties have been discussed in Chapter 8, which should be referred to.

The "dimerization" of the C_5 units is formulated as follows, the loss of a proton being shown as a concomitant step (as it is known to be in the natural process):



(6)

Geranyl pyrophosphate

Geraniol, the alcohol derived by hydrolysis of the pyrophosphate, is one of the most widely distributed *terpenes*.* It may be considered the "parent" compound of numerous terpenes known in nature. The following processes are some of the ways by which other terpenes are derived from geraniol.†

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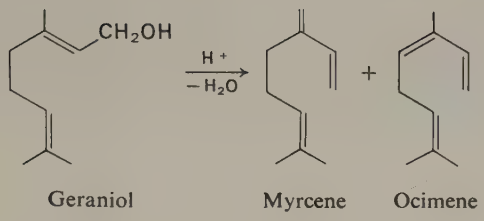
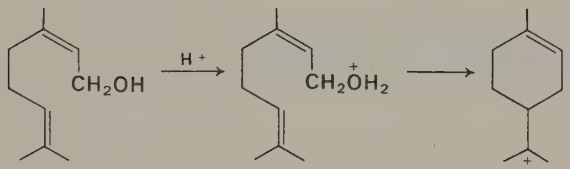
* In the strict sense, a terpene is a hydrocarbon of the composition $C_{10}H_{16}$ (for example, myrcene and limonene), but in common usage the name is used for the oxygenated compounds as well. The term "terpenoid" usually refers to all of the compounds of the larger class, including sesquiterpenes, diterpenes, triterpenes, etc.

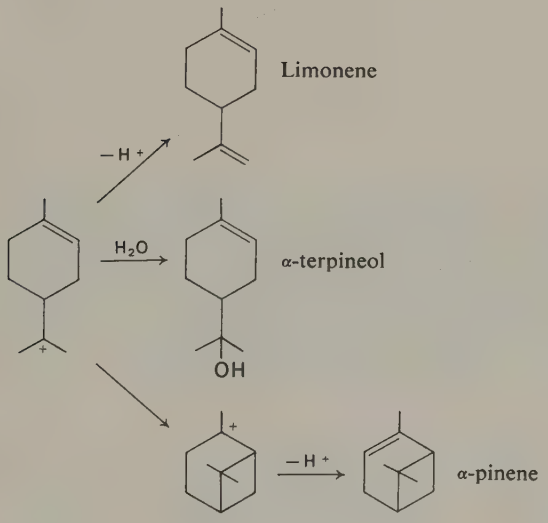
† Although in the living organism these reactions are enzyme-mediated and probably proceed from geranyl pyrophosphate, the acid-catalyzed reactions shown in (7)–(9) are mechanistically satisfactory (and have in many cases been carried out in laboratory experiments).



Geraniol Myrcene Ocimene (7)



Nerol (8)



(9)

Exercise 1

Citral is the α,β-unsaturated aldehyde formed from geraniol by simple oxidation (—CH_2OH → —CHO). Citronellal is 2,3-dihydrocitral (3,7-dimethyl-6-octenal).

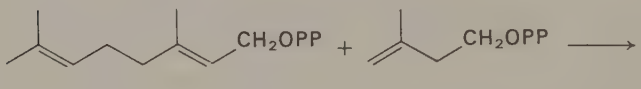
(*a*) Treatment of citral with strong mineral acid converts it into *p*-cymene (*p*-isopropyltoluene). Formulate this transformation.

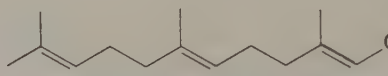
(*b*) Look up the structure of pulegone in a handbook or reference book, and devise a reasonable route for its biosynthesis.

Terpenes occur widely in the plant world. They are responsible for the characteristic odors of many plants—the fragrance of mint, of pines, and of eucalyptus leaves. They are important articles of commerce, widely used as food flavorings and as perfumes. Common and familiar terpenes include camphor, menthol, and those in peppermint.

38-4 Sesquiterpenes

It will be seen that geranyl pyrophosphate is a γ,γ-disubstituted allyl pyrophosphate and thus has the same reactive capability as the C_5 compound from which it is formed. It condenses with isopentenyl pyrophosphate in the same manner as the initial C_5-C_5 condensation, to give *farnesyl pyrophosphate*:

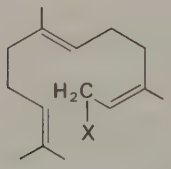




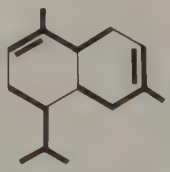
(10)

trans,trans-farnesyl pyrophosphate

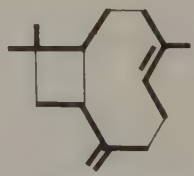
Sequiterpenes, the C_{15} terpenoids, are found in nature in an extraordinary range of structural variation, but most of them contain the unaltered C_{15} unit of the farnesyl carbon skeleton. The following typical sesquiterpenes are drawn in such a way as to show their derivation from farnesol, the latter being represented as two of the possible double-bond (*cis-trans*) isomers (in these formulas the pyrophosphate grouping is represented by X); the heavy bonds emphasize the C_5 units of the farnesyl skeleton:



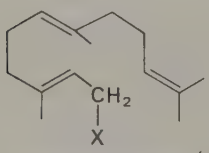
trans,cis-farnesyl pyrophosphate (X = OPP)



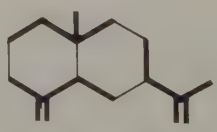
Cadinene



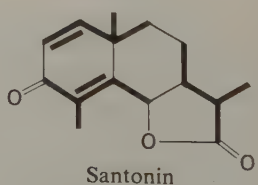
Caryophyllene



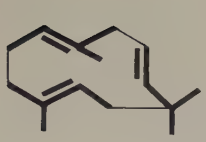
trans,trans-farnesyl pyrophosphate



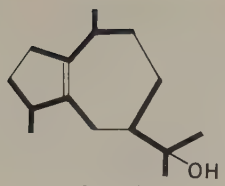
β-selinene



Santonin

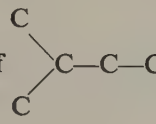


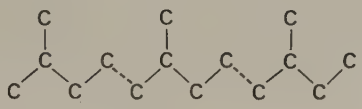
Humulene



Guaiol

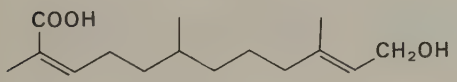
38-5 The isoprene rule

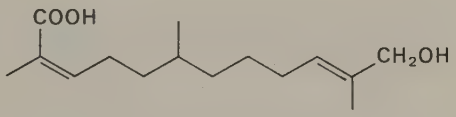
Inspection of the structures of the terpenes and sesquiterpenes discloses that most of them are constructed of  units joined "head-to-tail" in the following way:



Since each C_5 unit has the carbon skeleton of the simple diene isoprene, these compounds were at one time thought to arise by a linear head-to-tail polymerization of isoprene. We know now that isoprene itself plays no part in their biosynthesis, the "isoprene units" being the C_5 pyrophosphates described earlier. Nevertheless the term *isoprenoid* in practice embraces the many compounds having this carbon skeleton, and most terpenoid compounds are isoprenoid. The "regular" *isoprene rule* is of course only a structural correlation, but it has been found to be a useful guiding principle in structural investigation. Since the isoprene rule derives directly from the well-established biosynthetic origins of the terpenoid compounds, it has a rational basis.

For example, consider a C_{15} compound, isolated from a natural source, whose structure has been narrowed down to the two possibilities

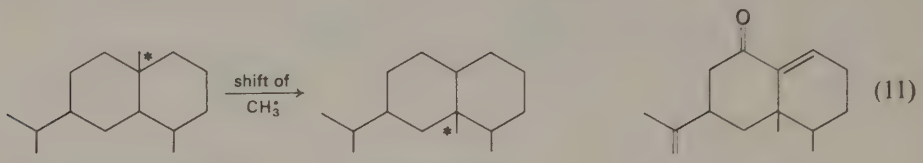




The first structure, which follows the regular isoprene rule, could be selected as correct with a high degree of probability.

However, departures from the regular isoprene rule are not unknown. The compound eremophilone does not follow the rule, for one of the projecting methyl groups is in the "wrong" position. Such departures from the regular isoprene rule

are considered to arise by a rearrangement of a "regular" isoprenoid precursor at some point in the biosynthetic sequence.



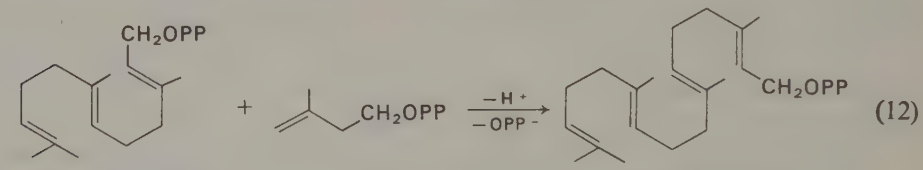
Precursor carbon skeleton (isoprenoid) — Non-isoprenoid carbon skeleton — Eremophilone (11)

Exercise 2

Upon dehydrogenation (aromatization) of the sesquiterpene β-selinene, a carbon atom is lost, with the formation of eudalene (1-methyl-7-isopropylnapthalene). With this evidence, write four plausible structures (carbon skeletons only) for β-selinene and advance arguments for selecting one of these as correct.

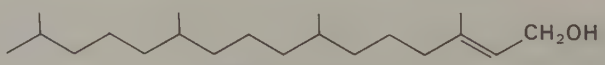
38-6 Diterpenes

Condensation of farnesyl pyrophosphate with a C_5 unit can occur in exactly the same manner as described above for the C_5-C_5 and C_5-C_{10} condensations. In the following equation the farnesyl pyrophosphate is written in a configuration chosen to show clearly the way in which subsequent steps, described further on, occur:



Farnesyl pyrophosphate — A diterpene alcohol pyrophosphate (12)

The only widely distributed acyclic diterpene is *phytol*, the alcohol present in ester combination in the photosynthetic pigment chlorophyll:

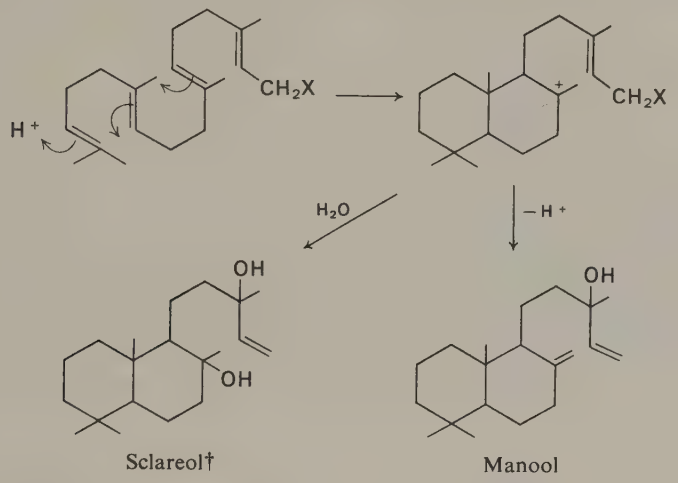


Phytol ($C_{20}H_{40}O$)

Most of the natural diterpenes are formed by cyclization of the initial C_{20} pyrophosphate shown in (12), the reactions being enzyme-mediated and mechanistically of the acid-catalyzed type. Because of the many opportunities for reaction at

various sites of the polyfunctional C_{20} precursor, a great many natural diterpenoids are known, of a wide variety of structures.

The simplest of the various cyclizations, shown in the following equation, leads to the two well-known diterpenes manool and sclareol. In this expression the cyclization is initiated by protonation (the pyrophosphate grouping is again indicated as X):*

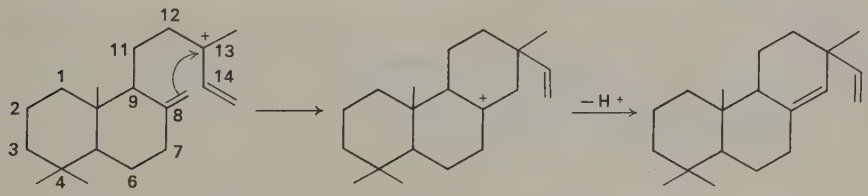


(13)

Sclareol† Manool

Further cyclization of diterpenoid compounds leads to tricyclic, tetracyclic, and a few pentacyclic compounds. These are so numerous and so diverse in structure that only two typical examples, illustrative of the processes that occur, will be given here.

Let us consider the cyclization product, manool pyrophosphate. This, like the allyl pyrophosphates we have seen in foregoing sections, is very apt to dissociate into the pyrophosphate anion and the carbonium ion shown. Attack of the C-8 carbon-carbon double bond at C-13 leads to the following ring closure:

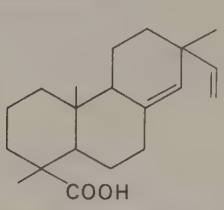


(14)

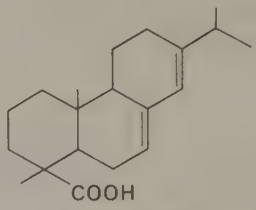
* The rearrangement of $-\underset{|}{C}=CHCH_2OH$ to $-\underset{|}{\overset{|}{C}}-CH=CH_2$ is an unexceptional allylic rearrangement that proceeds by way of the intermediate ion $-\underset{|}{C}=CH\overset{+}{C}H_2 \leftrightarrow -\overset{+}{\underset{|}{C}}-CH=CH_2$.

† It is also to be noted that it is impractical here to go into the stereochemical details of these ring closures. Sclareol, for instance, has five asymmetric centers, of which the configurations are all known. They are shown here in non-committal form.

Two common diterpenoid compounds are derived from this tricyclic system: dextropimaric acid and abietic acid, the latter by a subsequent rearrangement involving a shift of the methyl group at C-13.



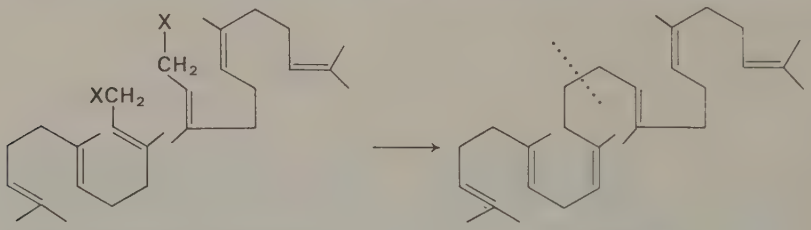
Dextropimaric acid



Abietic acid

38-7 Triterpenes. Squalene and its cyclization

Triterpenes are C_{30} compounds. However, they are not formed by a further head-to-tail extension of the isoprenoid C_{20} precursor. Rather, they arise by a *tail-to-tail* reductive condensation of two "regular" C_{15} units. This can be formulated as follows:



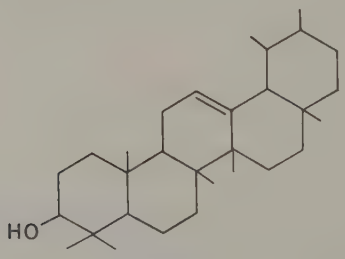
(15)

Two farnesyl pyrophosphates

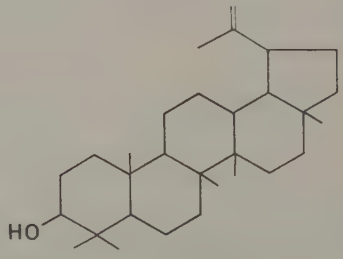
Squalene

The point of attachment of the two C_{15} units is indicated by the dotted line; the product of this reaction is the acyclic hydrocarbon *squalene*. Squalene is of special significance because it is known to be the precursor of the many naturally occurring polycyclic *triterpenes*.

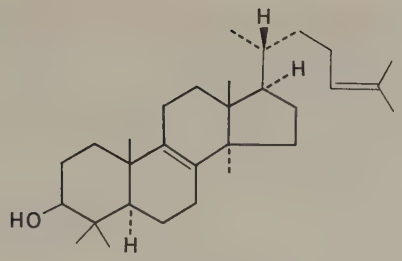
It can readily be appreciated that squalene, with its many carbon-carbon double bonds, arranged in such a way as to afford numerous possibilities for interaction, can undergo ring closures of many kinds to produce a variety of cyclic products. Three typical polycyclic triterpenes are α-amyrin, lupeol, and lanosterol:



α-amyrin



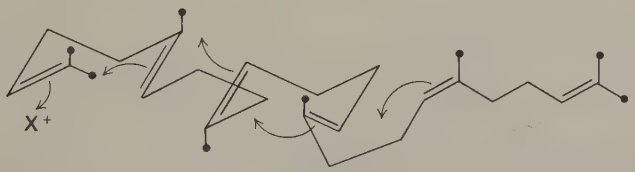
Lupeol



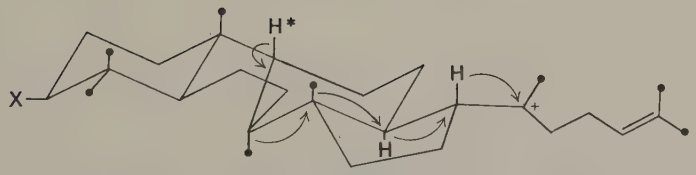
Lanosterol

38-8 The cyclization of squalene to lanosterol

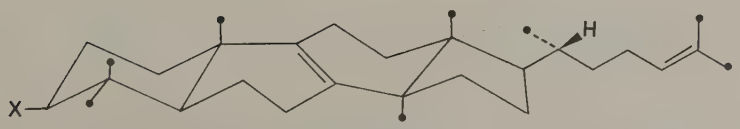
Lanosterol, the stereochemistry of which is shown above, occupies a position of special importance among the cyclization products of squalene. *It is the precursor of the steroids*, compounds of central significance in the metabolic activities of living organisms. The transformation of squalene to lanosterol, and the subsequent formation of cholesterol from lanosterol, are described in this and the following section. Conformational formulas are used to clarify the manner in which stereochemical specificity is achieved in these rather complex reactions. In the following equations, the symbol —● represents a methyl group:



Squalene



Carbonium intermediate

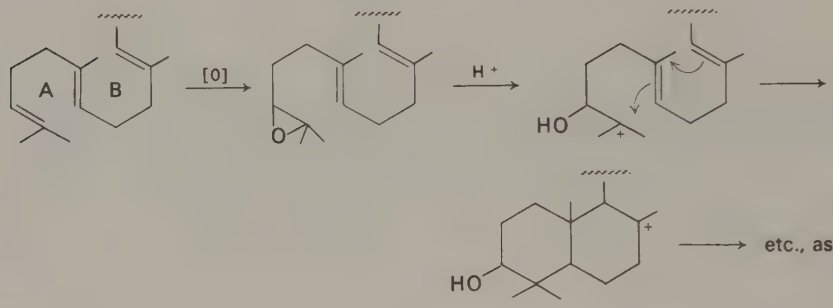


(16)

Lanosterol

Cyclization is initiated by the generation of an electron-deficient (carbonium) center at the (left-hand) terminal $=C(CH_3)_2$ group; this is shown in the equation as the attack of an electrophilic species X^+. The carbonium intermediate then undergoes loss of the proton marked *; concomitant rearrangements shown by the curved arrows lead to the product, lanosterol.

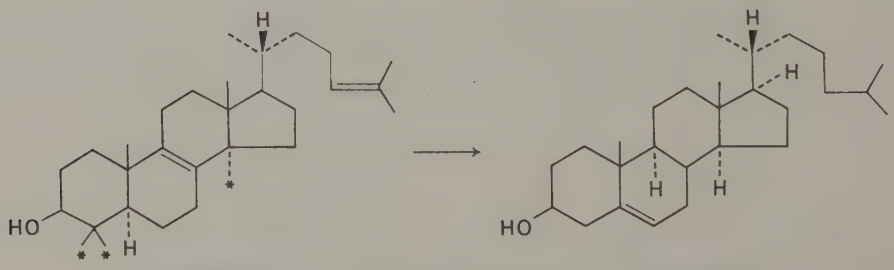
It has been established that the natural process occurs by way of an initial epoxidation, followed by electrophilic opening of the epoxide ring (for example, by protonation). Showing only the A/B rings and writing the structures in conventional form, the initial cyclization can be represented as follows:



(17)

38-9 Biotransformation of lanosterol into cholesterol

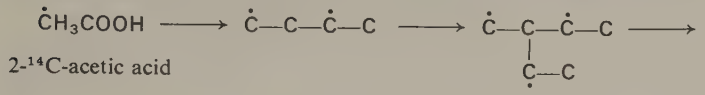
Cholesterol, the principal animal sterol and the precursor of numerous steroid compounds, is produced *in vivo* from lanosterol by (*a*) the loss (by oxidative processes) of three methyl groups (marked with asterisks); (*b*) the migration of the C-8/C-9 double bond to the C-4/C-5 position; and (*c*) the reduction of the side-chain double bond:

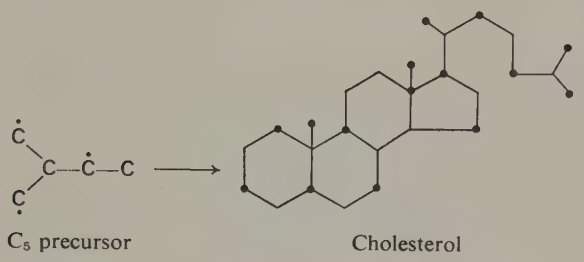


Lanosterol Cholesterol

The overall process can be summarized in the following way: mevalonic acid → farnesol → squalene → lanosterol → cholesterol (→ derived steroids).

The pathways of biosynthesis so far described have been established by years of investigation by scores of research workers, and verified by isotopic labeling techniques. If the initial precursor, acetic acid,* is labeled with ^{14}C (written $\dot{C}$) in the CH_3 group and administered to a suitably prepared animal-tissue preparation, the pattern of labeling is found to be as shown in the following scheme:





(18)

Exercise 3

Complete the sequence from the labeled C_5 precursor to cholesterol by showing the labeling pattern in the intermediate farnesol, squalene, and lanosterol.

38-10 Steroids of animal organisms

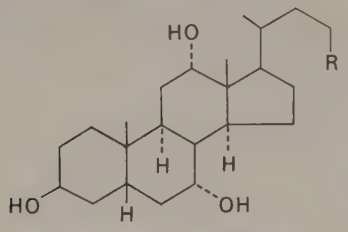
Cholesterol appears to be the sterol from which the numerous steroids that take part in the metabolic processes of higher animals are derived. These steroids belong to three general classes:

1. *The bile acids.* These are a group of hydroxylated steroid carboxylic acids represented by *cholic acid.* The bile acids, as conjugates with glycine or taurine

---

* In this summary account, coenzyme A and phosphorylated intermediates are ignored for simplicity.

($H_2NCH_2CH_2SO_3H$), are of importance in the process of emulsification and hence the absorption of fatty materials in the intestinal tract:

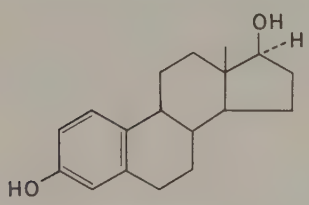


Cholic acid (R = COOH)

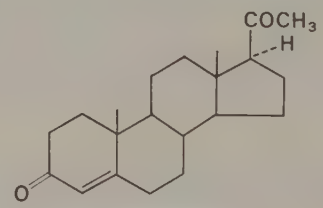
R = $CONHCH_2COOH$ (glycine conjugate)
R = $CONHCH_2CH_2SO_3H$ (taurine conjugate)

Numerous bile acids are known; various species of animals often produce highly characteristic structures, most of which differ from one another in the number and position of hydroxyl groups on the fundamental *cholanic acid* skeleton: thus, cholic acid is 3β,7α,12α-trihydroxycholanic acid.

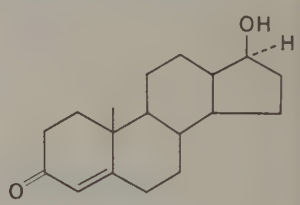
2. *The sex hormones.* These are steroidal compounds elaborated in the sexual glands of higher animals and transported to sites of action (for example, the ovaries, the uterus, and the seminal vesicles) at which their effects are produced. The sex hormones fall into three main classes: (1) the estrogenic hormones, represented by estradiol-17, which induce the development of secondary female sex characters and control the uterine cycle; (2) the gestogenic hormones, represented by progesterone, which bring about proliferation of the lining of the uterus to prepare it for implantation of the fertilized ovum; and (3) the androgens, represented by testosterone, which induce the development of the secondary male sexual characteristics:



Estradiol-17



Progesterone



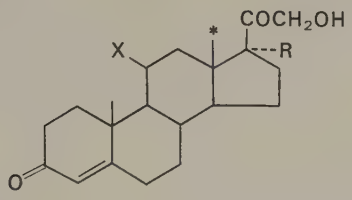
Testosterone

Progesterone is derived directly from cholesterol in the body. In view of the place occupied by cholesterol in the fundamental synthetic pathway acetate → squalene → lanosterol → cholesterol, it is probable that cholesterol is the parent substance from which other steroids are derived. However, direct interconversion has not yet been demonstrated in all cases.

3. *The steroidal hormones of the adrenal cortex.* The cortex (the outer layers of tissue) of the adrenal glands of mammals produces a large number of steroidal compounds, seven of which are of great importance in regulating physiological processes. Animals deprived of the adrenal glands (by disease or by excision) suffer

from many symptoms of a disease that, in man, is known as Addison's disease. The lives of such animals can be maintained by administering extracts of adrenal glands or the pure compounds known as the *adrenocortical hormones.*

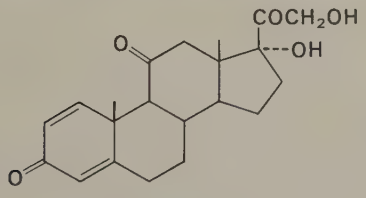
The metabolically most important of these steroids are characterized by two common structural features: an α-hydroxyacetyl grouping at the 17 position and a 3-one-4-ene grouping in the A ring:



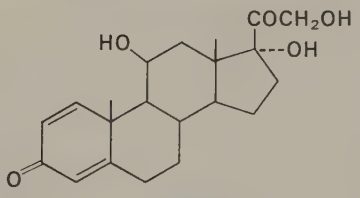
X = H, R = H	deoxycorticosterone
X = OH, R = H	corticosterone
X = =O, R = H	11-dehydrocorticosterone
X = H, R = OH	17-hydroxydeoxycorticosterone
X = OH, R = OH	17-hydroxycorticosterone
X = =O, R = OH	cortisone
X = OH, R = H, and CH_3^* replaced by CHO	aldosterone

38-11 Synthetic steroids of medicinal importance

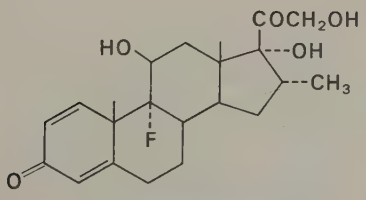
Synthetic analogues of the cortical hormones have found an important place in medicine. Three of these are prednisone, prednisolone, and dexamethasone, which are valuable in the treatment of rheumatic and other inflammatory diseases:



Prednisone

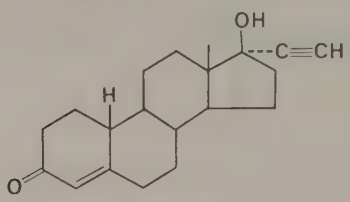


Prednisolone

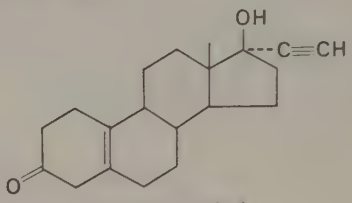


Dexamethasone

Certain synthetic analogues of the sex hormones have been found to suppress ovulation, and have come into widespread use as constituents of oral contraceptive drugs ("the pill"). Two of these are typical of the class:



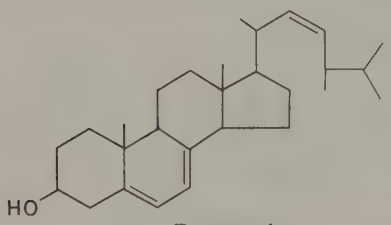
Norlutin



Norethynodrel

38-12 Vitamin D

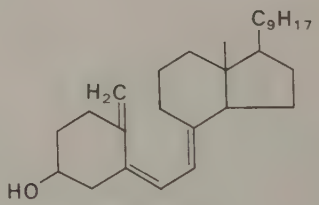
The deficiency disease known as *rickets*, a condition characterized by improper bone formation caused by the inadequate deposition of calcium phosphate during the process of bone growth, may be cured by administering the products obtained by irradiating ergosterol with ultraviolet light. Depending upon the conditions of the irradiation, a number of products may be formed from ergosterol, but the active principle, called *vitamin* D_2, has the following structure:



Ergosterol

$\xrightarrow{h\nu}$ lumisterol $\xrightarrow{h\nu}$

tachysterol $\xrightarrow{h\nu}$



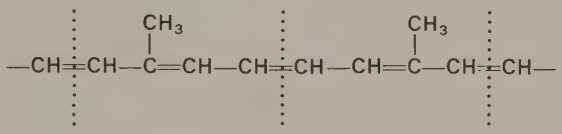
Vitamin D_2 (19)

Ergosterol is called a *provitamin D*. It is not the only sterol that can undergo transformation into a vitamin D by irradiation. 22-Dihydroergosterol (ergosterol with the side-chain double bond saturated) and 7-dehydrocholesterol are also provitamins D. The vitamin derived from ergosterol is called ergocalciferol; that from dehydrocholesterol (vitamin D_3) is called cholecalciferol. By irradiation of foodstuffs, the provitamins contained in them can be transformed into useful amounts of the vitamin. Similarly,

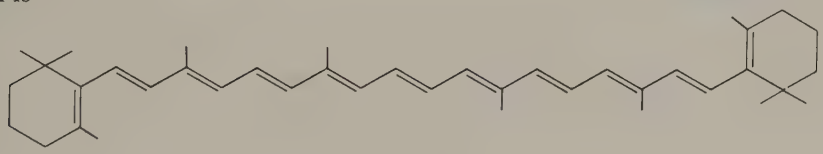
irradiation of persons suffering from the vitamin deficiency can produce therapeutic amounts of the vitamin from the provitamins in their bodies.

38-13 Carotenoids

The fat-soluble yellow pigments of plants, found chiefly in flowers and fruits, are compounds containing long chains of conjugated double bonds with an isoprenoid structure. The following fragmentary structure represents the essential nature of the polyene chain, with the isoprene units indicated:

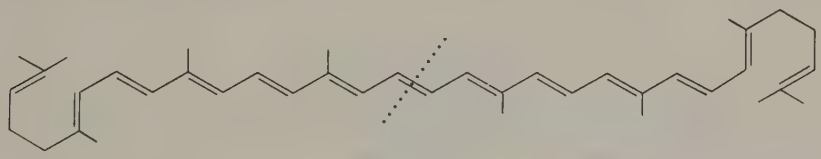


The most widely distributed of the carotenoids is *β-carotene*, the structure of which is



β-carotene ($C_{40}H_{56}$)

Lycopene, the pigment responsible for the red color of tomatoes, is the completely acyclic isomer of β-carotene:



Lycopene

It will be noted that the C_{40} carbon skeleton of the carotenoids is constructed of two diterpenoid fragments linked tail-to-tail to make the molecule symmetrical about the center. The dotted line drawn in the formula of lycopene is placed at the center of the chain. Squalene, it will be recalled, is similarly constructed of two "regular" isoprenoid C_{15} fragments.

The carotenoids are striking examples of the effect of long chains of conjugated carbon-carbon double bonds upon the light-absorbing properties of organic compounds; they were the first compounds in which this property was clearly recognized and thoroughly investigated. Table 38-1 gives the values of the prominent absorption maxima for a number of well-known carotenoid compounds; it shows that the

Table 38-1
Maxima in electronic absorption spectra of some carotenoid compounds. Values given are for solutions in carbon disulfide.

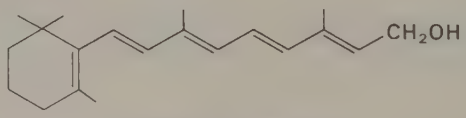
	Absorption maxima (mμ)		
α-carotene*	509	477	
β-carotene	520	485	450
γ-carotene*	533	496	463
lycopene	548	507	477

* For the structure of α- and γ-carotene, see Section 38-14.

electronic transitions, which are of the π^* type, occur at wavelengths extending well into the visible region.

38-14 Vitamin A

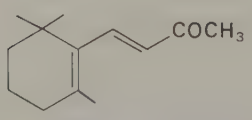
One of the most important aspects of the chemistry of the carotenoids is their relationship to vitamin A, which is responsible for the integrity of epithelial tissue and plays a central role in the process of vision. Vitamin A is a diterpenoid compound, having the carbon skeleton of one half of the β-carotene molecule. The terminal carbon atom is part of a carbinol group:



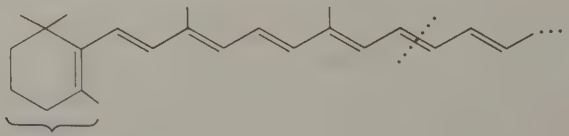
Vitamin A ($C_{20}H_{30}O$)

Vitamin A is found in liver, and in high concentrations in the livers of certain fishes (for example, sharks), where it is deposited after its formation by the cleavage of the C_{40} molecules of certain ingested carotenoids.

Not all carotenoids are precursors of vitamin A; those that are (known as provitamins A) have a β-ionine ring at one end of the carotenoid chain:



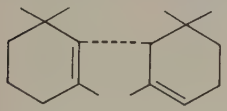
β-ionone



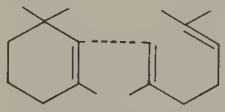
β-ionone ring

β-Carotene is the most efficient provitamin A, since the β-ionone ring is present at both ends of the molecule. A number of other naturally occurring carotenoid com-

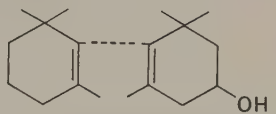
pounds also have vitamin-A activity; examples are α-carotene, γ-carotene, and cryptoxanthin (in the following structures the central part, which has been omitted for brevity, is like that in β-carotene):



α-carotene

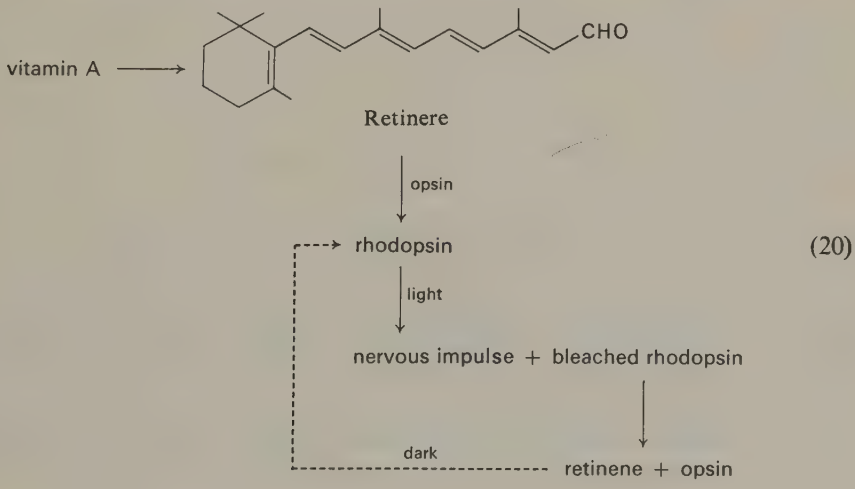


γ-carotene



Cryptoxanthin

The role of vitamin A in the visual process is of particular interest. It is well known that one of the symptoms of vitamin A deficiency is the condition known as *night blindness*, the impairment of visual acuity in dim light. The reason for the night-blindness syndrome is that the retina is deficient in the photosensitive pigment *rhodopsin*, which is a complex of a protein (opsin) and vitamin A aldehyde (retinene). The action of light upon rhodopsin causes bleaching of the pigment from red to orange, with a concomitant production of a nervous impulse that results in the sensation of vision. In the subsequent dark-adaptation phase rhodopsin is regenerated for renewed action. Thus in vision vitamin A functions as a constituent of rhodopsin; a summary of the process is given in the following scheme:

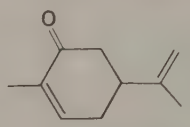


(20)

Problems

1. A useful intermediate in the synthesis of terpenoid compounds is 6-methyl-5-hepten-2-one. It can be synthesized from ethyl acetoacetate and "prenyl" bromide (1-bromo-3-methyl-2-butene). Show the steps in the synthesis.

2. Addition of HBr to carvone (A) gives a bromo compound (B), $C_{10}H_{15}BrO$. Treatment of B with alkali converts it into eucarvone (C), $C_{10}H_{14}O$. Catalytic hydrogenation of C gives 2,6,6-trimethylcycloheptanone. Eucarvone shows a strong IR absorption at 1660 cm^{-1} and a UV maximum at 303 nm ($\epsilon = 6300$).



Carvone

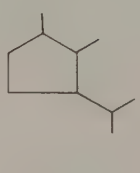
What is eucarvone and how is it formed?

3. A class of compounds widespread in nature, known as "iridoids," have the carbon skeleton A. (*a*) Is this to be regarded as a class of terpenoid compounds? (*b*) A synthesis of an iridoid compound has been accomplished as follows:

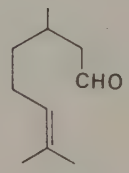
(1) Citronellal (B) + $HOCH_2CH_2OH \xrightarrow{H^+} C_{12}H_{22}O_2$ (C).

(2) Oxidation of C with $SeO_2 \rightarrow C_{12}H_{20}O_3$ (D), which has an IR maximum at 1685 cm^{-1} and a UV maximum at 228 nm ($\log \epsilon = 4.0$).

(3) When D is treated with aqueous acid and then with a trace of alkali, it cyclizes readily to give E (iridodial). E has no useful UV absorption but has a strong IR band at 1730 cm^{-1} and forms a dioxime when treated with hydroxylamine.



A

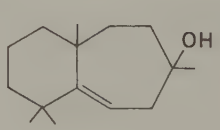


B

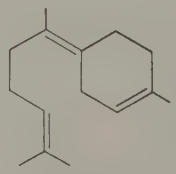
Formulate the series of reactions that leads from B to E.

4. Acid-catalyzed dehydration of farnesol gives two tetraenes, α- and β-farnesene. These correspond to ocimene and myrcene, formed by the dehydration of linalool (Section 40-2). What are the structures of the farnesenes?

5. The sesquiterpene alcohol widdrol has the structure A. Devise a reasonable course for its biosynthesis by acid-catalyzed steps starting from farnesol and proceeding through the initial intermediate B.



A



B

6. How could ozonolysis be used to distinguish between β-carotene and lycopene?

39

Secondary metabolites II: Aromatic compounds

39-1 The biosynthesis of compounds containing aromatic rings

Compounds containing one or more aromatic (benzenoid) rings are the most widely occurring natural products of secondary plant metabolism. The largest group of aromatic compounds in nature comprises those that contain phenolic hydroxyl groups, and ethers of these. Aromatic compounds are almost exclusively the products of the metabolism of plants (including fungi and microorganisms); those produced by animals are relatively few in number and are formed, for the most part, by modifications of aromatic compounds ingested as food or by the aromatization of nonaromatic cyclic precursors.

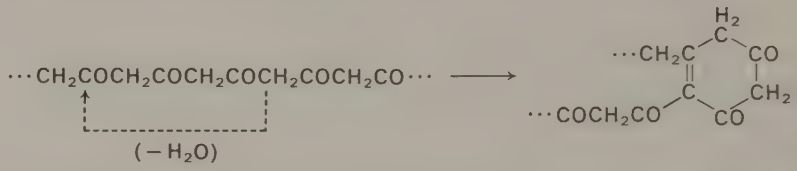
Most naturally occurring compounds that contain aromatic rings are formed by two biosynthetic pathways: (1) the acetate-mevalonate pathway, which utilizes acetyl coenzyme A (but in a manner different from terpenoid biosynthesis); and (2) the shikimic acid pathway, for which the starting compounds are carbohydrate derived.

All of the structural relationships described in the sections to follow have been verified by isotope-labeling experiments, using for the most part 2- or 1-^{14}C-labeled acetic acid, isotopically labeled shikimic and cinnamic acids, and so on. Much remains to be learned about these biosynthetic processes. Many of the intermediate steps are

still not known with certainty and only a few of the many enzyme systems involved in these complex synthetic sequences have been isolated and characterized.

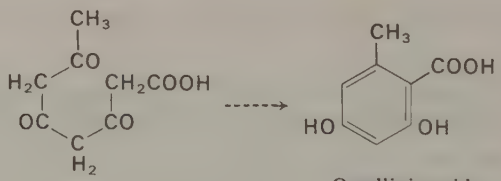
39-2 The acetate pathway of biosynthesis

A biosynthetic route to the formation, in plants, of a wide variety of aromatic compounds, including derivatives of benzene, naphthalene, and anthracene, consists in the formation and cyclization of a chain of two-carbon units that, at some stage in the synthetic sequence, may consist of a poly-β-ketomethylene ("polyketide") chain that cyclizes by aldol-like condensation reactions:



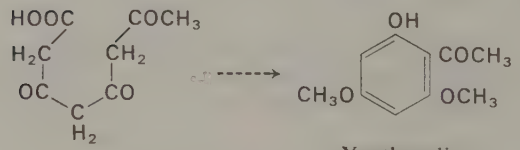
(1)

Some compounds formed by the acetate pathway are shown in the equations 2–6 (the presumptive precursors are shown). It will be noticed that in these examples a number of processes are involved in the formation of the final products: reduction, oxidation, methylation, and, in one case, the introduction of a nuclear chlorine atom. The dotted arrows in the above formulations indicate that the relationship between



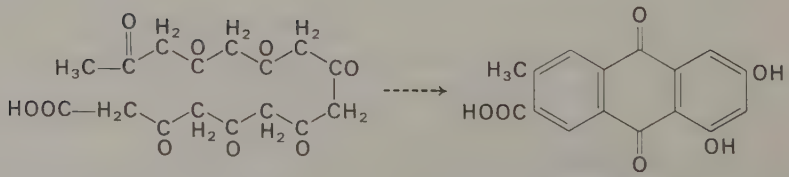
Orsellinic acid

(2)



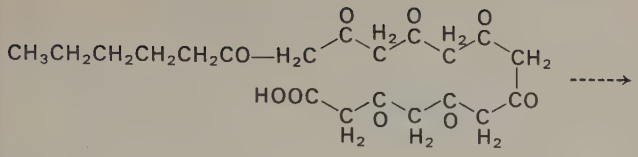
Xanthoxylin

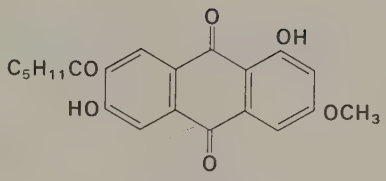
(3)



Endocrocin

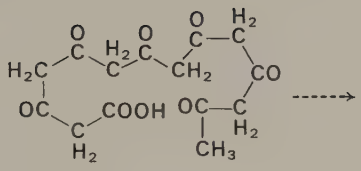
(4)

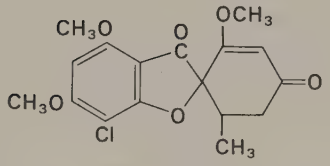




(5)

Solorinic acid



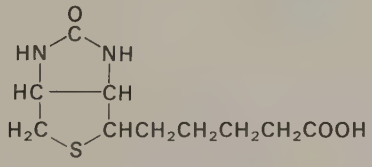


(6)

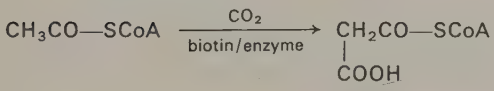
Griseofulvin

the precursor and the final compound is based on the carbon skeletons and the positions of oxygenation. The correlation between the positions of the phenolic hydroxyl groups and the carbonyl groups of the polyketomethylene chain is most striking, and is one of the strongest arguments in support of this synthetic hypothesis.

The formation of the polyketomethylene chain $CH_3(COCH_2)_nCOOH$ proceeds by self-condensation of "activated" acetyl units. The activation has been shown to proceed by the transformation of acetyl coenzyme A into a malonic acid derivative by reaction with carbon dioxide under the influence of an enzyme whose prosthetic group is biotin:



Biotin

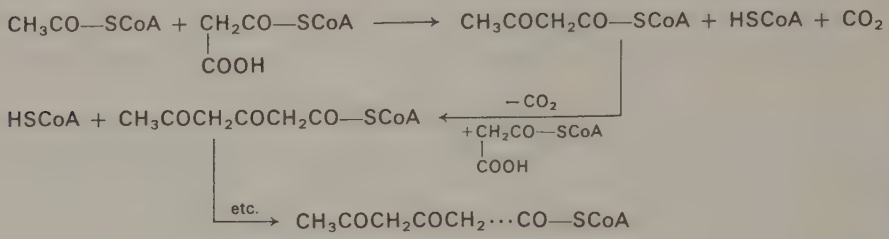


(7)

Malonyl coenzyme A

It will be apparent that the carboxylation of the methyl group converts it into a highly active methylene group, particularly susceptible to Claisen-type (acetoacetic

ester type) condensation. The formation of the polyketomethylene chain can now occur as follows:



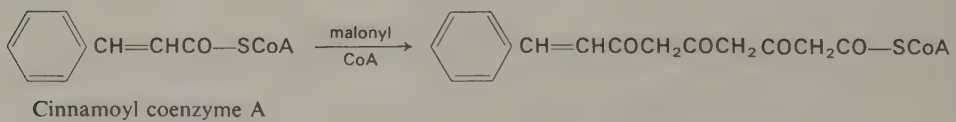
(8)

An important alternative to the extension of $CH_3CO—SCoA$ by condensation with malonyl coenzyme A involves the same kind of reaction *with some acyl coenzyme A other than acetyl.* Chain formation of this kind can lead to polyketomethylene chains that start with a group other than methyl:

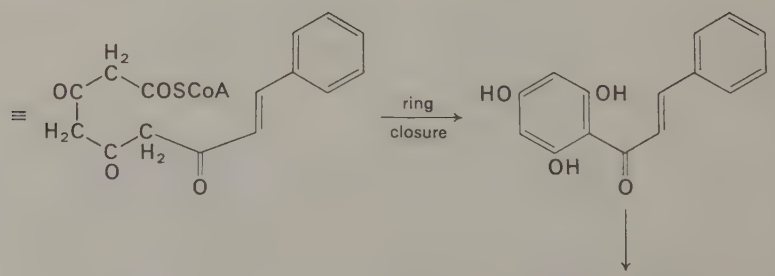
$$RCO—SCoA + \text{malonyl coenzyme A} \xrightarrow[\text{Equation (8)}]{\text{as in}} RCO(CH_2CO)_nCH_2CO—SCoA \qquad (9)$$

Thus, the general synthesis described in these expressions becomes a very versatile one, leading to the formation of many different compound types. It is probable that solorinic acid, shown above, has its origin in a process in which the precursor is the CoA derivative of hexanoic acid; this, by chain extension with malonyl coenzyme A, leads to the polyketomethylene precursor that gives rise to the final hexanoyl anthraquinone derivative.

A large and important group of naturally occurring compounds that are formed by this general pathway are fifteen-carbon-atom compounds called *flavonoid* compounds. These are formed by the pathway shown in the following expression, in which the acyl precursor is derived from cinnamic acid:



Cinnamoyl coenzyme A

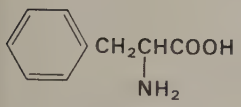


(10)

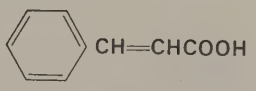
flavonoid compounds
(flavones, flavonols, anthocyanins, catechins, tannins)

39-3 The shikimic acid pathway

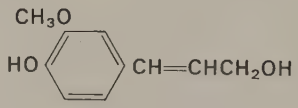
The formation of the aromatic ring in many naturally occurring compounds takes place by the cyclization of carbohydrate-derived precursors through the intermediate formation of a series of cyclohexanecarboxylic acid derivatives, the six-membered ring of which ultimately becomes aromatic. The fundamental structural unit of the compounds synthesized by this route is a nine-carbon-atom unit consisting of an aromatic ring attached to a three-carbon-atom side chain. This unit is often referred to as a C_6-C_3 unit, and compounds derived from it are often called *phenylpropanoid* compounds. Alterations of the C_6-C_3 unit by extension or degradation of the side chain give rise to a great variety of compounds; some typical naturally occurring compounds formed by this route are the following:



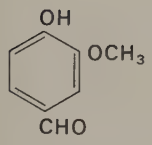
Phenylalanine



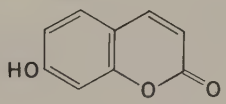
Cinnamic acid



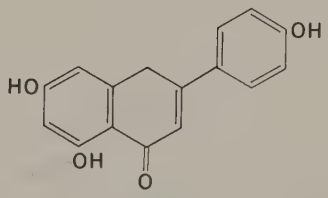
Coniferyl alcohol



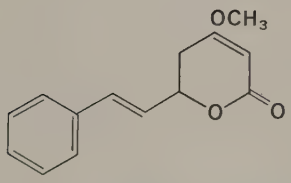
Vanillin



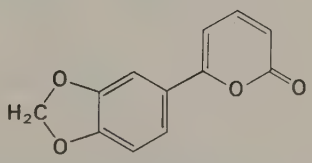
Umbelliferone



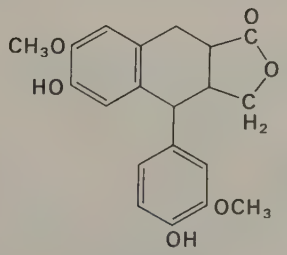
Apigenin



Kawain

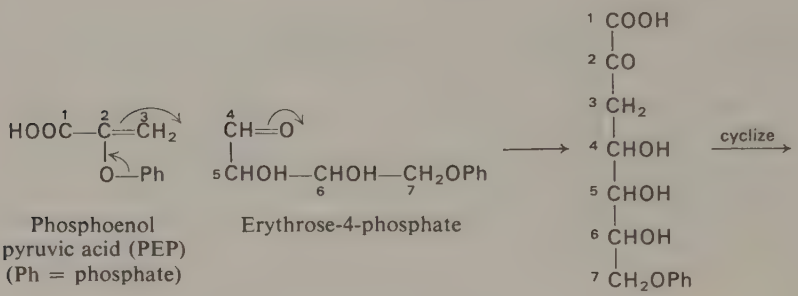


Paracotoin



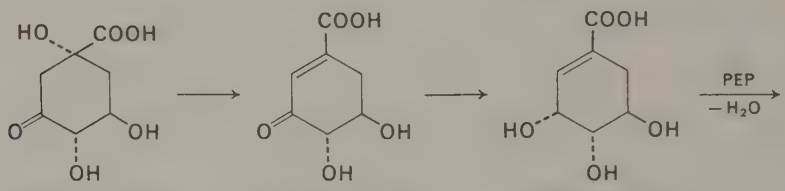
Conidendrin

A key compound in the synthesis of the C_6-C_3 unit is *shikimic acid*; this leads by way of *chorismic acid* to *prephenic acid*, which, it will be seen, contains the C_6-C_3 unit and is the immediate precursor of the final phenylpropanoid compounds. The following equations show the series of reactions in the shikimic acid route of biosynthesis:



Phosphoenol pyruvic acid (PEP) (Ph = phosphate)

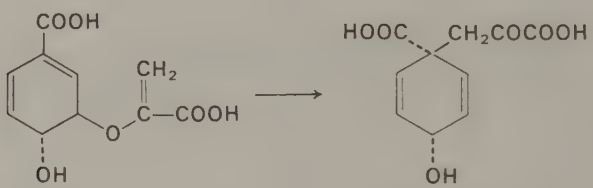
Erythrose-4-phosphate



Dehydroquinic acid

Dehydroshikimic acid

Shikimic acid

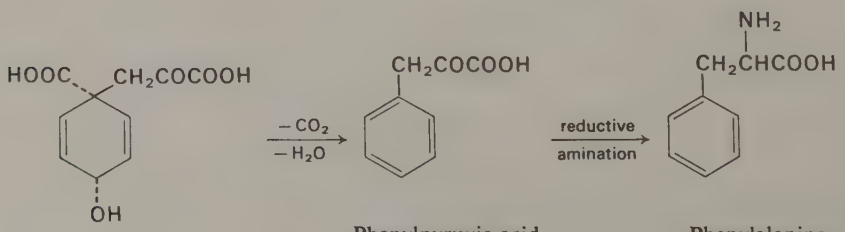


(11)

Chorismic acid

Prephenic acid

Prephenic acid is so called because it readily undergoes dehydration and decarboxylation to yield phenylpyruvic acid. Phenylpyruvic acid by transamination yields phenylalanine:



(12)

Phenylpyruvic acid

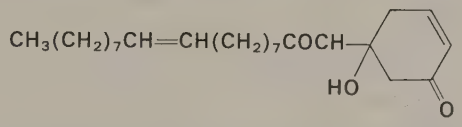
Phenylalanine

Although a great deal is known at the present time about the gross features of biosynthetic pathways—the probable precursors and the origin of the skeletal structures of the final products of biosynthesis—little is known about the details of the many reactions that intervene between the starting compound (for example, phenylalanine) and the elaborate end product of the synthesis (for example, apigenin). Such intermediate stages as the building up of chains by the acetate pathway, the formation of isoprenoid intermediates by the mevalonic acid pathway, ring closures of the several kinds that have been discussed, and such incidental reactions as the manner in which methyl groups, sugars, and certain other substituents are attached are understood; but of many structural alterations that lead to the introduction of oxygen, the creation and removal of double bonds, and the loss of fragments of the molecule, neither their place in the synthetic sequence nor the precise mechanism by which they are brought about is understood.

Problems

1. Look up the structure of erythromycin. It will be seen that this contains a series of linked "propionate" units (C-C-C). These could be regarded as derived (*a*) from C-C condensations by the acetate-malonate pathway, followed by *C*-methylation; or (*b*) from condensation by a methylmalonyl pathway. How could you show by experiment, using isotopically (for example, ^{14}C) labeled methionine and the organism in which erythromycin is synthesized, which of these pathways of biosynthesis is the correct one?

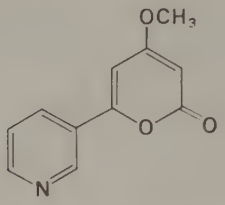
2. The following compound has been isolated from a seed oil:



   Comment on the significance of this structure with respect to the acetate-malonate theory of biosynthesis (assume a loss of CO_2 at some late stage in the synthetic pathway). What would be the most probable "starter" CoA ester?

3. Paeonol, 2-hydroxy-4-methoxyacetophenone, occurs in a species of *Paeonia*. If this plant were fed with methyl-labeled (^{14}C) sodium acetate and methyl-labeled (^{14}C) methionine, where would you expect to find the ^{14}C label in the isolated paeonol?

4. The compound anibine occurs in a Brazilian species of *Aniba*. Suggest a course for the later stages of the biosynthesis of anibine.



Anibine

5. A sample of cinnamic acid isolated from a plant used in a radioactive feeding experiment was found to contain one atom of ^{14}C per mole. Devise a scheme of degradation of the cinnamic acid that would show (*a*) whether the labeled C atom is in the ring or in the side chain and (*b*) if the latter, which of the three carbon atoms is labeled. Assume the availability of suitable equipment for the measurement of radioactivity.

40

Establishing the structure of an organic compound

This chapter describes, with specific examples drawn from the literature, the use of physical properties, degradative methods, and synthetic procedures in the determination of the structure of organic compounds. The topics chosen include a variety of naturally occurring classes of compounds, from simple terpenes to more complex phenolic compounds and alkaloids. The student will notice that nearly every example embraces numerous facets of the chemistry of organic compounds. It is for this reason that this chapter is placed at the end of the book, for the organic chemist, in solving problems of this kind, must utilize knowledge of many aspects of functional group behavior, synthetic procedures, interpretation of spectroscopic data, and so on. It will be noted that nearly all the methods of attack upon these problems are applications of general types of reactions described in the preceding chapters. It is recommended that for each example the student relate each stage in the solution to what he has learned earlier in more limited contexts.

40-1 Introduction

One of the principal tasks of the organic chemist is the determination of the structure of unknown organic compounds. At the present time, with the availability of

sophisticated instruments, these problems are much more easily solved than in earlier times, when often arduous and time-consuming methods had to be employed. In many cases, the measurement of UV, IR, nuclear magnetic resonance, and mass spectra now permit the ready assignment of a structure that is correct, or so nearly correct that a minimum of chemical procedures are needed to reach a final solution.

Before the advent of spectroscopic methods of analysis, which were not generally available in the first quarter of this century, chemists attacked problems of structure by degrading complex molecules to simpler ones that were either known or whose identity could be established either by their properties or by synthesis. By an assessment of the chemical behavior of the unknown compound, coupled with a knowledge of the structures of the products of its chemical degradation, a structure for the unknown compound could be proposed. This could be further confirmed by additional chemical tests, or established by a total or partial synthesis.

Although physical methods of analysis are now a normal part of laboratory work in organic chemistry, it should be recognized that a large part of the knowledge of the field has been gained by studies of chemical behavior and the mechanisms of chemical change, and by the development of methods of synthesis and chemical analysis. The instructional value of these procedures is such that it is appropriate to review some examples of how they have been used to determine structure. It should not be assumed, however, that the procedures to be discussed in the sections to follow are outmoded. Even though some of them represent the work of chemists of earlier decades, they are examples of experimental approaches that are still, and will continue to be, indispensable tools in the hands of the modern organic chemist.

The examples selected for discussion are drawn chiefly from terpenoid compounds and alkaloids. The problems of structure elucidation are presented from several standpoints: interpretation of molecular manipulations and degradations, synthesis of degradation products or total synthesis of the compound itself, and the application of physical methods to the solution or confirmation of structural or stereochemical features. The use (and occasional misuse) of structural analogy and biosynthetic origin also play a part in the studies described.

40-2 The structures of myrcene and ocimene

Terpenoid compounds occur widely in nature as components of *essential oils*, which are volatile materials responsible for the fragrance of such plants as pines, eucalypts, and mints. The term "terpenoid" is generic, and is generally applied to any of a large class of compounds that are characteristically constructed of five-carbon-atom units. Terpenes are C_{10} compounds, diterpenes C_{20}, and so on (Chapter 38).

Although the majority of natural terpenes contain oxygen, a number of acyclic and cyclic hydrocarbons of the composition $C_{10}H_{16}$ are known. Two of these are

myrcene, a constituent of oil of bay and turpentine, and *ocimene*, present in the essential oil of sweet basil.

Myrcene, $C_{10}H_{16}$, shows an ultraviolet absorption maximum at 225 nm (ϵ = 14,600). It is readily hydrogenated (platinum catalyst) to hexahydromyrcene, $C_{10}H_{22}$, and reacts with maleic anhydride to form a Diels-Alder adduct, $C_{14}H_{18}O_3$. These observations show that myrcene is acyclic and contains three double bonds of which two are conjugated and the third is isolated. (Why?)

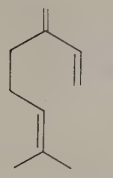
Ozonolysis of myrcene yields acetone, two moles of formaldehyde, and (after further oxidation) succinic acid. These results show that myrcene contains the structural elements

$(CH_3)_2C=$ two $>C=CH_2$ $=\overset{|}{C}-CH_2CH_2-\overset{|}{C}=$

All of this information can be accommodated by the structure

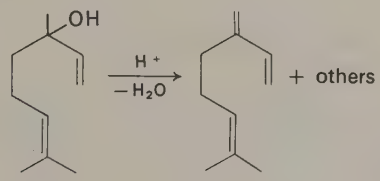
$$(CH_3)_2C{=}CHCH_2CH_2\overset{CH_2}{\overset{\|}{C}}CH{=}CH_2$$

often written as



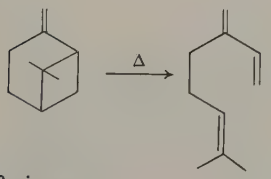
Myrcene

Myrcene can be obtained (along with other products) by dehydration of linalool and by pyrolysis of β-pinene:



(1)

Linalool



(2)

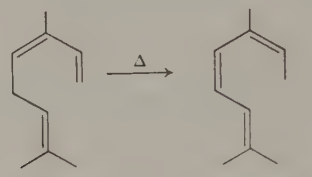
β-pinene

Ocimene, also $C_{10}H_{16}$, can be hydrogenated to hexahydroocimene (hexahydromyrcene). It has a UV absorption maximum at 237 nm. Upon ozonolysis there are produced acetone, one mole of formaldehyde, and methylglyoxal, CH_3COCHO. No succinic acid is obtained.

Upon heating, ocimene is isomerized to *alloocimene*, which has a UV absorption maximum at 275 nm. This indicates that the conjugated diene system present in ocimene (λ_{max} 237 nm) has been transformed into a conjugated triene in alloocimene by inclusion of the third double bond:

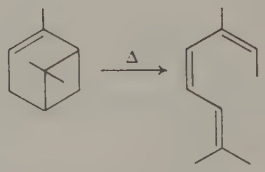
(3)

Structures for ocimene and alloocimene that conform to the above data are



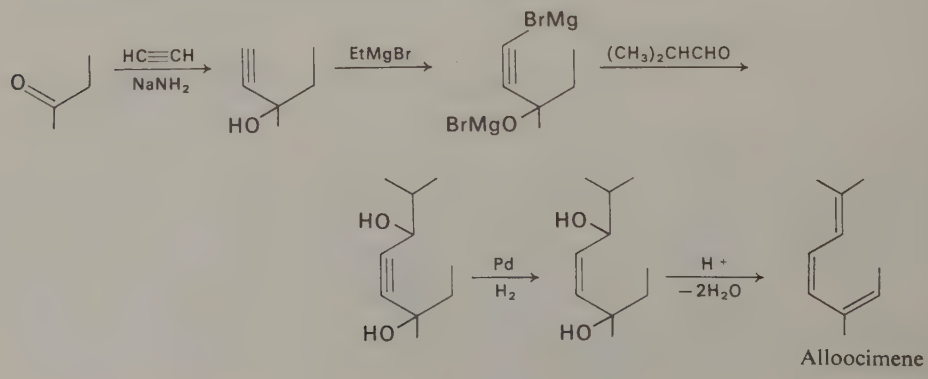
(4)

Alloocimene is formed by pyrolysis of α-pinene:



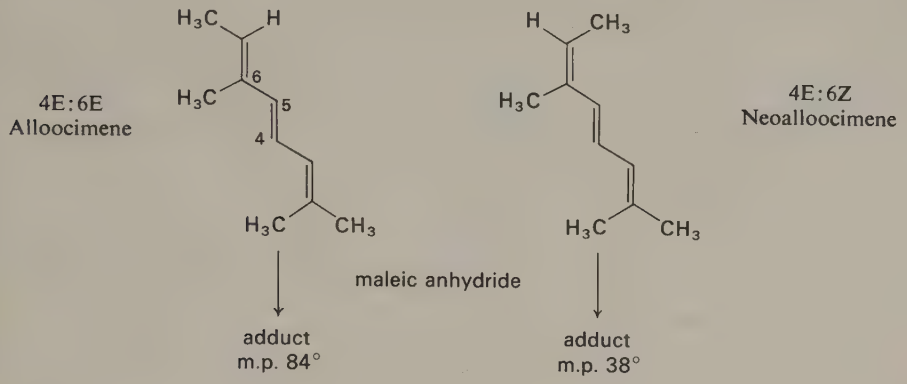
(5)

The synthesis of alloocimene has been carried out as follows:



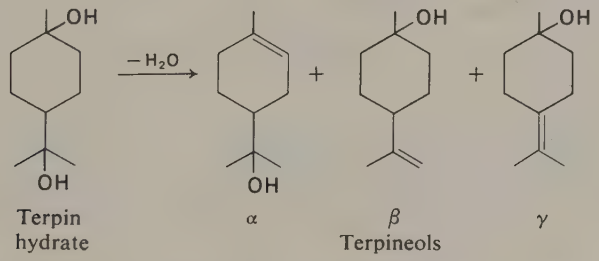
(6)

Although the conventional representation of alloocimene used above indicates that the 4,5 double bond is *cis*, it is known that alloocimene is in fact a mixture of stereoisomers, principally the 4-*trans*-6-*trans* (4E, 6E) and the 4-*trans*-6-*cis* (4E, 6Z) compounds:



40-3 The terpineols, terpinolenes, and terpins

The terpineols are isomeric monocyclic terpene alcohols derived from terpin hydrate by dehydration:

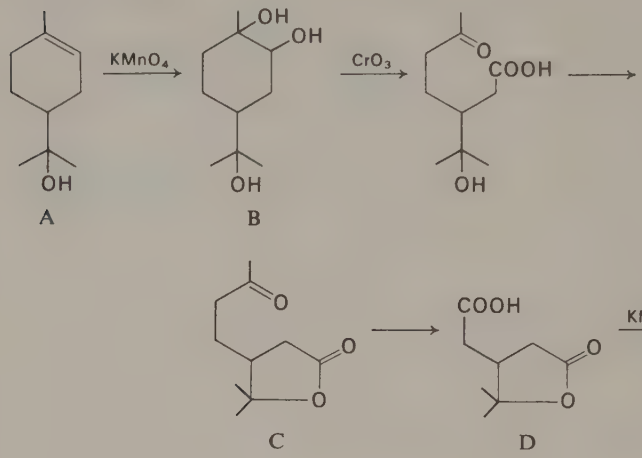


(7)

The terpineols can be obtained as individual compounds from natural sources or by separation (distillation, crystallization) of mixtures of the isomers.

α-Terpineol (A), $C_{10}H_{18}O$, is a crystalline compound that occurs in nature in both optically active and racemic forms. Its structure is established in the following way. It adds one mole of bromine, and takes up one mole of hydrogen on catalytic reduction. This establishes its structure as that of a monocyclic, monounsaturated compound. Careful oxidation of α-terpineol with dilute aqueous $KMnO_4$ yields a triol (B); this can be oxidized further to a carboxylic acid that lactonizes readily to yield a keto lactone (C). The keto lactone gives a positive iodoform reaction, indicating the presence of the CH_3CO— grouping. Further oxidation, in controlled stages, of

C yields terpenylic acid (D) and finally terebic acid (E). These steps can be formulated as follows:

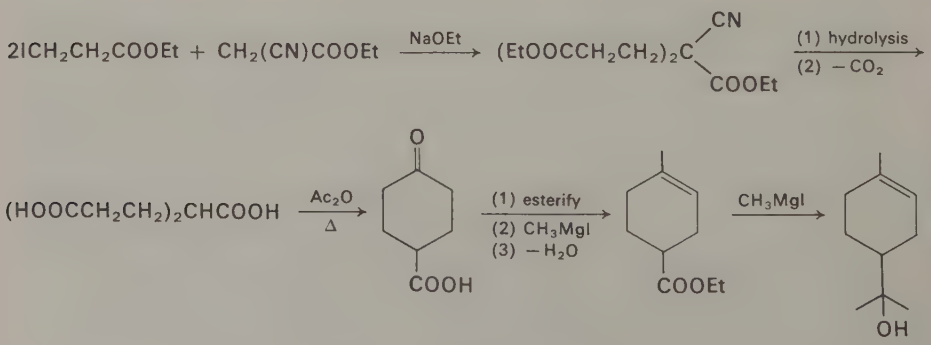


(8)

Exercise 1

Devise a synthesis for terebic acid (E), starting with ethyl acetoacetate and ethyl bromoacetate and using any other necessary reagents.

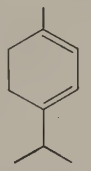
The structure of α-terpineol was established by its total synthesis, confirming the structural assignment made by earlier workers, which was based upon the synthesis of terpenylic and terebic acids (D, E). The synthesis of (±)-α-terpineol was the following:



(9)

Dehydration of (±)-α-terpineol yields two products, dipentene (F) and terpinolene (G).* Terpinolene, $C_{10}H_{16}$, has no UV absorption above 200 nm. It is a monocyclic diene in which the double bonds are not conjugated. When terpinolene is allowed to remain in contact with strong acid it isomerizes to α-terpinene (H). α-Terpinene has UV λ_{max} 262 nm ($\epsilon = 4200$) and forms a Diels-Alder adduct with maleic anhydride. It is readily dehydrogenated in good yield (by heating with sulfur) to *p*-cymene (*p*-isopropyltoluene).

The fact that α-terpinene is a diene, coupled with its UV absorption at 262 nm, can only be accounted for if it is a 1,3-cyclohexadiene, with the structure

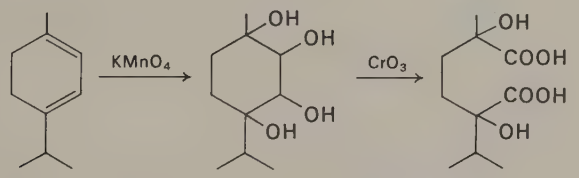


α-terpinene (H)

Careful oxidation of α-terpinene with $KMnO_4$ yields the tetrahydroxy compound I. Further oxidation of I leads to the dicarboxylic acid J.

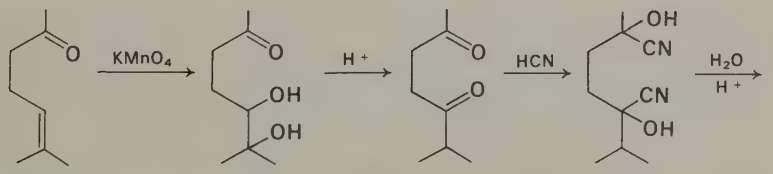
Exercise 2

What are the structures of terpinolene (G) and dipentene (F)?



H I J (10)

The structure of J was confirmed by the following synthesis:



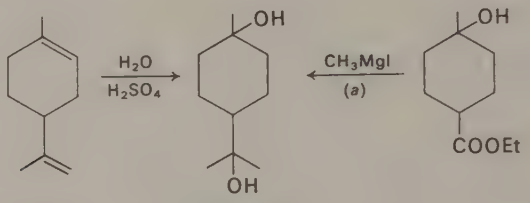
K L M (11)

* Dehydration of optically active α-terpineol yields optically active dipentene. This bears the special name *limonene*, and is widely distributed in nature, principally in oils of citrus fruits. Terpinolene is non-resolvable.

Exercise 3

Show the course of the acid-catalyzed conversion of L into M.

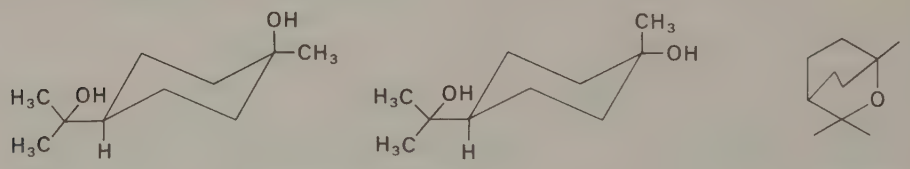
1,8-Terpin is formed by the hydration of dipentene (F) with aqueous (60%) sulfuric acid. It can also be prepared by the synthetic route shown (12*a*), in which the starting ester is one of the intermediates in the total synthesis of α-terpineol (9):



(12)

F 1,8-terpin

Terpin is known in two forms, *cis*-terpin and *trans*-terpin. One of these forms a stable hydrate, $C_{10}H_{20}O_2 \cdot H_2O$; the other does not. Both *cis*- and *trans*-terpin can be dehydrated with acids to the cyclic ether, 1,8-cineole. The isomer that forms the stable hydrate undergoes this dehydration much faster than the other.



Isomeric 1,8-terpins 1,8-cineole

Exercise 4

Which of the two terpins would you expect to form 1,8-cineole more rapidly? From this conclusion, can you suggest a reasonable explanation for the fact that this terpin is the one that forms the stable hydrate?

Exercise 5

Is 1,8-cineole capable of existing in enantiomeric forms?

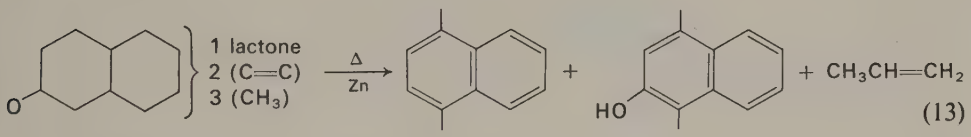
40-4 The structure of santonin

α-Santonin, $C_{15}H_{18}O_3$, is a compound occurring in certain European and Asian species of the plant genus *Artemisia*.* It has been known since 1829 and, like many plant products studied intensively in earlier years, was of interest because of its medicinal value. It is an anthelminthic compound used in both human and veterinary medicine, although its present-day clinical use is minimal.

Despite the efforts of many organic chemists, extending over fifty years, the correct structure for santonin was elusive, and was not arrived at until 1930. The correct stereochemistry was not established in all details until some thirty years later.

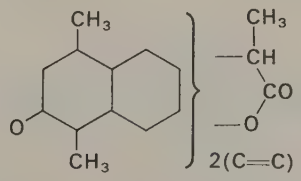
Santonin (A) is an optically active *lactone*. It is a neutral compound that dissolves in warm alkali as the salt of a hydroxy acid (B) and is regenerated unchanged on acidification. It is a *ketone*: it forms an oxime (C) and other carbonyl derivatives. It can be hydrogenated catalytically to a tetrahydro compound and thus contains *two carbon-carbon double* bonds. From these observations, and its elemental composition, it can be concluded that santonin contains two carbocyclic rings.

Among the observations made in early studies was that when santonin was strongly heated with zinc dust there were formed 1,4-dimethylnaphthalene, 1,4-dimethyl-2-naphthol, and propylene. These facts suggested that the two carbocyclic rings of santonin are present as a reduced naphthalene nucleus containing an oxygen substituent in the position shown in the following partial structure:



Santonin (13)

The 1,4 position of the methyl groups in these naphthalene derivatives led early investigators to assume that santonin could be represented by the partial structure



As will be seen in what follows, this assumption was incorrect; nevertheless, at that time it was supported by further evidence.

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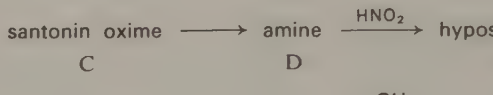
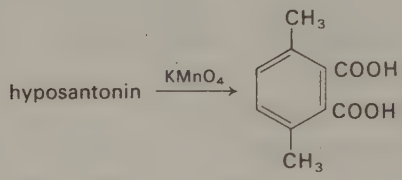
* Two stereoisomers, α- and β-santonin, occur in nature. In this discussion α-santonin will be referred to simply as santonin.

Santonin oxime (C) could be reduced to the corresponding amine (D) ($\rangle C{=}NOH \rightarrow \rangle CHNH_2$), and treatment of the amine with nitrous acid yielded hyposantonin (E), $C_{15}H_{18}O_2$. Oxidation of hyposantonin with potassium permanganate gave 3,6-dimethylphthalic acid:



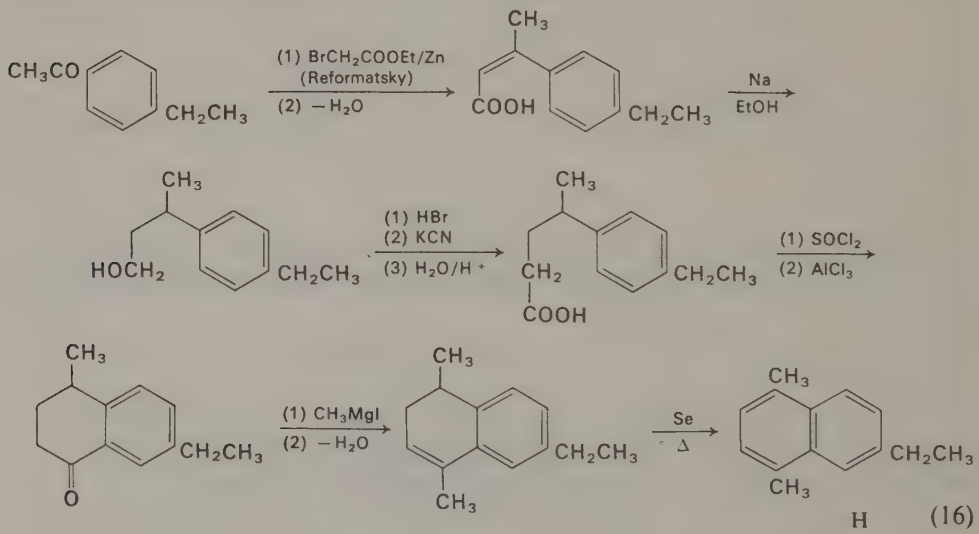
(14)



(15)

This result is clearly consistent with the partial structure shown above.

When hyposantonin was heated with hydrochloric acid it was converted into a carboxylic acid (F), $C_{15}H_{18}O_2$, and F could be aromatized to a naphthalene derivative (G) by treatment with iodine in acetic acid (a dehydrogenation). Decarboxylation of G yielded 1,4-dimethyl-6-ethylnaphthalene (H), the identity of which was established by the following synthesis:*



(16)

Treatment of santonin with concentrated hydriodic acid brings about aromatization and reductive opening of the lactone ring, with the formation of santonous acid:

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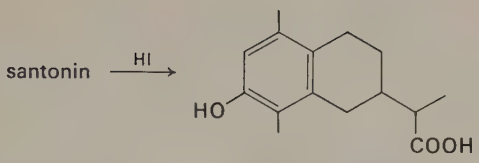
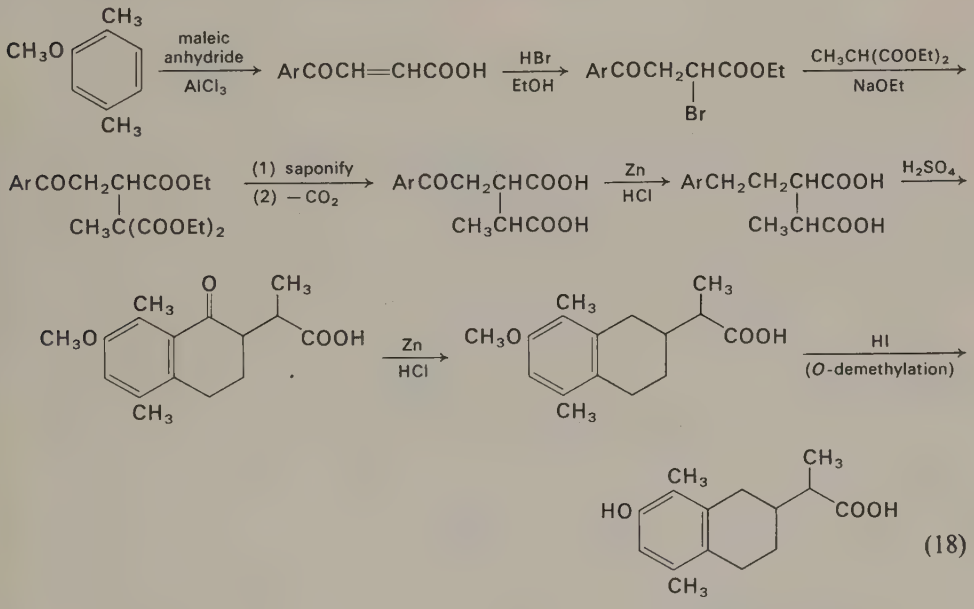
* Nearly all of the reactions shown in this chapter are examples of those discussed in earlier parts of the text. They should be referred to.



(17)

Santonous acid (I)

The structure of santonous acid was established by synthesis; the acid, prepared as follows, was the racemic compound identical with the product from santonin (in these equations, Ar = 2,5-dimethyl-4-methoxyphenyl):



(18)

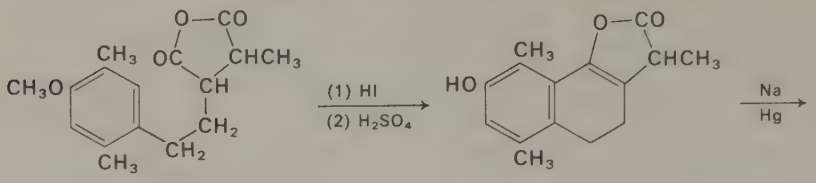
(±)-santonous acid (I)

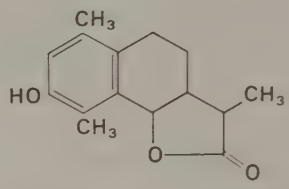
Exercise 6

In an alternative intermediate step (not shown) in the above sequence, the reaction of $ArCOCHCH_2COOEt$ (Br) with $Na[CH_3C(COOEt)_2]$ gave the product $ArCOCH_2CHCOOEt$ ($CH_3C(COOEt)_2$), rather than $ArCOCHCH_2COOEt$ ($CH_3C(COOEt)_2$). Explain; show the course of the reaction.

When santonin is heated with concentrated hydrochloric acid it is transformed into desmotroposantonin (J). Since desmotroposantonin could also be transformed

into santonous acid by reduction, it was formulated as the lactone J, the structure of which was established by the following synthesis:



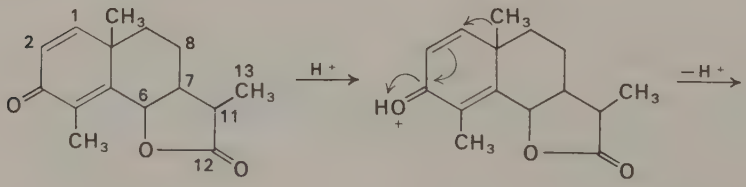


(19)

(±)-desmotroposantonin (J)

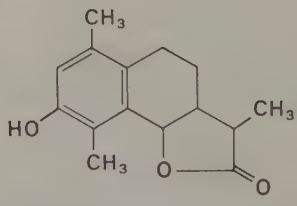
At this point, after some fifty years of studying santonin, the structures that had been advanced by various investigators were all based upon what was to prove to be the erroneous assumption that the two methyl groups found in the 1,4 positions of the several transformation products were in the same positions in santonin. Needless to say, none of these structures was entirely acceptable.

In 1929, Clemo, Haworth, and Walton (*Journal of the Chemical Society*, 1929, p. 2368) pointed out that such structures for santonin did not follow the isoprene rule, but that if hyposantonin and desmotroposantonin were assumed to be the products of rearrangement, the known facts could be accommodated by a new structure for santonin.*



A

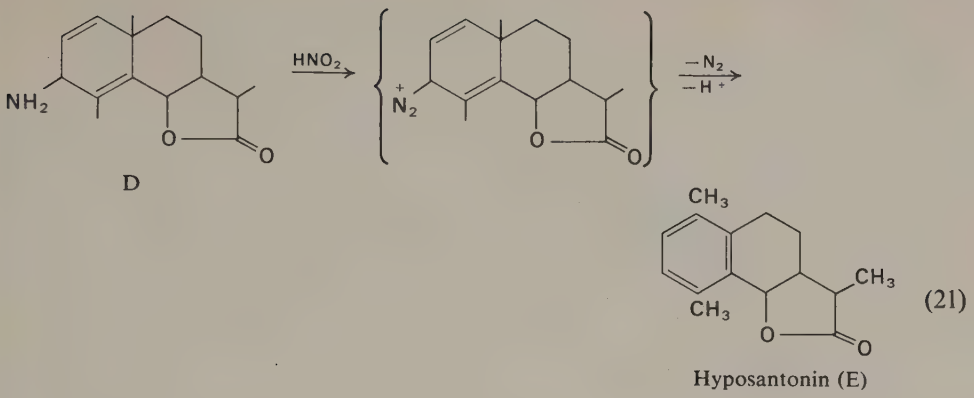
oxime (C)



(20)

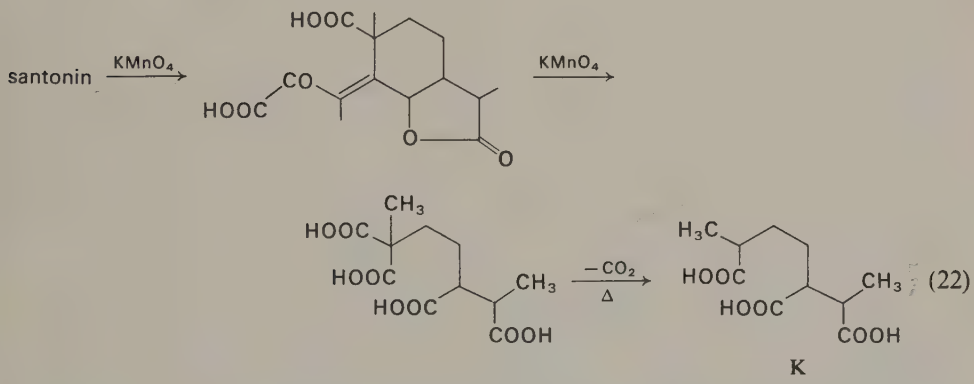
Desmotroposantonin (J)

* The lactone ring was incorrectly placed in the 1929 paper, but this was corrected (as in A) in *Journal of the Chemical Society, 1930*, p. 1110. Moreover, the stereochemistry was not known at this time.



(21)

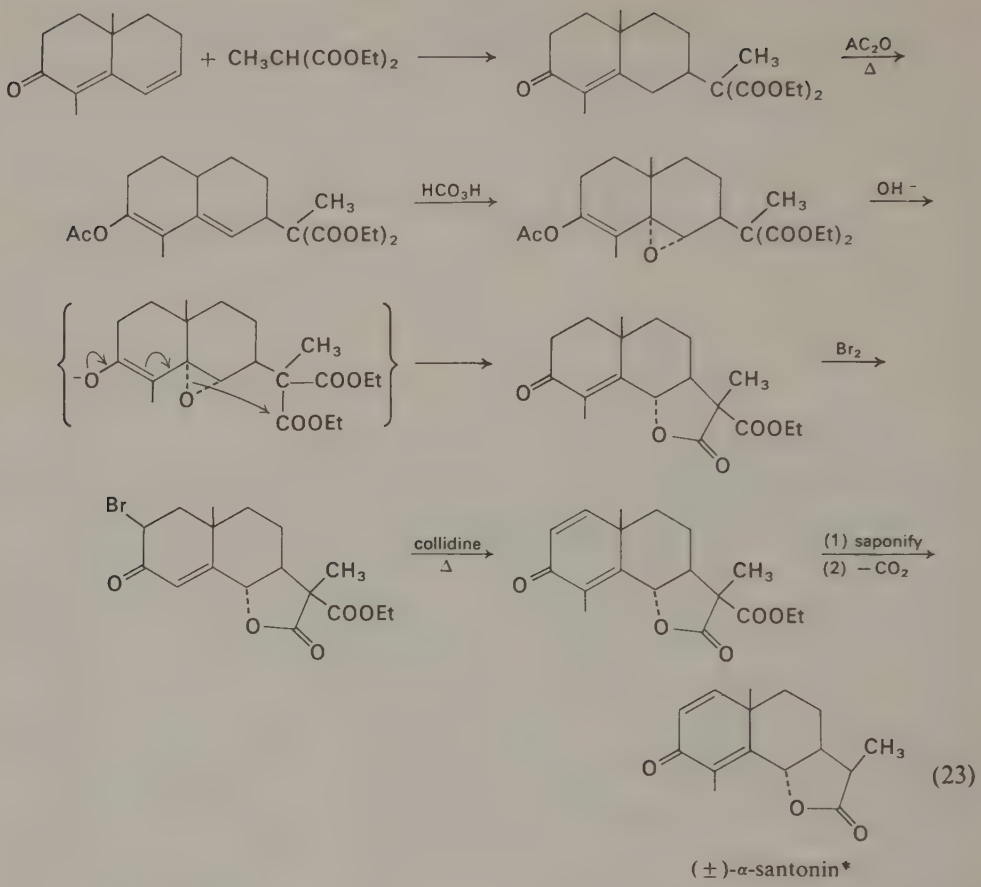
Further confirmation of the carbon skeleton of santonin was obtained by the extensive oxidative degradation of santonin to the tricarboxylic acid K (the structure of which was also confirmed by its synthesis):



(22)

The above structures of santonin and the various transformation products described are formulated without explicit designation of stereochemical configurations. Santonin has three asymmetric centers, and the natural compound could be any of eight stereoisomers. The studies up to 1930 were not of such a nature as to reveal stereochemical features of santonin and its derivatives, and it was not until some twenty years later that a part of the problem was resolved by a total synthesis of santonin. This was accomplished in the following way, and led to the conclusion, based upon the probable stereospecificity of the reactions used, that the lactone ring is *trans*, with the lactonic oxygen α and the C-7/C-11 bond β oriented (Eq. 23).

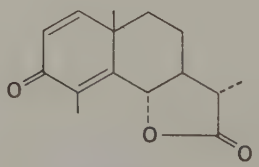
The configuration of the last asymmetric center, at C-11, remained in doubt for some time. Indeed, arguments based upon considerations of conformational probability led to the erroneous conclusion that in natural (α) santonin the C-13 methyl



(23)

(±)-α-santonin*

group was β oriented. At length a total structure determination by X-ray crystallographic methods showed that α-santonin has the structure shown below. β-Santonin, the naturally occurring isomer, differs from this only in that the C-13 methyl group is in the β configuration.

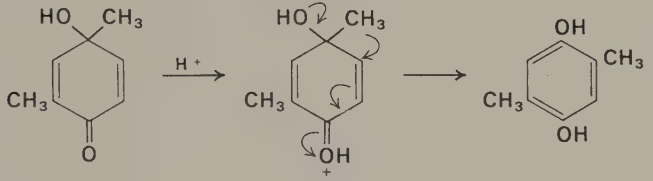


α-santonin (A)

* Natural (−)-α-santonin was prepared by resolution of the 11-carboxylic acid prior to the final decarboxylation step.

40-5 Physical properties of α-santonin

There is no doubt that the prolonged and often controversial chemical studies devoted to the determination of the santonin structure led to an enrichment of knowledge in organic chemistry. They made use of and contributed to concepts and techniques that were in the process of development during the early years of the present century. For example, a discovery announced by Bamberger in 1900, long overlooked in its application to the santonin problem, was cited by Clemo and his co-workers in support of their structural proposal. Bamberger had found that the following acid-catalyzed rearrangement occurred:



(24)

This was clearly analogous to the santonin → desmotroposantonin change and offered persuasive mechanistic support for placing the methyl group of santonin at the C-10 position.

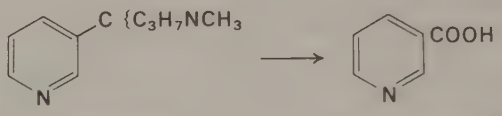
A modern attack upon the problem of the structure of santonin would have led to a quick solution. The UV, IR, and NMR spectra of santonin contain highly characteristic features that, along with the molecular formula and the assumption that santonin is terpenoid, would allow immediate construction of a formula complete in nearly all details except those of absolute configuration.

The UV spectrum of santonin shows a maximum at 238 nm ($\log \epsilon = 4.1$) that is characteristic for the cyclohexadienone system of the santonin A ring. The IR spectrum shows absorption at 1785 cm^{-1} (γ-lactone), 1668 cm^{-1} (α,β-unsaturated ketone), and 1639 cm^{-1} and 1619 cm^{-1} (carbon-carbon double bonds).

The NMR spectrum shows three 3-proton signals: (1) a doublet (J = 6 Hz) at δ = 1.30 (CH_3 at C-11); (2) a singlet at δ = 1.39 (CH_3 at C-10); and (3) a singlet at δ = 2.10 (CH_3 at C-4). The protons at C-1 and C-2 are seen as two doublets (J = 10 Hz) at δ = 6.18 and δ = 6.65, highly characteristic of the system —CO—$CH^{c}{=}$ CH— in the A ring. The lactonic proton at C-6 is seen as a 1-proton doublet, the coupling constant of which (J = 7 Hz) clearly indicates its *trans*-diaxial relationship with the proton at C-7. It is apparent that these observations are completely interpretable in terms of the structure A, except for the configuration at C-11 and the absolute stereochemistry of the compound.

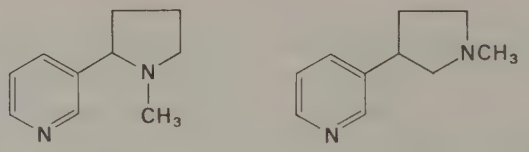
40-6 The structure of nicotine

The tobacco plant, *Nicotiana tabacum*, contains a number of alkaloids, most of them belonging to a group of compounds closely related in structure. The major alkaloid is (−)-nicotine (A), an optically active basic compound, $C_{10}H_{14}N_2$. Nicotine was first isolated in 1829 but its structure was not established until more than sixty years later. The formula of nicotine is derived from several degradation reactions. Direct oxidation with chromic acid yields nicotinic acid (B).* This result locates six of the ten carbon atoms of nicotine and places five of them in a pyridine ring:



Nicotine (A) Nicotinic acid (B) (25)

Nicotine contains an *N*-methyl group, as shown by the Herzig-Meyer analysis (Section 16-10). All that remains to be accounted for is the three-carbon portion (C_3H_7). Since nicotine contains no unsaturation, the elemental composition shows that the ($C_3H_7NCH_3$) portion must be cyclic. The most obvious assumption is that this fragment is a pyrrolidine ring, and that nicotine is either C or D:



C D

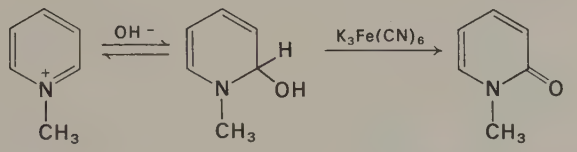
Either of these would account for the optical activity of the alkaloid. The correctness of this first (approximate) assumption is supported by the observation that when nicotine is strongly heated with zinc chloride extensive decomposition occurs with the formation of pyridine, pyrrole, and methylamine. While this supports C and D, it does not distinguish between them.

When nicotine and methyl iodide are allowed to react, two isomeric monomethiodides (as well as a dimethiodide) are formed, an indication that both nitrogen atoms are basic and nucleophilic. One of the methiodides (E) is the pyridinium methiodide, $(C_5H_4\overset{+}{N}CH_3 \cdot C_4H_7NCH_3)I^-$; the other (F) is the pyrrolidinium methiodide, $(C_5H_4N \cdot C_4H_7\overset{+}{N}(CH_3)_2)I^-$.

---

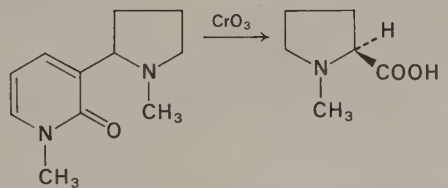
* Because of the abundance of tobacco, grown as an important commercial crop, nicotine is the principal source of the vitamin nicotinic acid (niacin), an important dietary supplement.

The position of attachment between the pyridine and pyrrolidine rings was established by application of a reaction characteristic of *N*-alkylpyridinium salts. Oxidation of an *N*-methylpyridinium salt with alkaline potassium ferricyanide yields *N*-methyl-2-pyridone:



(26)

When this procedure was applied to nicotine methiodide F, the pyridone G was formed. This compound was then oxidized further with chromic acid, with destruction of the pyridone ring, leaving L-hygrinic acid (H) as the product:



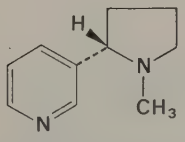
(27)

G L-hygrinic acid (H)

Exercise 7

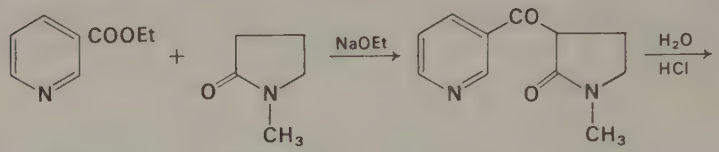
Does L-hygrinic acid have the R or the S configuration?

Since L-hygrinic acid is a compound of known stereochemistry, this result accomplishes a complete definition of the structure of (−)-nicotine, which is

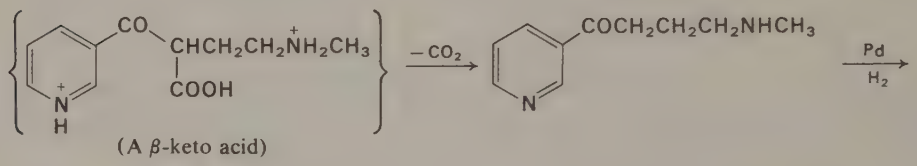


The synthesis of nicotine has been accomplished by various investigators using a

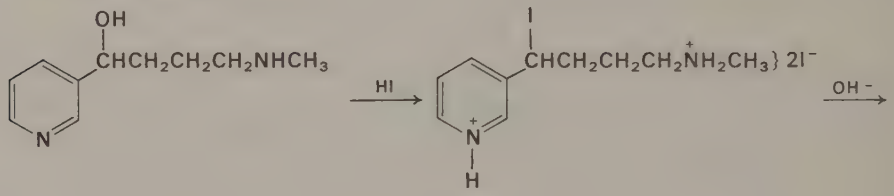
number of different routes. One of these, by Späth and Bretschneider (1928), is the following:

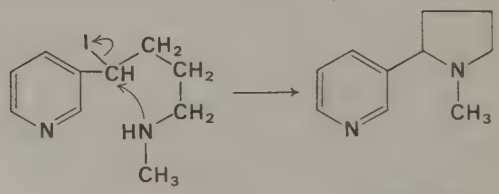


Ethyl nicotinate — *N*-methyl-2-pyrrolidone



(A β-keto acid)





(28)

(±)-nicotine
[resolved with tartaric acid→(−)-nicotine]

Exercise 8

Explain each step of this reaction sequence, either by pointing out the general reaction type of which it is a special example, or by a brief statement describing the mechanistic principle involved.

40-7 The structure of dioscorine

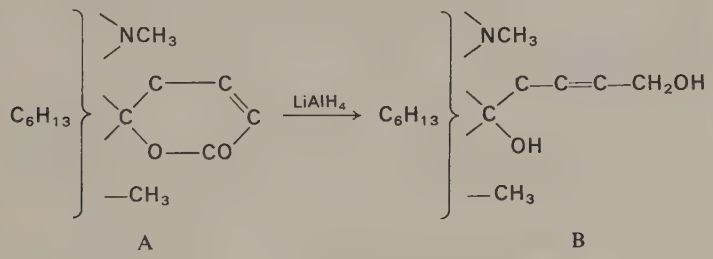
The alkaloid *dioscorine* occurs in plants of the genus *Dioscorea* (*D. hirsuta*, *D. hispida*). Dioscorine is bitter and poisonous. It was first isolated in 1894 and studied rather

inconclusively until 1911, at which time its structure was still not established. The investigation of dioscorine was taken up again about 1950 by three groups of chemists, with the results to be described.

Dioscorine (A), $C_{13}H_{19}O_2N$, is a tertiary amine, containing one *N*-methyl group. It contains one carbon-linked methyl group, and is a lactone that dissolves when warmed with alkali. Acidification regenerates the lactone. It can be reduced to a dihydro compound.

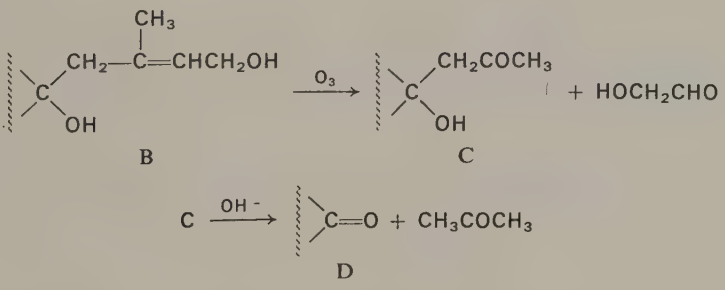
Its IR and UV spectra indicate that the compound contains an α,β-unsaturated δ-lactone. The UV spectrum showed a single maximum at 217 nm and the IR spectrum a band at 1712 cm^{-1}. These values, compared with those of simple model compounds (δ-hexenolactone, δ-hexanolactone) indicated the presence of an α,β-unsaturated δ-lactone ring.

Reduction of the alkaloid with lithium aluminum hydride gave an unsaturated diol (B). These results can be expressed in the following partial formulation:



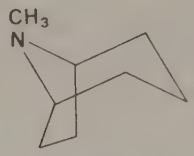
A B (29)

Ozonolysis of the diol B gave glycolic aldehyde ($HOCH_2CHO$) and a methyl ketone (C), $C_{11}H_{19}NO_2$. Treatment of the ketone C with alkali yielded acetone and a keto amine (D), $C_8H_{13}NO$.



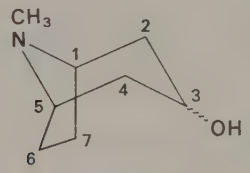
B C D (30)

At this point consideration was given to the fact that there occur widely in nature many alkaloids derived from tropane (E). Since a ketone derived from E has the composition $C_8H_{13}NO$, it was concluded that the keto base D was probably a tropane derivative.

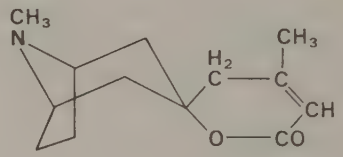


Tropane (E)
$C_8H_{15}N$

Although most naturally occurring tropane alkaloids are derived from 3-tropanol (F), it is clear that dioscorine, which is optically active, cannot be G. The keto base D would therefore be expected to be 2- or 6-tropanone.



3-tropanol (F)
(OH α or β)

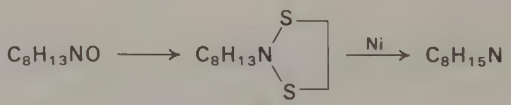


G

Exercise 9

Comment on the statement, "Dioscorine, which is optically active, cannot be G." Why is this true?

The keto base D from dioscorine was reduced to the oxygen-free compound by converting it into the cyclic thioketal (H), which upon desulfurization with Raney nickel gave a base (I), $C_8H_{15}N$. Base I was reported to be identical with tropane (E).



D H I (31)

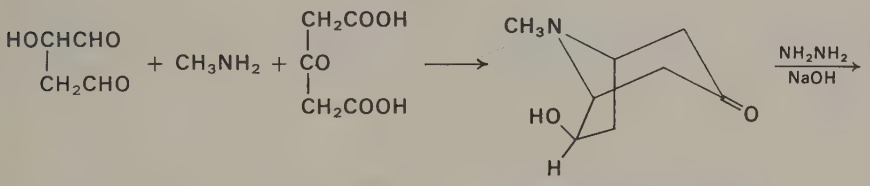
If D is indeed a tropanone, it must be either 2- or 6-tropanone; the latter was first chosen as most probable on two grounds: (1) the IR spectrum of D showed a carbonyl band at 1730 cm^{-1}, which is too high for a six-membered cyclic ketone; and (2) the methiodide of D underwent Hofmann elimination with extreme ease ($NaHCO_3$, 30°).

Exercise 10

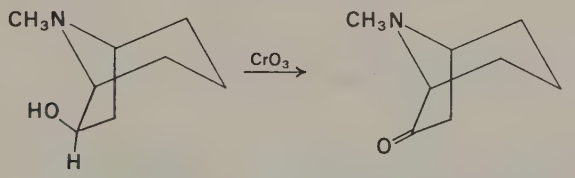
Why would Hofmann degradation of 6-tropanone be expected to proceed faster than that of 2-tropanone?

Both of these observations were accepted as strong indications that keto base D was 6-tropanone and that dioscorine was the corresponding 6-spirolactone.

The validity of these conclusions was then challenged by another investigator. The model compound 1-methyl-3-pyrrolidone was found to have IR absorption at 1765 cm^{-1}, not at 1730 cm^{-1} as observed for base D. Finally, 6-tropanone was synthesized and found to be different from base D:



6β-hydroxy-3-tropanone



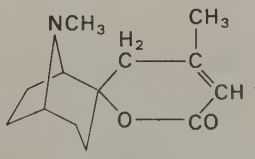
(32)

Tropane-6β-ol

6-tropanone (*not* identical with compound D from dioscorine), IR 1750 cm^{-1}

A repetition of the preparation of base D from dioscorine confirmed its non-identity with 6-tropanone (IR comparison).

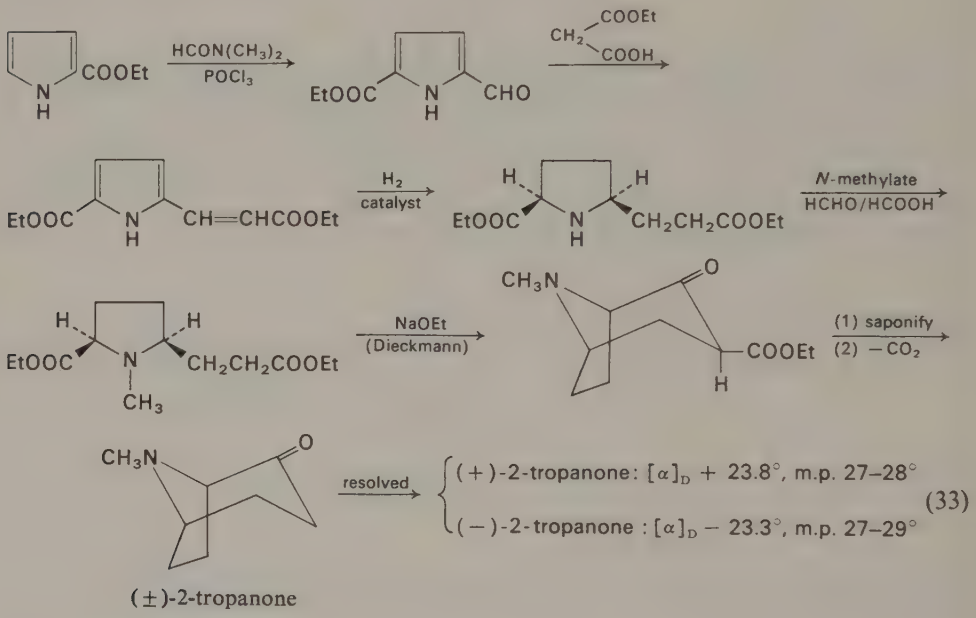
The conclusion from all of the above evidence was that, since keto base D was either 2- or 6-tropanone and was shown *not* to be 6-tropanone, dioscorine had the structure



J

As will be shown in what follows, all of the above conclusions are erroneous. *Dioscorine is not J, nor is it the corresponding compound with the spirolactone ring at the 6 position. In fact, it is not a tropane derivative.*

The synthesis of 2-tropanone provided final proof that the keto base D was not this compound:



(33)

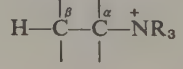
(+)-2-Tropanone prepared by another investigator had m.p. 27°, $[\alpha]_D$ +23°. 2-Tropanone was compared with the keto base D from dioscorine; they were different compounds. Thus, D is neither 2-, 3-, nor 6-tropanone.

It was now clear that the base I could not be tropane.

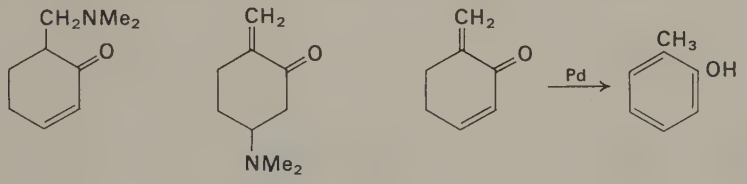
The Hofmann degradation of D methiodide, an unusually facile reaction, was then reexamined. Treatment of the methiodide of D with sodium bicarbonate solution (room temperature) resulted in the formation of two compounds, a base K and a neutral compound L:*

$$\underset{\text{D methiodide}}{C_8H_{13}NO\cdot CH_3I} \xrightarrow{HCO_3^-} \underset{\text{K}}{C_9H_{15}NO} + \underset{\text{L}}{C_7H_8O} \qquad (34)$$

* Hofmann degradation under such mild conditions usually indicates the presence of an *activated* β-hydrogen atom in the system



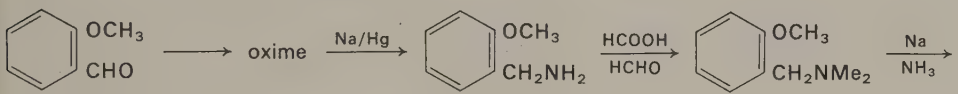
Compound L showed a UV maximum at 243 nm ($\log \epsilon = 4.06$) and IR absorption at 1675 cm^{-1} (α,β-unsaturated ketone), 1620 cm^{-1} (C=C), and 942 cm^{-1} (conjugated $\diagdown$C=CH_2). When an attempt was made to reduce it (Pd-hydrogen) it was isomerized (with no uptake of hydrogen) to *o*-cresol (35). These data show that L is 2-methylene-5-cyclohexenone, and that K has one of the structures K_1 or K_2:

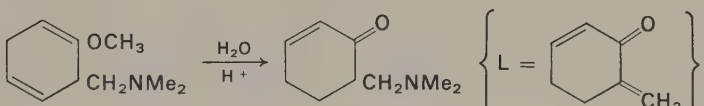


(35)

K_1 K_2 L

That base K is actually K_1 was proved by its synthesis:

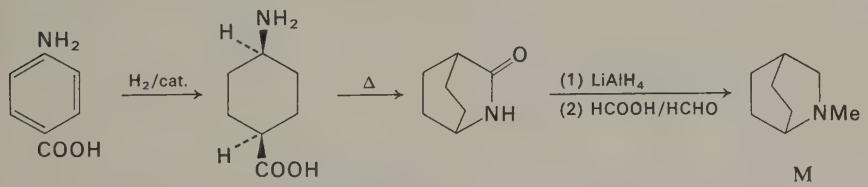




(36)

(±) K

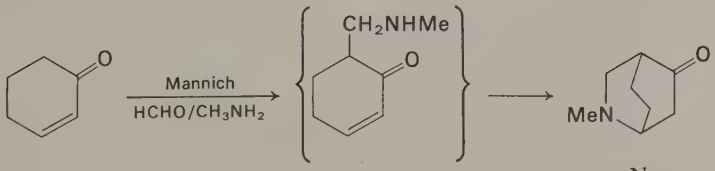
The amine (I) earlier obtained by reduction of the keto base D, and erroneously identified as tropane, was therefore M; this conclusion was substantiated by its synthesis:



(37)

M

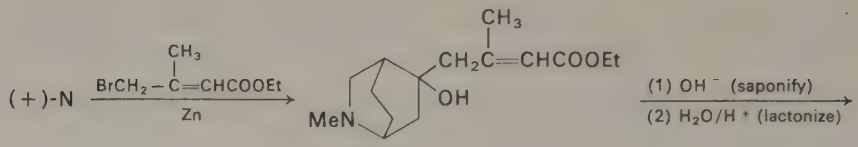
The structure of the keto base D can now be seen to be N. This was synthesized:

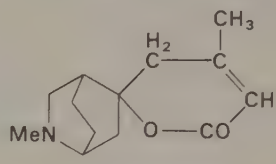


(38)

N
(keto base D)

A final synthesis of dioscorine itself started from N. This was first resolved into (+) and (−) forms, and the final step carried out as follows:

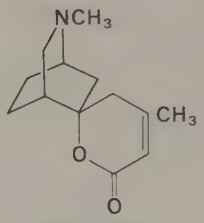




(39)

(−)-dioscorine

A recent final determination of the absolute configuration of (−)-dioscorine has established it as the following:

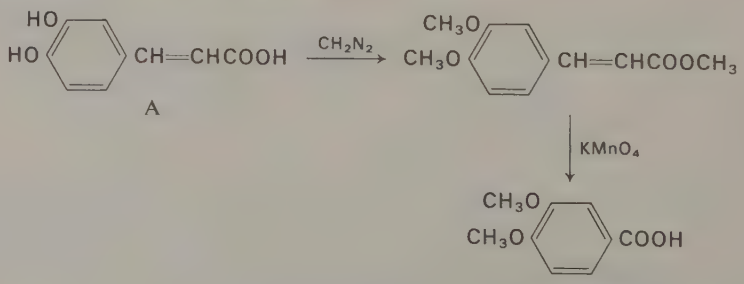


Dioscorine

40-8 Chlorogenic and quinic acids

Chlorogenic acid is a widely distributed phenolic compound that occurs in many plants. It is a colorless compound whose metabolic function in the organism is unknown. It consists of two structurally unrelated (but biosynthetically related) compounds combined in ester linkage. Saponification of chlorogenic acid yields caffeic acid (A) and quinic acid (B).

The structure of caffeic acid, $C_9H_8O_4$, can be established with ease. Methylation with diazomethane yields a trimethoxy compound, one methyl group of which is present in a methyl ester. Permanganate oxidation of the methylated compound yields veratric acid, a well-known compound:

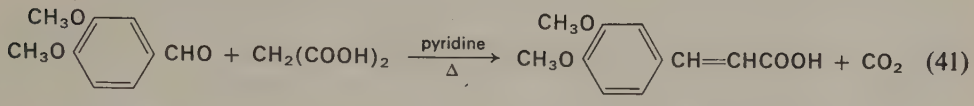


A

(40)

Veratric acid

The completion of the structure proof can be accomplished either by examination of the NMR spectrum, which is clearly that of a cinnamic acid, or by synthesis of the dimethyl ether of the acid:



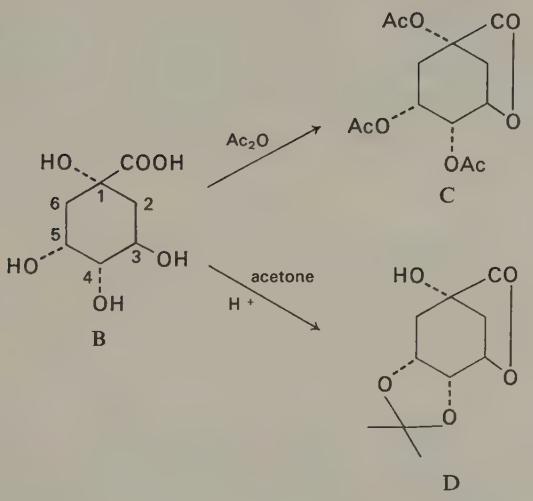
(41)

Veratraldehyde

Di-*O*-methylcaffeic acid

Quinic acid, first isolated as the free acid from cinchona bark in 1809, is an optically active tetrahydroxycyclohexanecarboxylic acid, of which three hydroxyl groups are in a 1,2,3 relationship. Its carbocyclic structure was long known, since early investigations showed that it was readily converted into aromatic compounds (for example, into 3,4-dihydroxybenzoic acid).* The disposition of the four hydroxyl groups was not established until H. O. L. Fischer took up its study in 1921.

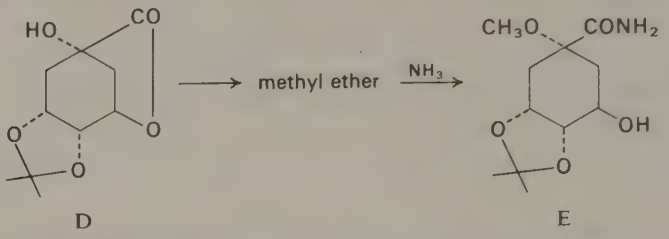
Upon treatment with acetic anhydride, quinic acid (B) readily forms a tri-*O*-acetyl lactone (C). This showed that the carboxyl group and at least one of the hydroxyl groups were *cis*-disposed. Treatment of quinic acid itself with acetone and an acid catalyst gave a di-*O*-isopropylidene derivative (an acetonide) of a hydroxyl lactone (D). These reactions can be formulated as follows (using the correct structure for quinic acid):



(42)

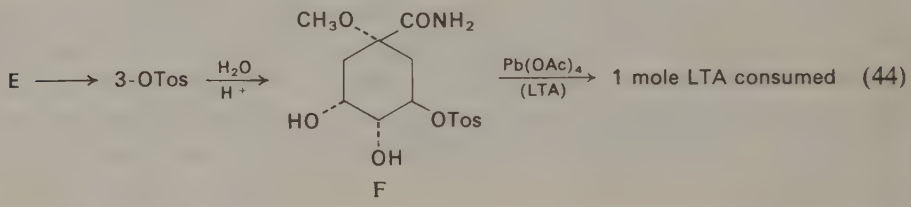
* Quinic acid can be oxidized to *p*-benzoquinone, often called simply *quinone*. The derivation of the name of this well-known compound is thus apparent.

Methylation of D with silver-oxide/methyl-iodide gave a monomethyl ether, and treatment of this with ammonia opened the lactone to the amide (E).



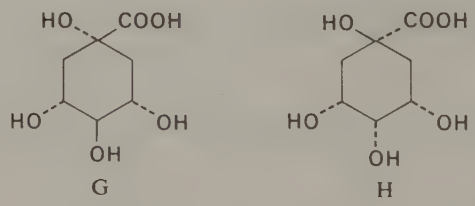
(43)

Preparation of the mono-tosylate (*p*-toluenesulfonate) of E and removal of the acetone grouping by aqueous acid gave the 4,5-diol (F). This consumed one mole of lead tetraacetate (LTA), showing the presence of one pair of adjacent —OH groups, presumably *cis* disposed.



(44)

Let us now examine some proposals. In the first place, the lactone must be either a 5- or 6-membered lactone (a 3- or 4-membered lactone would not form under the given conditions). If the lactone involved the —OH group at C-4, the acetone derivative would have to be that formed between hydroxyl groups at C-3 and C-5, which would require that they be *cis* to each other. Thus, these assumptions lead to the conclusion that quinic acid must be either G or H:



Neither of these can be correct, for neither could be optically active. The lactone ring, then, must be formed between —COOH and an —OH group at C-3. Further, because of the ease of formation of the acetonide, the two —OH groups (at C-4 and C-5) are probably *cis*. (NOTE: If they were *cis* and β oriented, and if OH at C-3 is also β, the compound would also be optically inactive and *non-resolvable*.)

Exercise 11

Why would the structure with *cis* relationships between —COOH and the —OH's at C-3, C-4, and C-5 (that is, structure H) be optically inactive?

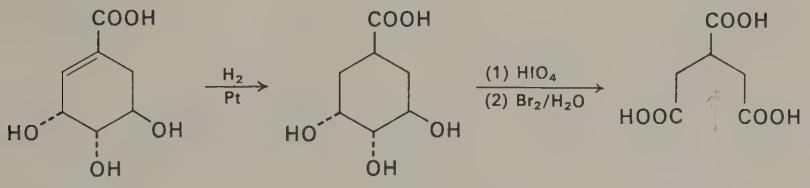
The conclusion from these observations is that quinic acid has the structure and configuration B. This was confirmed by studies on a related compound, shikimic acid, described in the following section.

40-9 Shikimic acid

Shikimic acid is a compound universally distributed in the plant world, and is the biological precursor of the important amino acids phenylalanine and tyrosine.* The proof of its structure and stereochemistry was also a final confirmation of the proof of the structure and stereochemistry of quinic acid.

Since shikimic acid (I) and quinic acid occur together in many plants, and because shikimic acid is simply quinic acid minus the elements of water, it was an early assumption that the two are closely related in structure.

Shikimic acid contains a carbon-carbon double bond and can be reduced catalytically to dihydroshikimic acid (J). Oxidation of J with periodic acid, followed by oxidation of the resulting dialdehyde with bromine water, gives the well-known tricarballylic acid K:



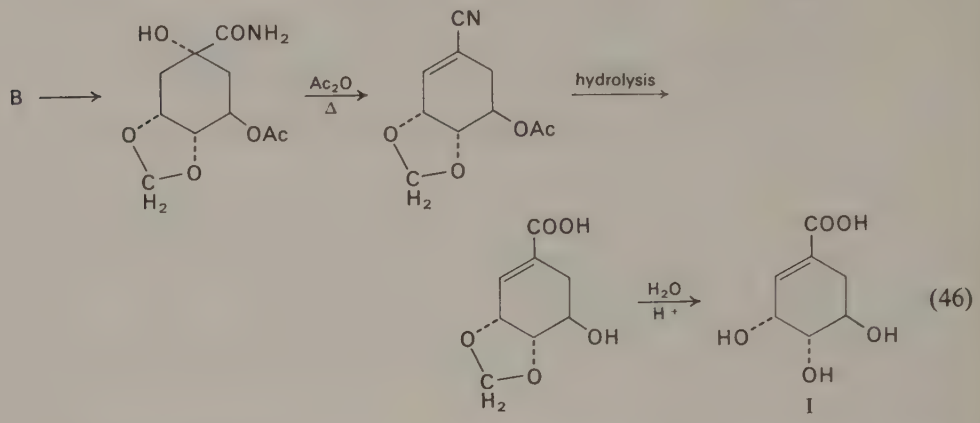
(45)

I J K

This was an immediate confirmation of the gross structure I; it did not, of course, disclose the steric disposition of the hydroxyl groups.

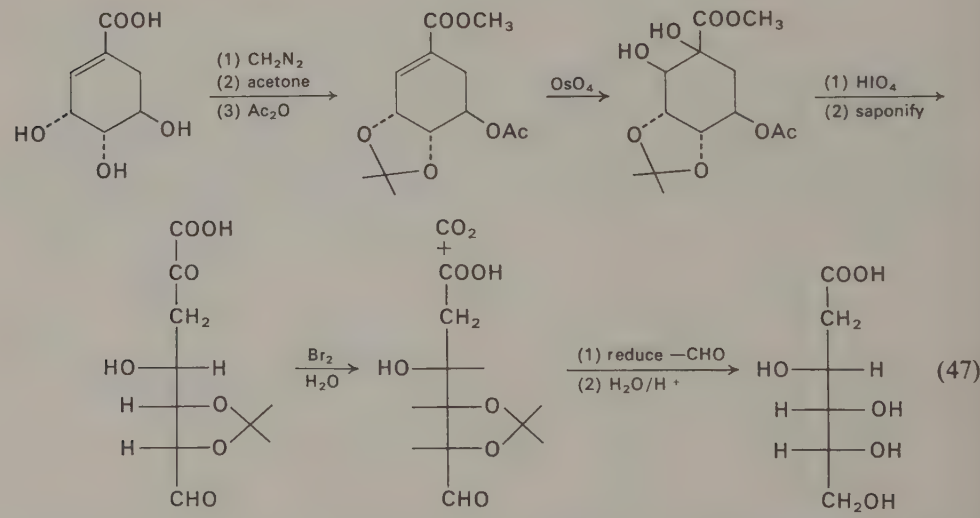
* Shikimic acid is not involved in animal biosynthesis. Phenylalanine is an *essential* amino acid: it is not synthesized in mammalian organisms and must be derived from dietary sources, ultimately from plants.

Quinic acid was converted into shikimic acid by the following steps:*



(46)

A final proof of the absolute configuration of shikimic acid (and therefore of quinic acid), as well as of the location of the double bond, was accomplished by converting shikimic acid into a D-glucose derivative of known configuration at C-3, C-4, and C-5 (2-deoxy-D-gluconic acid):

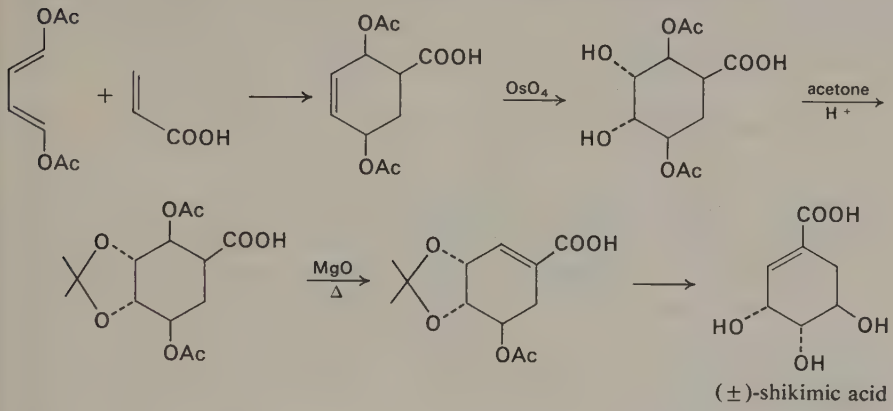


(47)

2-deoxy-D-gluconic acid (structure and configuration known)

* Note that the protection of the C-4 and C-5 hydroxyl groups in these transformations was effected with formaldehyde instead of acetone.

The total synthesis of shikimic acid has been carried out by a number of investigators, by a variety of routes. One such synthesis is the following:

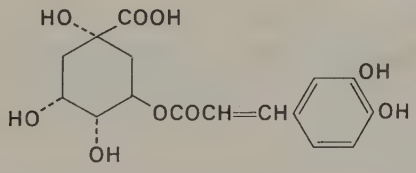


(48)

(±)-shikimic acid

40-10 Chlorogenic acid

Chlorogenic acid, the 3-*O*-(3,4-dihydroxycinnamoyl) ester of quinic acid, has the structure



It does not form the 1,3-lactone as does quinic acid, and possesses two free —OH groups at C-4 and C-5.

40-11 Physostigmine [(−)-eserine]

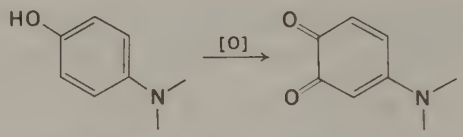
Physostigmine [(−)-eserine] is an alkaloid found in the Calabar bean, *Physostigma venenosum*. As the botanical name suggests, it is a highly toxic compound. Its physiological effects result from its action as an inhibitor of the enzyme acetylcholinesterase (Section 23-16), with resulting symptoms caused by high tissue levels of acetylcholine. It has long been known for its use in certain tribal societies as an "ordeal poison," a means of detecting the guilt of persons accused of crime. A guiltless defendant, secure in the knowledge of his innocence, would be inclined to take the whole dose without qualms, with the result that immediate vomiting would remove the poison.

A guilty defendant would be inclined to take the dose in a more tentative way, ingesting quantities too small to cause immediate vomiting but sufficient to cause toxic effects.

Physostigmine (A) is an amine with the composition $C_{15}H_{21}N_3O_2$. It is dibasic, and forms salts such as $C_{15}H_{21}N_3O_2 \cdot 2HBr$. It is a carbamic acid ester, and is hydrolyzed by alkali to give the phenol *eseroline* (B), methylamine, and CO_2:

$$\underset{\text{A}}{\text{physostigmine}} \xrightarrow[H_2O]{OH^-} \underset{\text{B}}{\text{eseroline}}\ (C_{13}H_{18}N_2O) + CH_3NH_2 + CO_2 \qquad (49)$$

When physostigmine is treated with sodium ethoxide the products are eseroline and ethyl *N*-methylcarbamate, $CH_3NHCOOEt$. This shows that physostigmine contains the grouping $CH_3NHCOO—R$. Eseroline is very sensitive to oxidation, and when exposed to air is transformed into the red compound *rubreserine*, $C_{13}H_{16}N_2O_2$ (C). This is a strong indication that one of the nitrogen atoms is *para* to the phenolic hydroxyl group, for *p*-aminophenols are known to be sensitive to oxidation. This suggests the partial structures

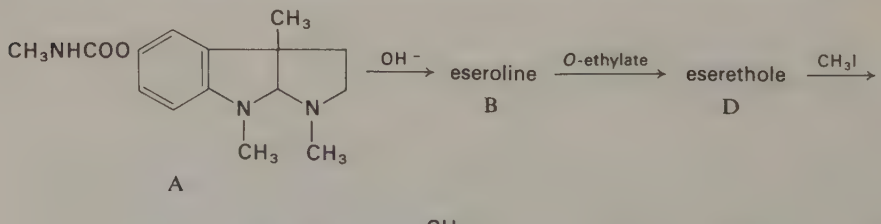


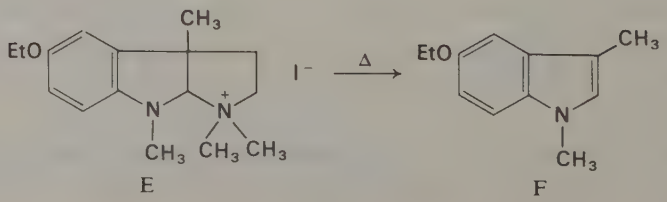
(50)

Eseroline Rubreserine

O-Ethylation of eseroline yields *eserethole* (D), which can be mono-*N*-methylated by reaction with methyl iodide to form a quaternary salt (E). This suggests that one of the nitrogen atoms is more basic than the other. Since one of them appears to be the nitrogen of a *p*-hydroxyaniline derivative, the other would be present in an aliphatic system as a tertiary amino group.

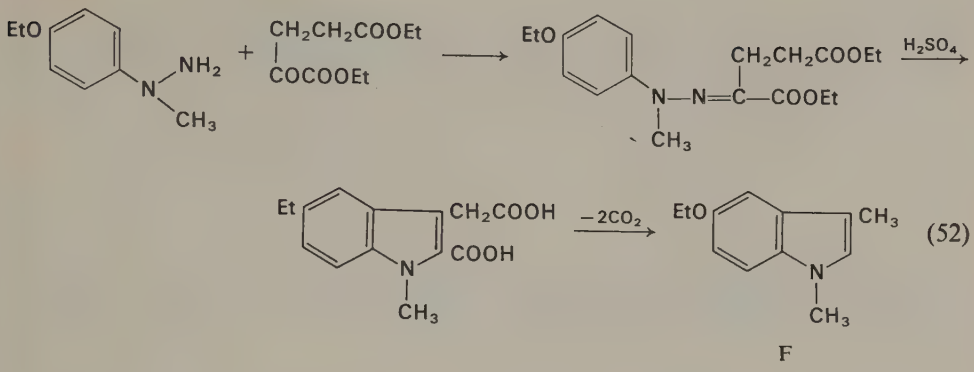
When the methiodide E is strongly heated it decomposes to yield *physostigmol ethyl ether* (F), identified as 1,3-dimethyl-5-ethoxyindole. The above observations can now be formulated as follows, assigning structure A to physostigmine:





(51)

The structure of F was established by synthesis:*

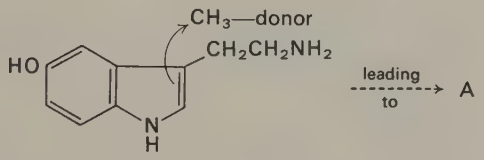


(52)

F

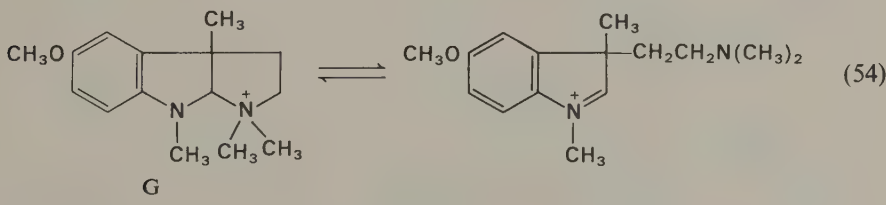
The structure of eseroline can be seen to be represented by [physostigmol + (C_2H_4—NCH_3)], from which the correct structure of physostigmine shown above was postulated.

This structure was initially suggested by the above results, coupled with the conjecture that the biosynthesis occurs by way of a methylation of 5-hydroxytryptamine, a naturally occurring compound:



(53)

Mono-*N*-methylation of eseroline methyl ether leads to *esermethole methiodide* (G). It will be recognized that this structure can be regarded as deriving from the addition of a tertiary amino group to an iminium ($-CH=\overset{+}{N}R_2$) grouping:

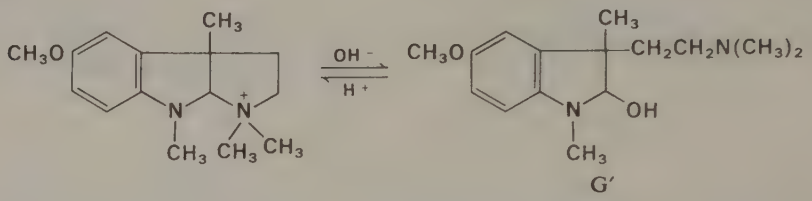


(54)

G

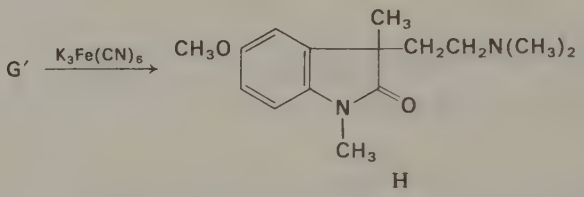
* This series of reactions constitutes what is known as the Fischer indole synthesis (Section 35-22).

In alkaline solution, esermethole methiodide is in reversible equilibrium with a pseudo-base (G′):



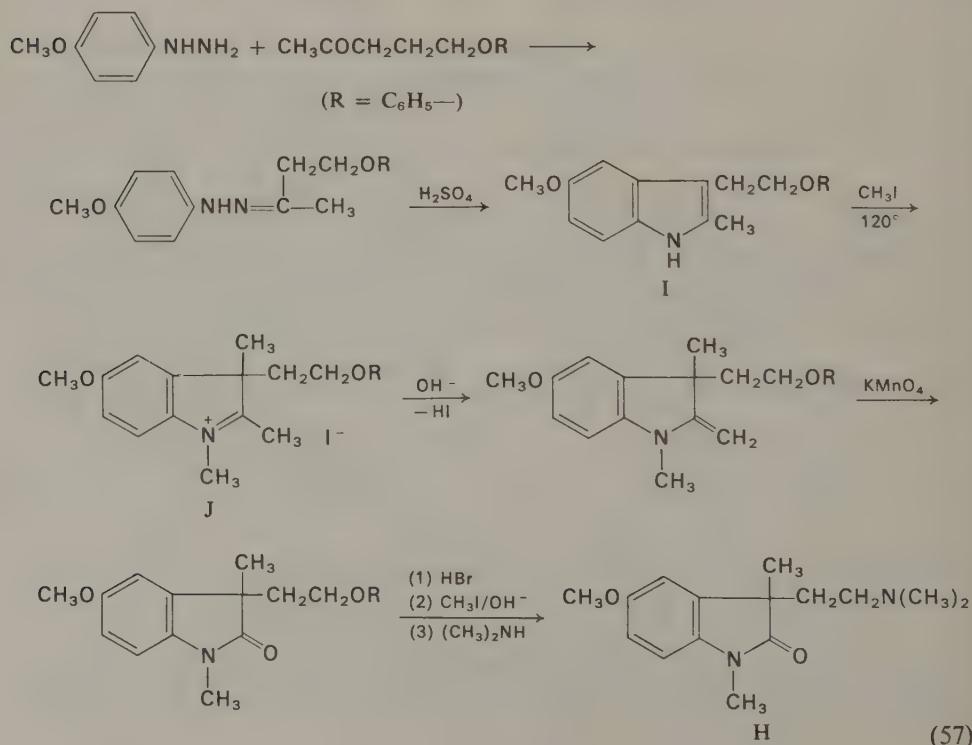
G′ (55)

In fact, oxidation of esermethole methiodide with alkaline potassium ferricyanide converts it into *dehydroesermethole methine* (H):



H (56)

The synthesis of H confirmed its structure and thus that of physostigmine (A):

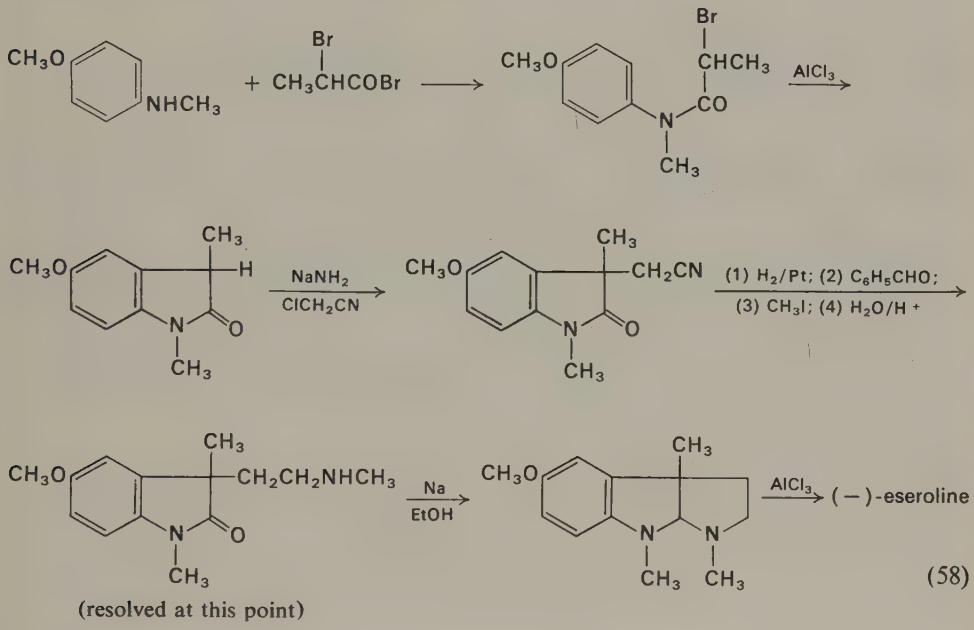


H (57)

Exercise 12

Formulate the course of the methylation of indole I to the quaternary salt J. HINT: It will be noted that I has the essential structural element of an enamine.

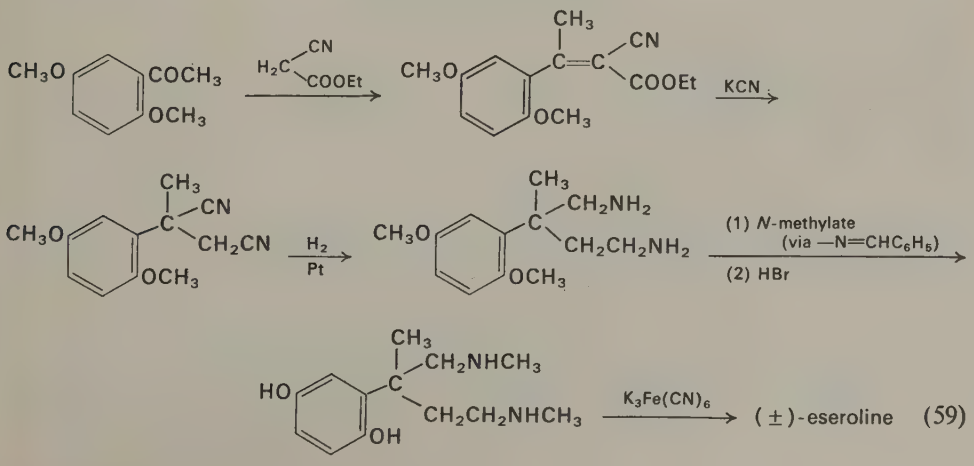
A final step in the structure proof of physostigmine was the total synthesis of (−)-eseroline (B):



(58)

(resolved at this point)

A more recent synthesis of (±)-eseroline was carried out as follows:



(59)

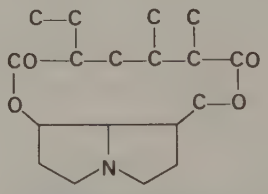
Exercise 13

Formulate the transformation of the hydroquinone into eseroline by ferricyanide oxidation. HINT: Assume an initial oxidation to the *p*-quinone.

40-12 Mikanoidine and the structure of mikanecic acid

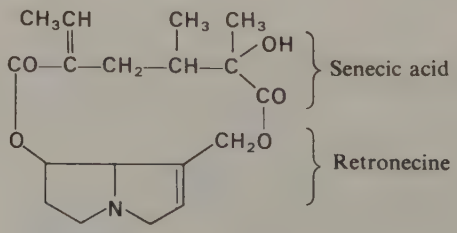
One of the results of intensive early studies by a number of investigators of the alkaloids of plants of the genus *Senecio* was the isolation of an alkaloid named *mikanoidine* (from *S. mikanoides*). Although the alkaloid was not completely characterized, the general nature of its structure was inferred from the results of its alkaline hydrolysis to give a base, *platynecine* ($C_8H_{15}NO_2$), and a dicarboxylic acid, *mikanecic acid* ($C_{10}H_{12}O_4$).

Extensive studies on the *Senecio* alkaloids had earlier revealed that the structure of many of them comprised a hydroxylated *pyrrolizidine* base esterified with a ten-carbon dibasic acid to form a cyclic diester of the skeletal structure



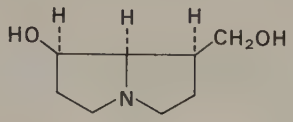
The skeletal structure of many *Senecio* alkaloids

A typical representative of these is *senecionine*, a cyclic diester of *senecic acid* and the pyrrolizidine base *retronecine*:



Senecionine

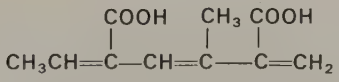
The base platynecine derived from mikanoidine was identified as the known pyrrolizidine with the structure



so the problem of the structure of mikanoidine appeared to devolve upon the question of the structure of mikanecic acid.

In view of the fact that senecic acid (and other acids possessing the same C_{10} skeleton) are common in *Senecio* alkaloids, it was reasonable to suggest that mikanecic acid, a C_{10} acid, possessed the same skeletal structure. Since only a very small amount of mikanecic acid was available for study,* little could be done except to examine its absorption spectra and to carry out a hydrogenation on a micro scale. It will be seen at once that if mikanecic acid has the C_{10} senecic acid skeleton, the formula $C_{10}H_{12}O_4$ requires that it include some combination of three rings or carbon-carbon double bonds. The result of a microhydrogenation gave figures for hydrogen uptake that showed the addition of three moles of hydrogen, indicating the presence of three carbon-carbon double bonds. Unfortunately, this result was in error, as the following discussion will show.

The UV spectrum of mikanecic acid showed a maximum at 216 nm (ϵ = 11,000), a value characteristic of α,β-unsaturated acid. It will be recognized, however, that it is not possible to write a structure of a triply unsaturated compound of the senecic acid type without having at least two of the double bonds in conjugation. On the basis of these considerations and the comparison of hexahydro mikanecic ester with a synthetic compound, the following structure was proposed:



The discrepancy between the observed UV spectrum and what would be expected for such a conjugated (1,3,5) triene casts doubt upon this structure, but because of the unavailability of mikanecic acid certain obvious experimental operations could not be performed.†

Because of the remaining uncertainties about the structures of mikanoidine and mikanecic acid, a reexamination of *S. mikanoides* was undertaken. It was found that

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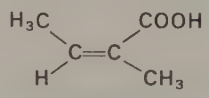
* The study of mikanecic acid was undertaken with access to only a small specimen that remained from the original, earlier investigation.

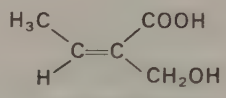
† The early studies were carried out before the development and general use of nuclear magnetic resonance and mass spectrometers.

the plant* yielded a mixture of two alkaloids, A and B, one of them (B) being the *N*-oxide of the other (A). Reduction of the *N*-oxide yielded the alkaloid A, which was a crystalline compound found to be identical with *sarracine*, an alkaloid previously found in *Senecio sarracenius*.

Sarracine, $C_{18}H_{25}NO_5$, was found to be a diester of platynecine with *angelic* and *sarracenic* acids, the former a well-known compound and the latter having the structure shown:



Angelic acid

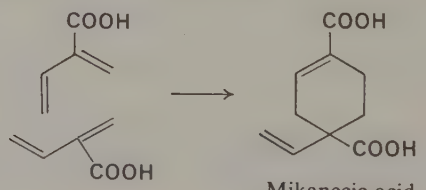


Sarracenic acid

No alkaloid containing a cyclic ester of platynecine and a C_{10} dibasic acid was found in the plant.

Hydrolysis of sarracine or its *N*-oxide under acidic conditions gave platynecine (or its *N*-oxide), along with angelic acid and a C_5 acid (or mixture) that could not be obtained in crystalline form. Alkaline hydrolysis, on the other hand, proceeded readily to give platynecine, angelic acid, and a C_5 acid that could be crystallized and was identified as a sarracenic acid. In addition to these there was isolated a small amount of an acid, $C_{10}H_{12}O_4$, that was recognized as mikanecic acid. The revealing observation was then made that on prolonged treatment with alkali, the hydrolysis products contained *less* sarracenic acid and correspondingly *more* mikanecic acid. Finally, it was found that treatment of sarracenic acid itself with hot aqueous alkali yielded mikanecic acid. It was then apparent that *mikanecic acid was an artefact* formed by the action of alkali upon sarracenic acid.

Further investigation showed that alkaline hydrolysis of 2-cyano-1,3,butadiene gave, instead of 1,3-butadiene-2-carboxylic acid, a crystalline ten-carbon acid identical with mikanecic acid, as proved by direct comparison of the "natural" and synthetic materials. Indeed, it was found that 1,3-butadiene-2-carboxylic acid spontaneously dimerizes by the following Diels-Alder addition:

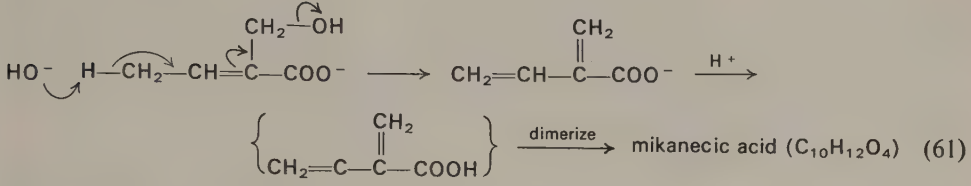


Mikanecic acid

(60)

* As is sometimes the case in repetition of studies on plant material, there was no absolute certainty that the plant used in the later studies was identical with that from which mikanoidine was first obtained, although it was highly probable.

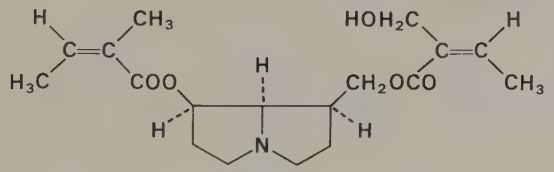
It was now clear that sarracenic acid loses the elements of water by the action of strong alkali to yield 1,3-butadiene-2-carboxylic acid, which dimerizes to mikanecic acid. A plausible course is the following:



(61)

Mikanecic acid is an α,β-unsaturated acid and the UV absorption maximum (216 nm) is now consistent with the structure. The early report that fully reduced mikanecic acid (as the diester) gave the same IR spectrum as a synthetic 2,3-dimethyl-5-ethylhexanedioic acid diester indicates only that infrared spectra of compounds lacking in functionality (except for the two —COOR groups) may not show sufficient difference to permit their distinction.

A final experiment revealed the complete structure of sarracine. Controlled alkaline hydrolysis under mild conditions resulted in the rapid loss of the sarracenic acid residue, followed by a slower hydrolysis of the second acyl residue (angelic acid). This showed that the sarracenoyl grouping is attached to the primary hydroxyl group and that sarracine has the complete structure



Sarracine

There is no longer any reason to believe that an alkaloid "mikanoidine," a cyclic diester of platynecine and a C_{10} dibasic acid, exists in *S. mikanoides*.

40-13 The structure of a sesquiterpenoid ketone. α-Cyperone

α-Cyperone (A), $C_{15}H_{22}O$, is a sesquiterpene found in the essential oil of the plant *Cyperus rotundus*. It is a ketone, forming the usual derivatives (2,4-dinitrophenylhydrazone, semicarbazone); it shows an ultraviolet absorption maximum at 251 mμ (ϵ = 19,000; Figure 40-1). This shows that it is an α,β-unsaturated ketone that is α,β,β trisubstituted. Ozonolysis of α-cyperone yields formaldehyde. The tetrahydro compound B, $C_{15}H_{26}O$, is a saturated ketone; thus, α-cyperone is bicyclic.

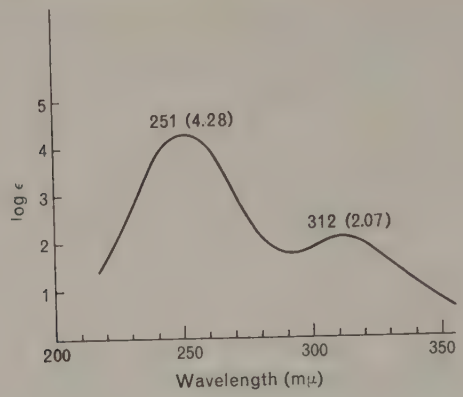
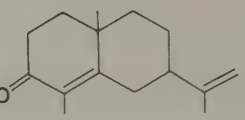
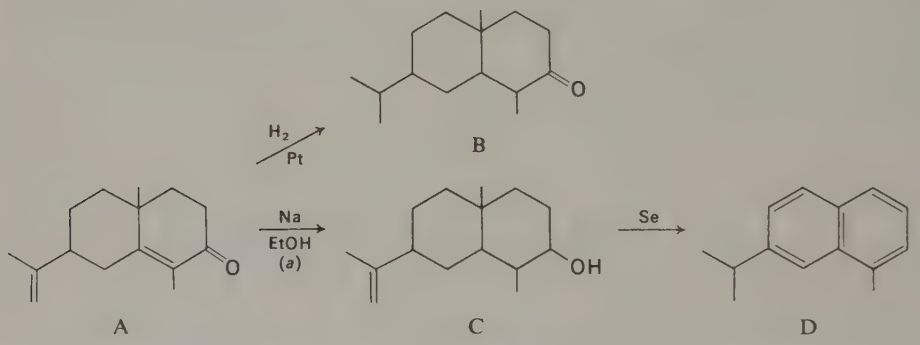


Figure 40-1
Ultraviolet absorption spectrum of α-cyperone,

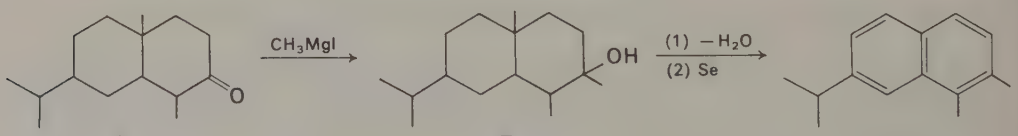


Reduction of α-cyperone with sodium and alcohol gives dihydro-α-cyperol (C) [Note (*a*)], dehydrogenation of which yields eudalene (D):*



(62)

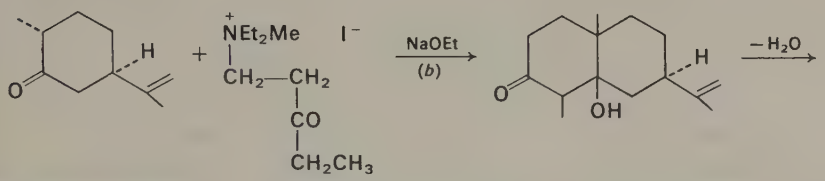
The position of the carbonyl group was established in the following way. Treatment of tetrahydro-α-cyperone (B) with methylmagnesium iodide gave a carbinol (E), which upon dehydration and dehydrogenation gave 1,2-dimethyl-7-isopropylnaphthalene (F):



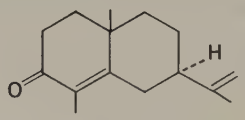
(63)

* The letters (*a*), (*b*), and (*c*) refer to explanatory notes that follow Equation (65). Reactions referred to may be found in the Index.

These experimental observations, coupled with an assumption about the position of the methyl group that is lost on dehydrogenation, imply the structure A for α-cyperone:



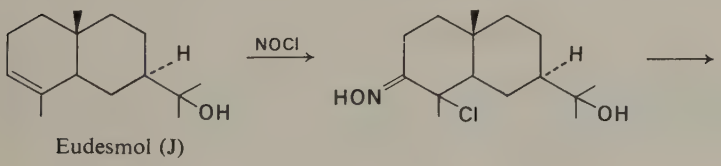
(−)-dihydrocarvone G H



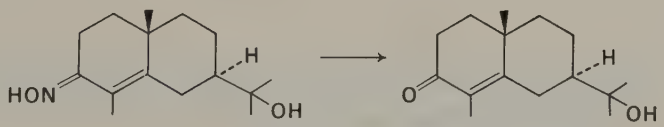
α-cyperone (A) (64)

This structure is "normal" with respect to the isoprene rule and its carbon skeleton corresponds with eudesmol, selinene, carissone, and numerous other eudalene-yielding sesquiterpenes.

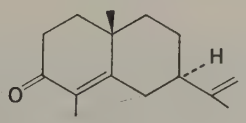
α-Cyperone has been synthesized in a way that confirms the stereochemistry shown in A. The reaction of the Mannich base (as the methiodide G) obtained from methyl ethyl ketone [Note (*b*)] with (−)-dihydrocarvone yields the keto alcohol H, which on dehydration gives α-cyperone [Note (*c*)]. This stereochemistry has been confirmed in several ways, one of which is the synthesis of carissone (I) from eudesmol (J):



Eudesmol (J)



Carissone (I)

carissone $\xrightarrow{-H_2O}$  (65)

α-cyperone

(*a*) The reduction with sodium and ethanol does not affect the isolated carbon-carbon double bond in the isopropenyl side chain, but does reduce the α,β-unsaturated

ketone to the saturated ketone (first product, not isolated) and then to the secondary alcohol.

(*b*) The Mannich base is prepared by the reaction of methyl ethyl ketone with diethylamine hydrochloride and formaldehyde:

$$CH_3CH_2COCH_3 \xrightarrow[HCHO]{Et_2NH\cdot HCl} CH_3CH_2COCH_2CH_2NEt_2 \qquad (66)$$

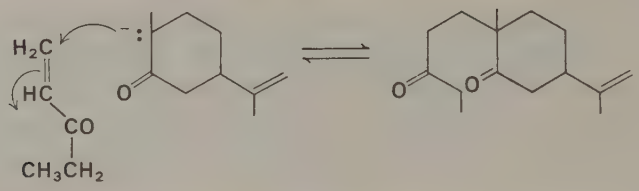
Reaction of the tertiary amine with methyl iodide gives the quaternary salt.

When a compound such as 1-diethylamino-3-pentanone methiodide is allowed to react in the presence of the strong base sodium ethoxide, the first reaction is the elimination of methyldiethylamine, with the formation of the vinyl ketone:

$$CH_3CH_2COCH_2CH_2\overset{+}{N}R_3 \rightleftharpoons[OEt^-] CH_3CH_2C\overset{\cdot\cdot}{O}CH{-}CH_2{-}\overset{+}{N}R_3 \longrightarrow$$

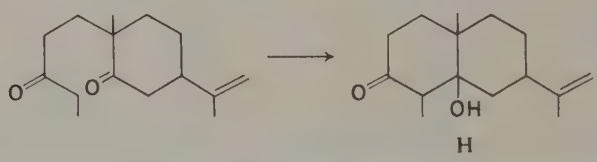
$$CH_3CH_2COCH{=}CH_2 + NR_3 \qquad (67)$$

The addition of the vinyl ketone to the cyclohexanone ring (dihydrocarvone) is an example of the Michael reaction:



(68)

and the final ring closure is an unexceptional aldol condensation:



H (69)

(*c*) Since the aldol H is a β-hydroxy ketone, the loss of water occurs with ease, giving the α,β-unsaturated ketone. (Compare this with the dehydration of diacetone alcohol to give mesityl oxide.)

40-14 The structure of perezone

Perezone is an orange crystalline compound found in the roots of the plant *Trixis pipitzahuac*, a Mexican composite. The compound has a melting point of 102–103°; it dissolves in alkali to give a purple color; and when treated with aniline in hot ethanol solution it yields a monoanilino derivative. Perezone can be reduced to a colorless

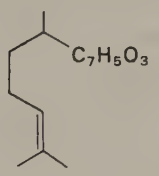
dihydro derivative that is readily reoxidized to the original orange compound. These properties suggest that perezone is a quinone. Perezone has the elementary composition $C_{15}H_{20}O_3$. Ozonolysis of perezone yields acetone, an indication that the structural grouping $=C(CH_3)_2$ is present in the molecule. These observations, in addition to the knowledge that perezone is a C_{15} compound and that upon chromic acid oxidation somewhat more than two moles of acetic acid per mole of compound are produced, showing the presence of (probably) three carbon-linked methyl groups, suggest a terpenoid structure.

When oxidized with alkaline hydrogen peroxide, perezone yields acetic acid and an unsaturated acid, $C_9H_{16}O_2$, which can be catalytically hydrogenated to the saturated acid, $C_9H_{18}O_2$. The latter was found to be 2,6-dimethylheptanoic acid, which can be synthesized as follows:

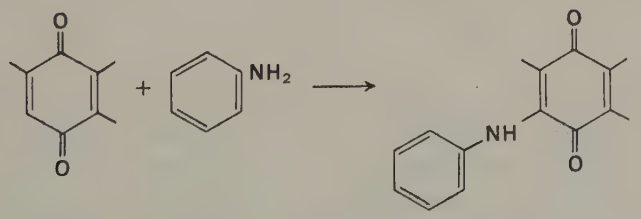
$$(CH_3)_2CHCH_2CH_2CH_2Br + CH_3CH(COOEt)_2 \xrightarrow{NaOEt}$$

$$(CH_3)_2CHCH_2CH_2CH_2\underset{\displaystyle COOEt}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-COOEt \xrightarrow[(2)\ \text{decarboxylate}]{(1)\ \text{saponify}} (CH_3)_2CHCH_2CH_2CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCOOH \qquad (70)$$

These results show that perezone can be partially represented as



The C_7 fragment shows the properties of a benzoquinone with but one unoccupied position, since the addition of aniline yields a monoanilino derivative:



(71)

If the quinone had two unoccupied positions in the ring, a dianilino compound would have formed. Since perezone has three carbon-linked methyl groups that yield acetic acid upon oxidation, two of which are in the aliphatic side chain that appears as the nonenoic acid, the other must be on the quinone nucleus.

When perezone is distilled with zinc dust (which causes a thorough reduction

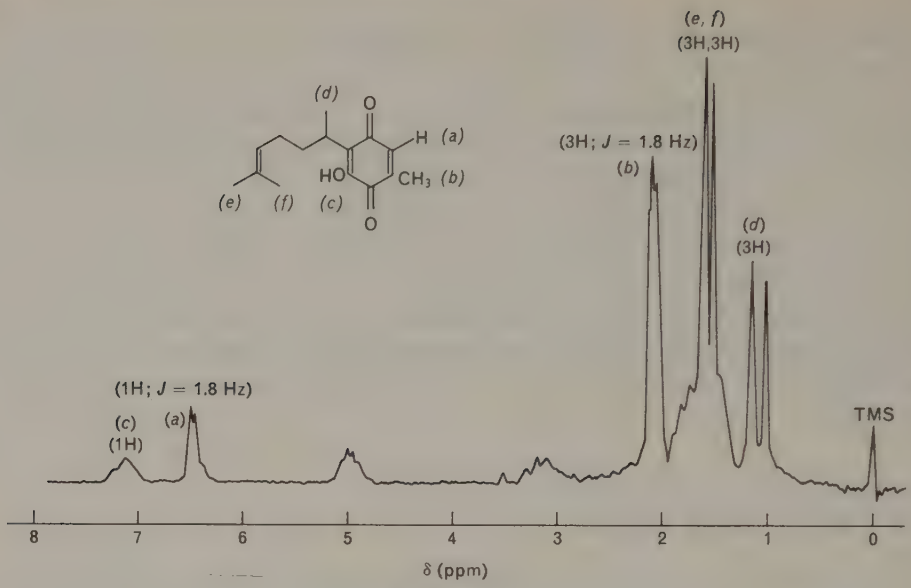
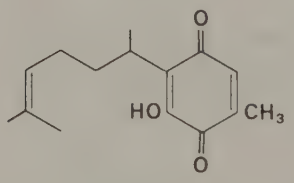


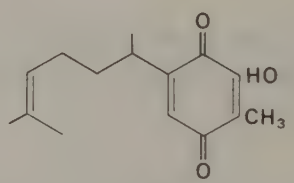
Figure 40-2
NMR spectrum of perezone.

of aromatic and near-aromatic nuclei to the skeletal structures) a product (uncharacterized) is formed that yields terephthalic acid upon oxidation with potassium permanganate. This shows that the side chain and the methyl group are in the 1,4 positions with respect to one another.

With all of this information, we can now write two possible structures for perezone:



I



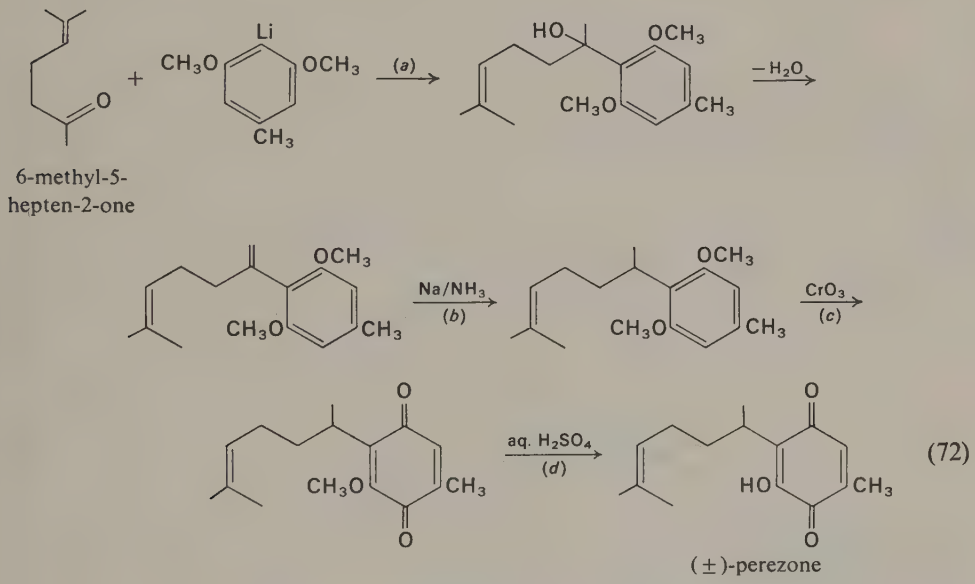
II

The first of these was at length shown to be the correct structure for perezone.* The most useful information leading to the establishment of this structure was obtained from the nuclear magnetic resonance spectrum. The NMR spectrum of perezone itself is shown in Figure 40-2. The most significant features of this spectrum are the signals for the methyl group on the quinone ring and for the hydrogen atom in

* Structure II was first proposed for perezone in 1935, and was regarded as correct until NMR studies led to the conclusion that the correct structure was indeed I. The revised structure (I) was published in 1965.

the adjacent position. These signals are both doublets with a small coupling constant (1.8 Hz). This shows that they are coupled in a manner that is quite in accord with their location in adjacent positions (as in I); were the structure that shown in II, with the methyl group and hydrogen atom in the distant positions on opposite sides of the quinone ring, no such coupling would be expected. The NMR structure of other derivatives of perezone, which will not be detailed here, are in agreement with this conclusion.

Convincing proof of the structure of perezone was obtained by its synthesis according to the following scheme:



(72)

(*a*) The formation of the lithium derivative of 3,5-dimethoxytoluene is the same reaction as that used to prepare 2,6-dimethoxybenzoic acid from resorcinol dimethyl ether.

(*b*) The sodium-ammonia reduction affects only the double bond conjugated with the aromatic ring. The isolated isopropylidene group is unaffected.

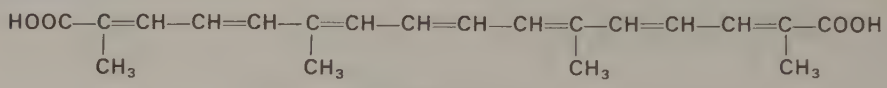
(*c*) Although the yield in this oxidation is quite low, the formation of a methoxyquinone involves no ambiguity in its structure because the dimethoxytolyl group is symmetrical about its point of attachment to the side chain.

(*d*) The methoxyquinone, a vinyl ether, is readily hydrolyzed.

40-15 The synthesis of a carotenoid. Crocetin

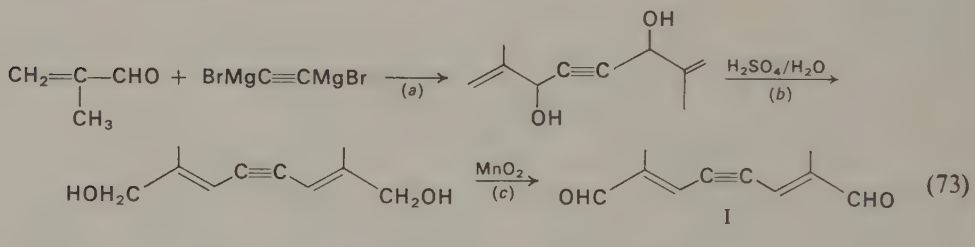
Crocetin is one of the simpler carotenoid compounds. It occurs naturally as a diester of the disaccharide gentiobiose (Chapter 15) in the flowers of the Crocus family,

which appear in commerce as an orange-yellow coloring matter called *saffron*. Hydrolysis of the diester, called crocin, yields two moles of gentiobiose and the dibasic acid *crocetin*. Crocetin is a deep orange-red crystalline compound of the composition $C_{20}H_{24}O_4$. It contains four carbon-linked methyl groups (by estimation of the acetic acid produced upon chromic acid oxidation), and upon catalytic hydrogenation absorbs seven moles of hydrogen to give the completely saturated perhydrocrocetin, $C_{20}H_{38}O_4$. An early synthesis of perhydrocrocetin led to the suggestion that crocetin has the structure

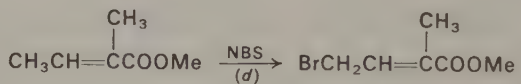


Crocetin (all *trans*)

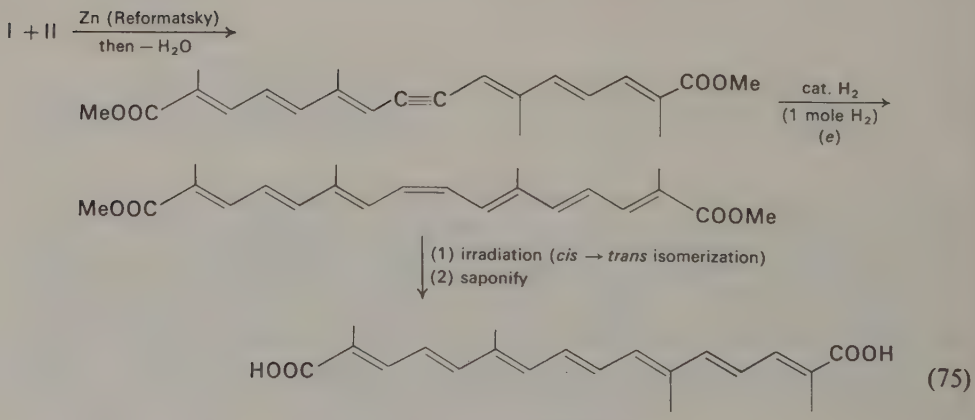
The confirmation of this structure by a total synthesis was accomplished in 1953 by a group of Swiss chemists headed by H. H. Inhoffen:



(73)



(74)



(75)

Crocetin

The identity of the synthetic and natural crocetin was established by their melting point (285°C) and by their distinctive absorption spectrum. Crocetin is a conjugated

polyene with seven carbon-carbon double bonds flanked at each end of the chain by carboxyl groups. It is a brick-red crystalline compound; its absorption spectrum (in carbon disulfide solution) shows maxima at 482, 453, and 426 mμ.

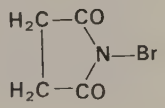
(*a*) The formation of the organomagnesium compound of acetylene is carried out by passing acetylene into a convenient Grignard reagent, such as ethylmagnesium bromide.

(*b*) This is an allylic rearrangement of the general form

and is catalyzed by acid, probably by way of the carbonium ion formed from the protonated alcohol.

(*c*) The MnO_2 oxidation of allylic alcohols occurs under mild experimental conditions; other oxidizable functions are unaffected.

(*d*) Bromination of a methyl group attached to a carbon-carbon double bond can be effected by the reagent *N*-bromosuccinimide (NBS):

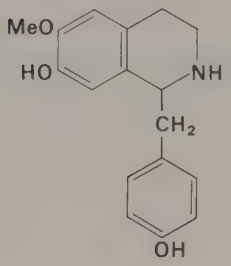


(*e*) The catalytic hydrogenation of the triple bond can be carried out without affecting the remaining double bonds, the hydrogenation being interrupted after one mole has been absorbed. It will be noted that the double bond produced is in the *cis* configuration. Isomerization of the *cis* double bond to the more stable *trans* configuration was carried out by irradiation with short-wavelength light in the presence of a trace of iodine as a catalyst.

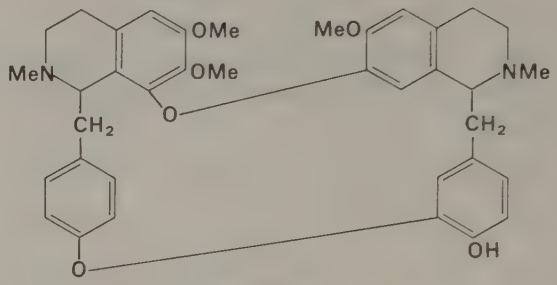
40-16 The structure, proof, and synthesis of an alkaloid. Coclaurine

Coclaurine is of special interest and importance among the alkaloids (Chapter 35) because it possesses the hydroxylation pattern found in a number of other benzylisoquinoline alkaloids. Some of these, the bisbenzylisoquinoline alkaloids, have structures that suggest their origin by an oxidative coupling of two molecules of coclaurine or two molecules of a precursor very similar to coclaurine in structure. An example is

oxyacanthine, whose structure shown below, is written in such a way as to indicate its possible genesis from coclaurine:



Coclaurine



Oxyacanthine

The structure of coclaurine ($C_{17}H_{19}O_3N$), an alkaloid found in the plant *Cocculus laurifolius*, was first deduced from the following evidence. It is a secondary amine that was found, by the preparation and analysis of the *N*- and *O*-methyl derivatives, to contain one —OMe group, two —OH groups, and one $\rangle$NH group. Upon zinc-dust distillation there was obtained *p*-cresol, indicating that the structural element

was present in the alkaloid.

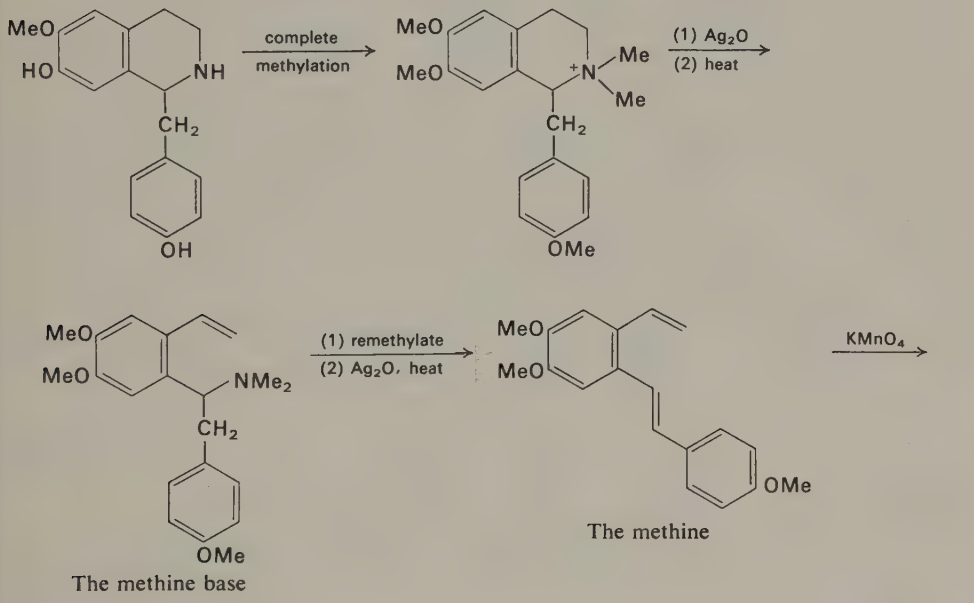
Complete methylation (to the *N*-methyl methiodide of the *O*-dimethyl derivative), followed by Hofmann degradation, led to a methine base that could be further degraded in the same way to a nitrogen-free methine [see equation (77)]. This compound gave 4,5-dimethoxyphthalic acid (*m*-hemipinic acid) and anisic acid (*p*-methoxybenzoic acid) on oxidation with potassium permanganate. The analogous coclaurine *O*-diethyl ether gave, on a similar degradation, 3-ethoxy-4-methoxy-6-ethylbenzoic acid and *p*-ethoxybenzoic acid.

The Hofmann degradation (Chapter 10), of great importance in the study of nitrogen-containing compounds, particularly alkaloids, is an elimination reaction related to the dehydrohalogenation of alkyl halides, in which a quaternary ammonium grouping is displaced by internal attack and formation of a double bond:

(76)

In one method of carrying out the degradation, the quaternary iodide is treated with a suspension of silver oxide in water, with the formation of silver iodide and the quaternary hydroxide. Concentration of the filtered aqueous solution, followed by heating, leads to the reaction formulated above. In some cases it is sufficient to heat the quaternary iodide in an aqueous or alcoholic solution of alkali.

The degradation of fully methylated coclaurine outlined above can be formulated as follows:



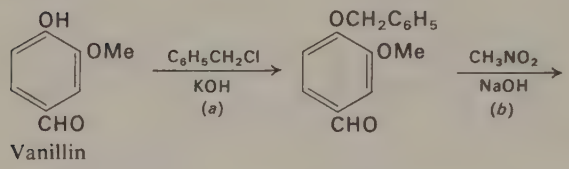
(77)

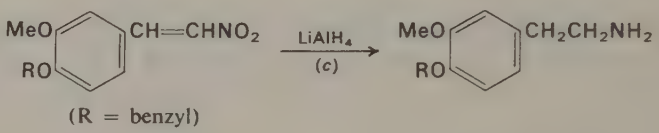
When *O*-ethylation, instead of *O*-methylation, of coclaurine was the first step in the degradation outlined in (77), and the methine was hydrogenated prior to the $KMnO_4$ oxidation, there was obtained 3-ethoxy-4-methoxy-6-ethylbenzoic acid.

These results can be accommodated by the structure written above for coclaurine. The final proof of the structure was provided by the total synthesis of the alkaloid (J. Finkelstein, 1951). This synthesis illustrates the protection of phenolic hydroxyl

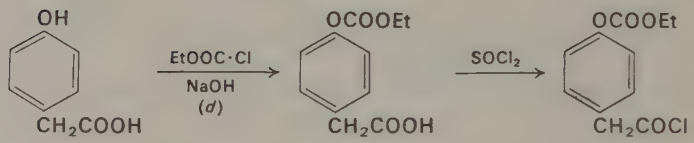
groups during a synthetic sequence, and their eventual regeneration by removal of the protecting groups.

The synthesis consists of three parts: the synthesis of the requisite phenylethylamine; the synthesis of the fragment that will constitute the final benzyl grouping; and the combining of these two parts in an isoquinoline synthesis of the final alkaloid:

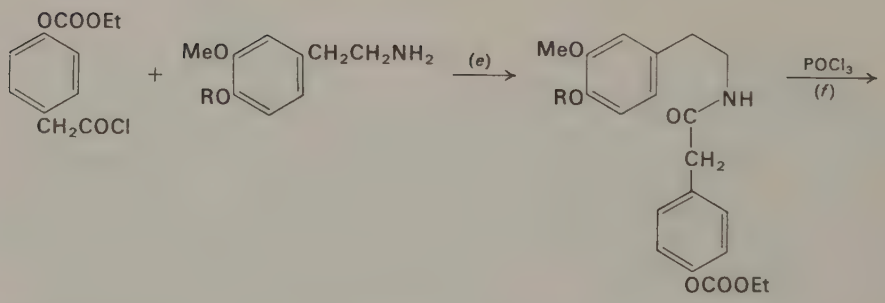


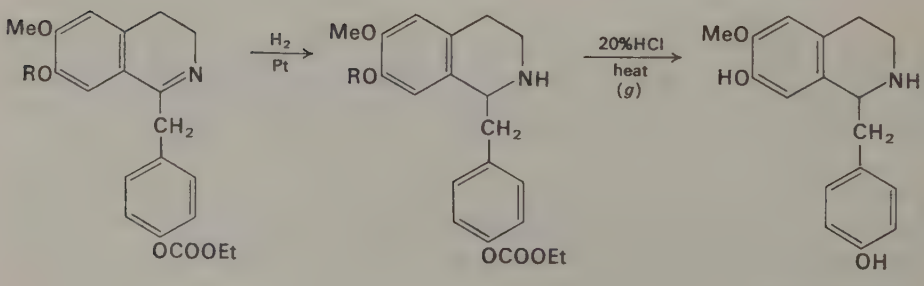


(78)



(79)

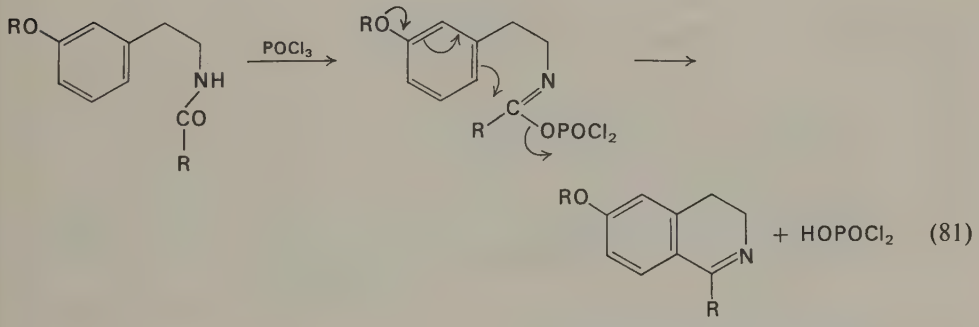




(80)

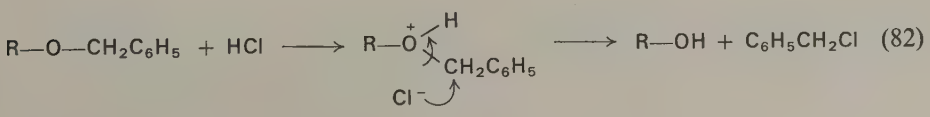
The following notes describe briefly the steps in the above equations. All of these have been discussed in earlier chapters, and the student is advised to refer to them along with his study of this total synthesis:

(*a*) This is a straightforward alkylation (benzylation) of the phenolic hydroxyl group and needs no further comment.
(*b*) The aldol-like condensation of nitromethane with an aromatic aldehyde.
(*c*) Reduction of a β-nitrostyrene to a β-phenylethylamine is a useful method for the preparation of amines of this kind.
(*d*) Ethyl chloroformate (the half-ester, half-acid chloride of carbonic acid) is prepared from phosgene ($COCl_2$) and ethanol. It is useful for the protection of phenolic hydroxyl groups, because the eventual regeneration of Ar—OH by hydrolysis of Ar—OCOOEt is readily accomplished at the end of the synthetic sequence.
(*e*) This is simply the acylation of a primary amine with an acid chloride. The formation of a β-phenylethyl amide in this way is the first step in the Bischler-Napieralski synthesis of isoquinolines.
(*f*) This is the ring-closure step of the Bischler-Napieralski synthesis. It is clearly an electrophilic aromatic substitution reaction, and may be represented in the following (formal) manner. This is illustrative only, for the exact nature of the phosphorylated intermediate and the phosphorus-containing displaced group is, while reasonable, conjectural.



(81)

(*g*) The final step involves the hydrolysis of the —OCOOEt and *O*-benzyl groupings, with regeneration of the phenolic hydroxyl groups. The demethylation of phenylmethyl ethers has been described earlier. Debenzylation is mechanistically the same but because of the much greater S_N2 reactivity of benzyl compounds it occurs with greater ease and under less severe conditions:



(82)

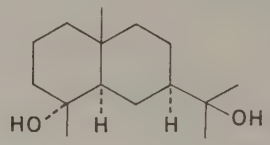
Problems

1. (*a*) A naturally occurring terpenoid hydrocarbon A, $C_{10}H_{16}$, can be reduced (Pt/H_2) to a hexahydro compound B, $C_{10}H_{22}$. The UV λ_{max} of A is 237 nm (log ϵ about 4). Ozonolysis of A yields formaldehyde, acetone, and methylglyoxal. When A is passed through a heated tube, it is isomerized to C, which has λ_{max} 275 nm (log ϵ about 4.5). Ozonolysis of C yields acetaldehyde, acetone, and methylglyoxal. What are the structures of A, B, and C?
   (*b*) Compound C was synthesized as follows:

   2-butanone + acetylene ($NaNH_2$) → $C_6H_{10}O$ (D)
   D + EtMgBr → E
   E + 2-methylpropanal → F
   F + H_2(1 mole, Pd) → G
   G (dehydrated) → H

   What are the structures of D, E, and F; G and H?

2. Starting with geranyl pyrophosphate, write the steps of a reasonable course for the biosynthesis of the sesquiterpene alcohol cryptomeridiol:



   HINT: Note that farnesol is $C_{15}H_{26}O$ and cryptomeridiol is $C_{15}H_{28}O_2$; these differ only by the elements of water, H_2O.

3. The sex-attractant of the codling moth is *trans*-8-*trans*-10-dodecadien-1-ol. Starting with 1-bromohepta-3-5-diene and 5-bromo-1-pentanol as the principal reagents, show how the pheromone can be synthesized.

4. Devise a reasonable mechanism for the acid-catalyzed conversion of prephenic acid into phenylpyruvic acid.

5. A pigment occurring in certain fungi is 2,5-dihydroxy-3,6-diphenyl-*p*-benzoquinone. This has been shown to arise biosynthetically by a route starting with prephenic acid. Show a probable course of the biosynthesis of the quinone. NOTE: A coenzyme A ester is a probable intermediate.

APPENDIX A

Systems of nomenclature

A-1 Naming of organic compounds

Clarity and precision in the use of language are essential to effective communication of ideas in any field of human activity, and an important part of the language in any well-defined discipline is the terminology that is used to identify the materials and concepts dealt with by its practitioners. In chemistry, and particularly in organic chemistry, the communication of information is carried out largely with use of the formulas of chemical substances. These can be written in chemical symbols or they can be translated into names that are clear equivalents of the structural formulas. The proper and comprehensible naming of organic compounds is an important preliminary to a discussion of their chemical behavior.

Names should first of all be unambiguous: a name should not be used unless it refers to one specific substance, and no other. Names should be simple; but when there is a choice between two or more names for a certain compound, as is often the case, the selection of one of these—not always the simplest—can sometimes aid a discussion by evoking the clearest mental image of the substance.

Organic compounds are named in three ways:

1. Trivial, or common, names.
2. Substitution names, often based upon the trivial names.
3. Systematic names, based upon rules set forth by the International Union of Pure and Applied Chemistry (IUPAC).

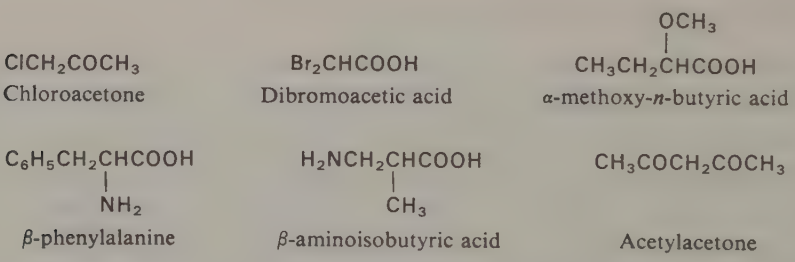
A-2 Trivial or common names

Trivial names are of two kinds: (1) Those of long-known, familiar compounds whose names are in the common vocabulary of chemists; for example, acetone, acetic acid, aniline, and chloroform. (2) Those of very complex, usually naturally occurring compounds for which systematic (IUPAC) names would be unwieldy and often confusing; for example, glucose, morphine, camphor, salicin, and atropine.

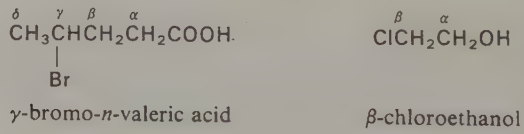
Chemical Abstracts has begun in recent years to index all organic compounds by systematic names, and so the principles of systematic naming must be regarded as indispensable to the organic chemist.

A-3 Substitution names

Substitution names are widely used but, with the growing use of IUPAC nomenclature, are becoming less common. Substitution names are systematic and logical and are usually readily comprehensible. Recognizing most of them requires knowledge of relatively few common names. Some examples of substitution names are the following:



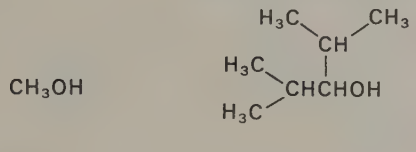
When Greek letters are used to indicate the position of the substituent, the lettering starts at the carbon atom *adjacent* to the functional group:



Although certain of these devices are being replaced in present-day literature by systematic naming, it must be recognized that they are found in earlier literature. It is of course necessary for a reader who encounters such a name to understand what it means. We can revise our preferences for naming but we cannot expunge what is already in the permanent record of the past.

Methanol (carbinol) and methane systems of naming are often used at the present time. These are in a way a hybrid of common substitution names and systematic names.

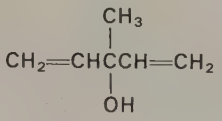
In the *methanol system* of naming, alcohols are regarded as substitution products of the simplest member of the series, methanol.



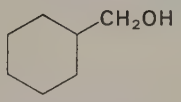
CH_3OH

Methanol

Diisopropylmethanol



Methyldivinylmethanol

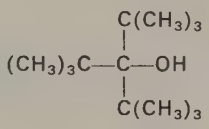


Cyclohexylmethanol

$(C_6H_5)_3COH$

Triphenylmethanol

It must also be pointed out that until recently the word "carbinol" was more often used than "methanol." Thus, *divinylmethanol* was formerly called *divinylcarbinol.* Naming by the methanol (carbinol) system is often much more convenient and less cumbersome than by the IUPAC system. The compound tri-*t*-butylmethanol (or -carbinol)



would bear the name 2,2,4,4-tetramethyl-3-*t*-butyl-3-pentanol according to the formal IUPAC rules for nomenclature (to be discussed below). It is apparent that the methanol name is more immediately recognizable.

The *methane system* of naming corresponds to the methanol system in that compounds are named as substitution products of methane. A few examples will illustrate:

$(CH_3)_4C$
Tetramethylmethane

$(C_6H_5)_3CH$
Triphenylmethane

$C_6H_5COCH_2COC_6H_5$
Dibenzoylmethane

$(BrCH_2)_4C$
Tetra(bromomethyl)methane

$(CH_3CO)_3CH$
Triacetylmethane

Many substitution names are based upon trivial names. Reference to relevant chapters in the text will reveal that such names as tetra-*O*-methylglucose, 4-bromo-

resorcinol, di-*O*-acetylmorphine, and diallyl ether are based upon the common names for the "parent" compounds.

A-4 Systematic nomenclature. The International Union of Pure and Applied Chemistry (IUPAC) system

The systematic naming of organic compounds is based upon a set of rules adopted by the International Union of Pure and Applied Chemistry, whose predecessor first met in Geneva in 1892. The term "Geneva nomenclature" is still sometimes encountered, but the term "IUPAC system" is now used.

Compounds are named as derivatives of a "parent" compound by adding to the name of the parent system the designations for the attached groups or, in the case of unsaturated compounds, designations for carbon-carbon double and triple bonds.

Table A-1
The normal paraffin hydrocarbons (normal alkanes) and group names

Hydrocarbon		*Formula*	*Alkyl group*	*Formula*
CH_4	methane	CH_4	methyl	CH_3—
C_2H_6	ethane	CH_3CH_3	ethyl	CH_3CH_2—
C_3H_8	propane	$CH_3CH_2CH_3$	*n*-propyl	$CH_3CH_2CH_2$—
			isopropyl	CH_3CHCH_3 (CH$_3$ branch)
			n-butyl	$CH_3CH_2CH_2CH_2$—
			isobutyl	$(CH_3)_2CHCH_2$—
C_4H_{10}	butane	$CH_3CH_2CH_2CH_3$	*sec*-butyl	$CH_3CH_2CH(CH_3)$—
			tert-butyl	$(CH_3)_3C$—
C_5H_{12}	pentane*	$CH_3CH_2CH_2CH_2CH_3$		
C_6H_{14}	hexane	$CH_3(CH_2)_4CH_3$		
C_7H_{16}	heptane	$CH_3(CH_2)_5CH_3$		
C_8H_{18}	octane	$CH_3(CH_2)_6CH_3$		
C_9H_{20}	nonane	$CH_3(CH_2)_7CH_3$		
$C_{10}H_{22}$	decane	$CH_3(CH_2)_8CH_3$		
$C_{11}H_{24}$	undecane	$CH_3(CH_2)_9CH_3$		
$C_{12}H_{26}$	dodecane	$CH_3(CH_2)_{10}CH_3$		
$C_{20}H_{42}$	eicosane	$CH_3(CH_2)_{18}CH_3$		

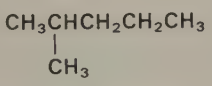
* It is not often necessary to use the names of alkyl groups larger than butyl.

The names of open-chain (acyclic) hydrocarbons and derivatives are based upon the names of the parent hydrocarbons of the methane series (Table A-1), the traditional names methane, ethane, propane, and butane, followed by names derived from Greek: pentane, hexane, and so on. Group names derived from these are used universally; for example, propylbenzene and isopropylbenzene.

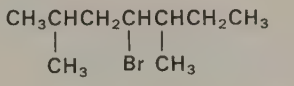
The following summary is necessarily a brief one, for systematic rules exist for naming organic compounds of all kinds, including sugars, phosphorus compounds, heterocyclic compounds, polycyclic compounds, and so on. A complete summary of IUPAC nomenclature is found in the Index volume of the *Journal of the Chemical Society* (London), 1952; additions and revisions are found in succeeding volumes.

A-5 Summary of the basic rules of nomenclature

Basic rules. (1) Find the longest continuous chain of C atoms (even though it may not be written in a straight line) and name it as the parent. (2) Name the substituent atoms or groups. (3) Number the chain in such a way as to give the substituents the smallest possible numbers.

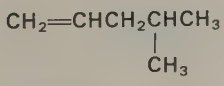


2-methylpentane

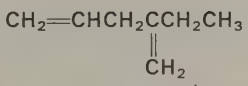


2,5-dimethyl-4-bromoheptane

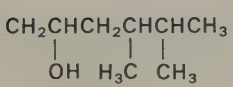
But when a functional group is present, the longest chain is selected so as to contain this group (C=C, OH, CO, and so on), and numbered so as to give this group the lowest possible number.



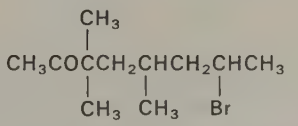
4-methyl-1-pentene
(not 2-methyl-4-pentene)



2-ethyl-1,4-pentadiene



4,5-dimethyl-2-hexanol
(not 2,3-dimethyl-5-hexanol)



3,3,5-trimethyl-7-bromo-2-octanone

Note that one does not say 3,3,5-*methyl*-; indicate the number of groups by di-, tri-, and so on. Note also that one says 3,3-dimethyl-, not 3-dimethyl-.

Endings.

(*a*) Saturated hydrocarbons: -ane.

(*b*) Unsaturated hydrocarbons: -ene.

(*c*) If more than one double bond: -diene, -triene, and so on.

(*d*) Acetylenic hydrocarbons: -yne.

(*e*) Double bonds and triple bonds: -enyne, -dienyne, and so on.

(*f*) Alcohols: -ol, -diol, -triol, and so on.

(*g*) Ethers are regarded as alkoxy-substituted alkanes: $CH_3CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2CH_3$ is 3-methoxypentane.

(*h*) Names such as methyl isopropyl ether (separate words) for $CH_3OCH(CH_3)_2$ can be used.

(*i*) Ketones: -one, -dione, and so on.

(*j*) Aldehydes: -al (—CHO necessarily numbered 1).

(*k*) Acids: -oic acid (—COOH necessarily numbered 1).

(*l*) Additional functions are included in the body of the name.

Examples

(*a*) methane, ethane, propane, butane, pentane, hexane, heptane, octane, and so on.

(*b*) $CH_2{=}CHCH_2CH_2CH_3$
1-pentene

(*b*) $CH_3CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CH_2CH_2CH_3$
3-methyl-2-hexene
(note that only the lower end of $-\overset{2}{C}{=}\overset{3}{C}-$ is numbered)

(*c*) $CH_3CH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2CH_2CH{=}CH_2$
5-methyl-1,5-heptadiene

(*d*) $CH_3C{\equiv}CH$
Propyne

(*d*) $CH_3C{\equiv}C\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$
5-methyl-2-heptyne

(*e*) $CH_2{=}CHCH_2C{\equiv}CH$
1-penten-4-yne

(*f*) $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H{-}\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$
6-bromo-5-methyl-3-octanol

(*f*) $HOCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$
1,2,4-butanetriol

(*f*) $CH_2{=}CHCH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}H{-}\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$
6-heptene-2,3-diol

(*i*) $CH_3COCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$
4-methyl-2-pentanone

(*i*) $CH_3COCOCH_2CH_2CH_3$
2,3-hexanedione

(*j*) $CH_3CHCH_2CH_2CHO$ (Br on the second carbon)
4-bromopentanal

(*k*) $CH_3CHCH_2CH_2CH_2COOH$ (CH_3 on the second carbon)
5-methylhexanoic acid

(*k*) $HOOCCH_2CH_2COOH$
Butanedioic acid

(*i*) $CH_2{=}CHCH_2COCH_2CH_3$
5-hexen-3-one

(*j*) $CH_2{=}CHCH_2CH_2CH(CH_3)CHO$
2-methyl-5-hexenal

(*k*) $CH_2{=}CHCH_2CH_2COOH$
4-pentenoic acid

Notes

1. Only one ending is used. Thus, $CH_3CHCH_2COCH_3$ (OH on the second carbon) is *not* called a pentanolone or a pentanonol; it is named 4-hydroxy-2-pentanone.

2. The endings -al- and -oic acid necessarily define the basic name. Note that numbering begins at C of —CHO and —COOH:

$CH_3CHCH_2CH_2COOH$ (OH on the second carbon)
4-hydroxypentanoic acid

$CH_3COCH_2CH_2CH_2CHO$
5-ketohexanal

3. The suffixes -ene and -yne are subordinate in numbering to functional-group endings:

$CH_2{=}CHCH_2COCH_3$
4-penten-2-one
(not 1-pentene-4-one)

4. The suffix -one has preference over the suffix -ol:

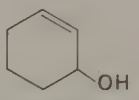
$CH_3CHCH_2CH_2COCH_2CH_3$ (OH on the second carbon)
6-hydroxy-3-heptanone
(not 5-keto-2-heptanol)

5. The suffix -ene precedes the suffix -yne [see (*g*) above].

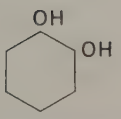
Cyclic compounds (non-aromatic). Names are based upon the parent hydrocarbons: cyclopropane, cyclobutane, cyclopentane, cyclohexane, and so on. Functions are named in the usual way:

Cyclohexene

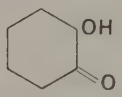
1,3-cyclohexadiene



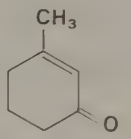
2-cyclohexene-1-ol



1,2-cyclohexanediol
(*cis*- or *trans*- should be specified)

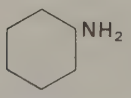


2-hydroxycyclohexan-1-one

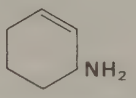


3-methyl-2-cyclohexen-1-one

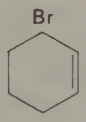
The name 2-cyclohexen-1-ol (rather than 2-cyclohexenol) is used in *Chemical Abstracts*, even though it could be argued that the -1- is not necessary for clarity.



Cyclohexylamine
or aminocyclohexane

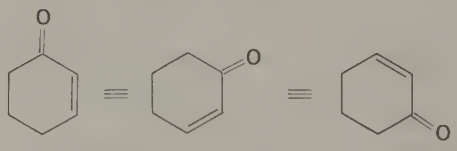


3-aminocyclohexene



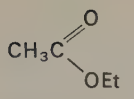
3-bromocyclohexene

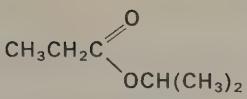
Note also that the ring of a cyclic compound may be written in various attitudes:

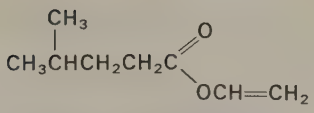


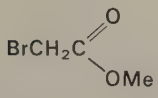
Naming of acid derivatives. The common names formic, acetic, and propionic are usually used for these simple acids. For acids of four or more C atoms, IUPAC names are preferred: HCOOH, formic acid; CH_3COOH, acetic acid; CH_3CH_2COOH, propionic (or propanoic) acid; $CH_3CH_2CH_2COOH$, butanoic acid. $(CH_3)_2CHCOOH$ can be called isobutyric (not isobutanoic!), 2-methylpropanoic, or dimethylacetic acid.

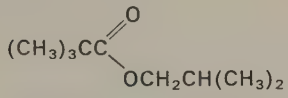
Esters are named by naming the groups corresponding to the alcohol and acid from which they are formed; the acid name ends in "ate":

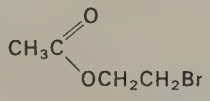

Ethyl acetate

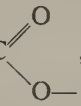

Isopropyl propionate

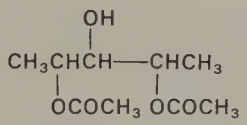

Vinyl 4-methylpentanoate

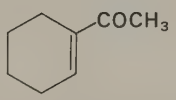

Methyl bromoacetate


Isobutyl trimethylacetate


2-bromoethyl acetate

The groups  , CH_3CO—, and CH_3CH_2CO— are *acyl* groups and are named formyl, acetyl, and propionyl. The groups  , , and so on are formyloxy, acetoxy, and so on. These can be named as substituents:

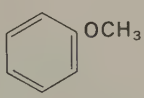
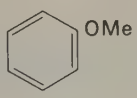

2,4-diacetoxy-3-pentanol


1-acetylcyclohexene

$CH_3C(OCOCH_3)_3$
1,1,1-triacetoxyethane

$CH_3COCH{=}CHCOCH_3$
1,2-diacetylethene
(or 3-hexene-2,5-dione)

Writing structural formulas. In many cases, abbreviated formulas may be written, in which groups are named by contractions of their names or even by arbitrary symbols. For example:

 ≡ 

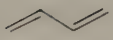
$(CH_3)_3COH$ ≡ *t*-BuOH

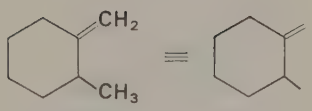
$(CH_3)_2CHCOCH(CH_3)_2$ ≡ iPr_2CO

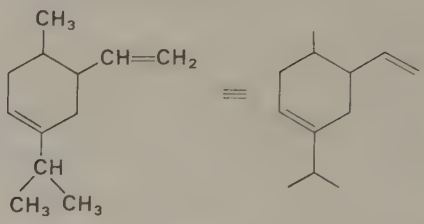
$CH_3COCH_2CH_3$ ≡ MeCOEt

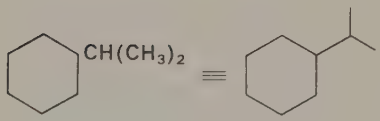
Normally, only the lower alkyl groups are written in this abbreviated way: Me, Et, Bu, Pr, *i*-Bu, and so on.

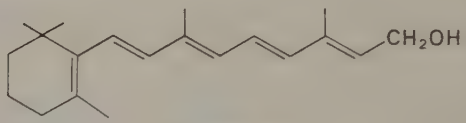
Groups are often represented as simple lines:

$CH_2{=}CHCH{=}CH_2$ may be represented 

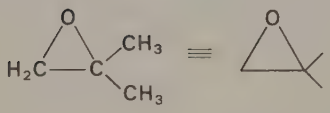


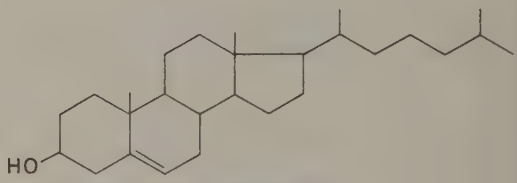




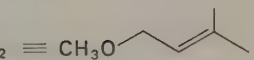


Vitamin A_1

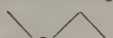


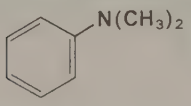
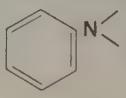
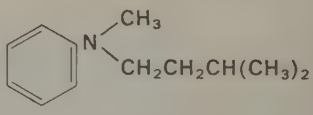


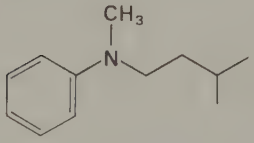
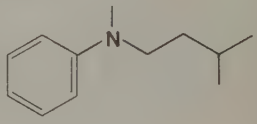
Cholesterol

$CH_3OCH_2CH{=}C(CH_3)_2 \equiv$ 

$(CH_3)_3COC(CH_3)_3 \equiv$ 

The use of —O for CH_3O is not recommended. Thus, one would not write $CH_3OCH_2CH_3$ as  . Indeed, for so short and uncomplicated a structure there is no need to use abbreviations other than, for example, MeOEt.

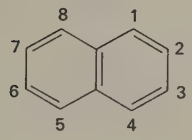
 would not be written  ; but more complex groups may be so represented. For example, one could write 

as  . In this case one would not write 

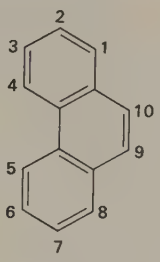
As in all things, the best guides are clarity, comprehensibility, and good judgment. Do not use an abbreviated representation that might be ambiguous or misinterpreted.

A-6 Aromatic compounds

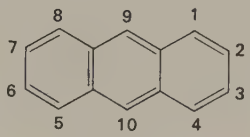
Aromatic compounds include, besides benzene derivatives, substitution products of naphthalene, phenanthrene, anthracene, and higher polycyclic compounds:



Naphthalene



Phenanthrene

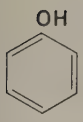


Anthracene

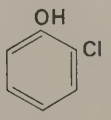
Substitution products of these are named by straightforward numbering, with the provision that the ending -ol is often used for phenolic compounds; for example, 2-naphthol and 1-phenanthrol. The substituent term "hydroxy" is, however, correct and for polyhydroxy compounds it is usually preferable; for example, 2,3-dihydroxynaphthalene rather than 3-hydroxy-2-naphthol.

Benzene derivatives can also be named with the use of numbers only, but for disubstituted benzenes the prefixes *o*-, *m*- and *p*- are usually employed. Thus: *p*-dibromobenzene, *o*-chlorobenzoic acid, *p*-nitrotoluene.

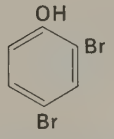
Because many mono- and di-substituted benzenes have been well known for many years, they bear common names that continue to be used. The following examples include some of them and illustrate the ways in which their derivatives are named (the starred names are the ones still most commonly used):



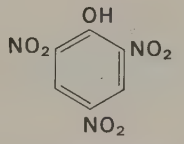
Phenol



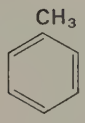
o-chlorophenol



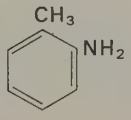
2,4-dibromophenol



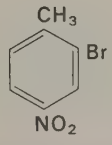
2,4,6-trinitrophenol
(picric acid*)



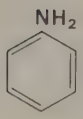
Toluene



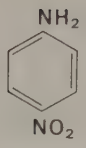
o-aminotoluene
(*o*-toluidine*)



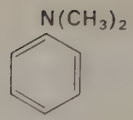
2-bromo-4-nitrotoluene



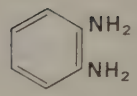
Aniline



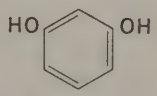
p-nitroaniline



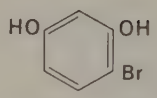
N,*N*-dimethylaniline



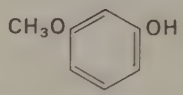
o-diaminobenzene
(*o*-aminoaniline,
o-phenylenediamine*)



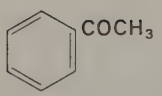
Resorcinol



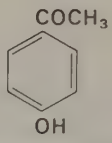
4-bromoresorcinol



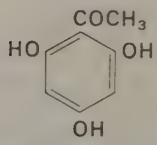
Resorcinol monomethyl
ether



Acetophenone

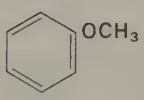


p-hydroxyacetophenone

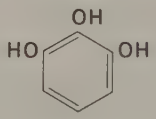


2,4,6-trihydroxyacetophenone
(phloroacetophenone*)

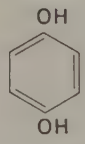
Other familiar benzene derivatives are



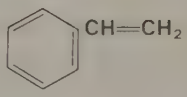
Anisole



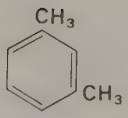
Pyrogallol



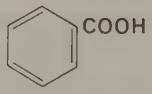
Hydroquinone



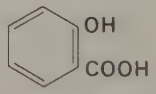
Styrene



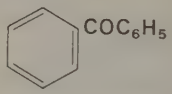
m-xylene



Benzoic acid

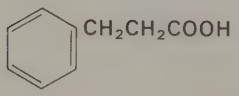


Salicylic acid
(numbering starts
with —COOH)

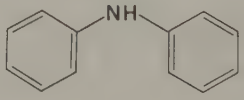


Benzophenone

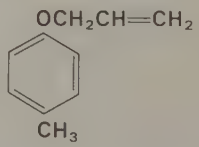
Finally, it is to be noted that the aromatic grouping may be named as a substituent:



β-phenylpropionic acid
(3-phenylpropanoic acid)



Diphenylamine



Allyl *p*-tolyl ether

APPENDIX B

Answers to selected problems

Chapter 1

1. If the salt is water soluble, precipitate the silver as AgCl with HCl. If the salt is not water soluble, dissolve in HNO_3 and then add HCl. From the weight of the silver chloride, calculate the % Ag as follows:

$$\frac{\text{wt. of AgCl} \times 107.88}{107.88 + 35.45} \times \frac{1}{\text{wt. of sample}} \times 100 = \% \text{ Ag}$$

3. To remove HCN, which will form a precipitate of AgCN with silver nitrate.

6. 4.52 mg of $(CH_3)_2S$ (mol. wt. 62) = 0.073 millimole. This will give 0.073 mM of $BaSO_4$ = 17.03 mg.

10. 9.17 mg CO_2 = (12/44) × 9.17 = 2.50 mg C,
3.87 mg H_2O = (2/18) × 3.87 = 0.422 mg H;
% C = (2.50/6.23) × 100 = 40.10;
% H = (0.422/6.23) × 100 = 6.78;
357 ml at 27°, 750 mm = 330 ml at STP. This weighs 0.890 g.; thus, 0.890/0.330 = 2.60 g/liter; and 22.4 liter weighs 2.60 × 22.4 = 60 g (= mol. wt.).

11. 100 − (69.95 + 11.70) = 18.35. If this 18.35% represents N only, the formula $C_9H_{18}N_2$ will fit. But if both N and O are present, the minimum weight of

these per mole is 14 + 16 = 30, and for a combined percentage of 18.35, the molecular weight must be 30/0.1835 = 163. Given the % C as 69.95, the grams of C per mole = 0.6995 × 163 = 114. Since this represents 9.5 C atoms it is clear that no empirical formula with mol. wt. less than 170 can be fitted. For more than one N or O the minimum molecular weight will be greater than 170. (For example, for a formula with ON_2 the minimum molecular weight will be 16 + 28/0.1835 = 240.)

15. $C_{21}H_{22}N_2O_2$.

16. The composition is $C_7H_{12}O$. This lacks 4H from the non-cyclic, saturated compound ($C_7H_{16}O$) and so there must be a double bond or ring in addition to the C=O group. For example, the compound $CH_3CH{=}CHCH_2CH_2$-$CH_2CH{=}O$ is $C_7H_{12}O$.

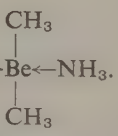
Chapter 2

1. (*b*)  ; (*c*) salicyclic acid; (*f*) $CH_3COCOCH{=}CH_2$;

   (*g*) $CH_2{=}CHCH{=}CHCONH_2$.

3. 1-*e*; 2-*i*; 5-*d*; 10-*h*; 12-*k*; 14-*l*.

Chapter 3

2. To form $H_3N{\rightarrow}Be(CH_3)_2$ and  .

3. In $Na:^-$ the external electrons are distant from the nucleus; thus one is easily removed from $Na\cdot$ to give the stable Na^+ ion. In $H:^-$ the external electrons are close to the nucleus and are more tightly bound.

7. $(C_2H_5)_2O + BF_3 \longrightarrow BF_3\cdot(C_2H_5)_2O$ (cf. Prob. 2).

8. $(CH_3)_3B$ has no unshared (nonbonding) electrons on boron to coordinate with an acceptor atom, in contrast to $(CH_3)_3N:$, in which the nonbonding pair can form a bond to the $\ddot{O}:$ atom.

9. H_2Se should resemble H_2S more than H_2O because of the large Se atom. Since the H—S—H bond angle is about 90°, the H—Se—H bond should be (and is) about 90°.

11. The C—B—C bond angle in trimethylboron is 120°. In forming the coordination complex with trimethylamine, both B and N assume tetrahedral configurations with C—B—C and C—N—C bond angles of 109.5°.

13. There would be steric repulsions in the change ftom the trigonal planar structure of tri-*t*-butylamine to the tetrahedral configuration in the N-B complex. This would involve a "compression" of the C—N—C bond angles by bringing the bulky *t*-butyl groups closer together.

15. The fifth bond to N would require the use of a 3-shell orbital distant from the attractive force of the nucleus. Therefore NR_5 is theoretically possible of existence, but energetically proscribed.

Chapter 4

2. Hydronium perchlorate.

4. (*a*) $CH_3COO^- + H_3O^+ \rightleftharpoons CH_3COOH + H_2O$
(*b*) $CH_3COO^- + CH_3OH_2^+ \rightleftharpoons CH_3COOH + CH_3OH$
(*d*) $CH_3COO^- + C_2H_5OH \rightleftharpoons CH_3COOH + C_2H_5O^-$
(*f*) $CH_3COO^- + H_3PO_4 \rightleftharpoons CH_3COOH + H_2PO_4^-$ and
$CH_3COO^- + H_2PO_4^- \rightleftharpoons CH_3COOH + HPO_4^=$

6. In part, $H_2ONO_2^+ > CH_3COOH_2^+ > HClO_4 > Cl_3CCOOH$.

10. $H_2O + HBr$ (in SO_2) $\rightleftharpoons H_3O^+ + Br^-$ (conducting). HBr in SO_2 is undissociated, non-conducting.

Chapter 6

2. Examples: $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$; $CH_3CH_2\overset{*}{\underset{\displaystyle CH_3}{\underset{|}{C}}}HCH_2CH_2CH_3$;

$(CH_3)_2CHCH_2CH(CH_3)_2$; $(CH_3)_2CH\overset{*}{\underset{\displaystyle CH_3}{\underset{|}{C}}}HCH_2CH_3$.

3. Only (*b*) and (*e*) are resolvable; but (*e*) is resolvable because it contains an asymmetric carbon atom, and not as an allene.

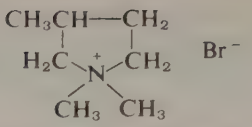
5. The displacement of —Br by $—OCOCH_3$ would give *sec*-butyl acetate (2-acetoxybutane) of configuration opposite to that of the original 2-bromobutane.

7. Four: the esters of (+)-acid/(+)-alcohol and (−)-acid/(+)-alcohol; unchanged (±)-acid; and unchanged (+)-alcohol. Note that it is possible (but unlikely) that the (−)-acid/(+)-alcohol ester would be optically inactive. Why?

Chapter 7

2. Because the S_N1 route is favored in the case of the α-chloro ether, but is a high-energy pathway for the β-chloro ether, $ClCH_2CH_2OCH_3$.

4. (*a*) $CH_3CH_2Br + CH_3COO^-K^+ \longrightarrow CH_3CH_2OCOCH_3 + KBr$
(*c*) $CH_3CH_2CH_2CH_2CH_2Br + K^+CN^- \longrightarrow CH_3CH_2CH_2CH_2CH_2CN + KBr$
(*e*) $C_6H_5CH_2Br + Na^+OH^- \longrightarrow C_6H_5CH_2OH + NaBr$
(*f*) $CH_3SO_2OCH_2CH_3 + (C_2H_5)_2NH \longrightarrow (C_2H_5)_3NH^+ + CH_3SO_2O^-$

6. The product would be 

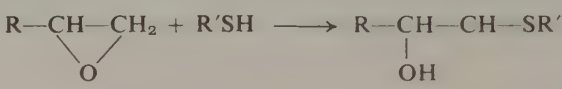
8. Fastest, $BrC(CH_3)CH{=}CH_2$; slowest, $ClCH_2CH_2CH_3$.

Chapter 8

1. The following would be most likely to show some useful activity: (*b*), (*c*), (*e*).

3. Ring-closure will occur, with displacement of $CH_3SO_2O^-$ and formation of ethylene oxide.

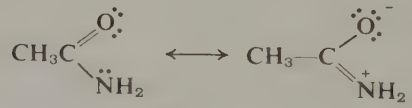
5. By nucleophilic attack and opening of the oxide ring; for example, using —SH as the nucleophilic grouping,

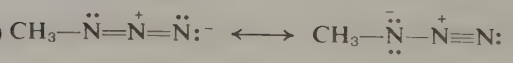


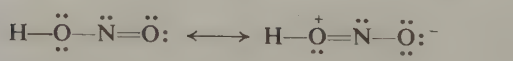
6. By addition of a nucleophile to the system $H_2C{=}C(\text{—})C(\text{—}){=}O$ in the manner described for acrolein (Section 8-6).

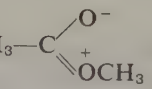
Chapter 9

1. (*b*) 

(*e*) 

(*g*) 

(*i*) 

3. (*b*) Contribution of  makes the C—O bond (a) shorter than the normal C—O single bond; the C—O bond (b) is unchanged.

(*c*) $CH_3C{\equiv}N \longleftrightarrow H^+CH_2{=}C{=}N^- \longleftrightarrow CH_3\overset{+}{C}{=}N^-$; thus, the H_3C—C bond is shorter than the normal saturated C—C bond.

(*d*) $CH_2{=}CH{-}CH{=}O \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}O^-$; thus, C—C bond (a) is longer than the normal C=C, and C—C bond (b) is slightly shorter than the normal C—C single bond.

4. The ion $CH_3\overset{O^-}{\overset{|}{C}}=CHCOOEt$ is a resonance hybrid with the contributing form $CH_3C(=O)-CH=C(O^-)(OEt)$. In the ion $CH_3\underset{O^-}{\underset{|}{C}}HCHCOOEt$ there is no charge delocalization.

5. $CH_3-\overset{+}{N}(=O)(O^-) \xrightarrow{OH^-} {}^-:CH_2-\overset{+}{N}(=O)(O^-) \longleftrightarrow CH_2=\overset{+}{N}(O^-)(O^-)$

6. The anion ${}^-:CH_2-CH=CH-CH=O$ derived from crotonaldehyde is stabilized by resonance:

$$\{:CH_2-CH=CH-CH=\ddot{O}: \longleftrightarrow CH_2=CH-CH=CH-\ddot{\underset{\cdot\cdot}{O}}:\}^-$$

Chapter 10

1. (*a*) Ethene; (*b*) propene; (*c*) 3-hexene; (*d*) 2-methylpropene; (*e*) 4-bromo-1-butene; (*f*) 1,3-pentadiene; (*g*) 1,2,3-hexatriene; (*h*) 2,3-dimethyl-2-butene; (*i*) 2,2,5,5-tetramethyl-3-hexene.

2. (*b*) $CH_3\underset{Br}{\underset{|}{C}}HCH_3$ (*e*) $BrCH_2CH_2\underset{Br}{\underset{|}{C}}HCH_3$

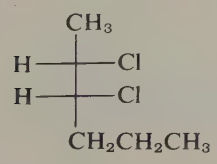
(*f*) largely $CH_3\underset{Br}{\underset{|}{C}}HCH=CHCH_3$ (*i*) $(CH_3)_2\underset{Br}{\underset{|}{C}}CHCH_2C(CH_3)_3$ with CH_3 on the CBr carbon

3. (*a*) Ethanol; (*b*) *t*-butyl alcohol; (*c*) 5,5-dimethyl-2-hexanol, (*d*) dimethyl-*n*-propylcarbinol; (*e*) methyldiethylcarbinol; (*f*) 3-hexanol.

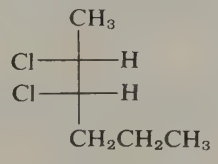
4. (*a*) $CH_3CH_2\underset{Br}{\underset{|}{C}}HCH_3$

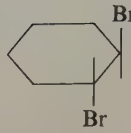
(*b*) $CH_3\underset{Br}{\underset{|}{C}}HCH_2CH_2CH_3$ and $CH_3CH_2\underset{Br}{\underset{|}{C}}HCH_2CH_3$

(*c*) $CH_3\underset{Cl}{\underset{|}{C}}H\underset{Cl}{\underset{|}{C}}HCH_2CH_2CH_3$ as the following (±) mixture:



and



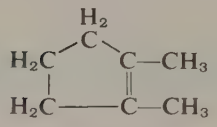
(*d*)  [(±)mixture]

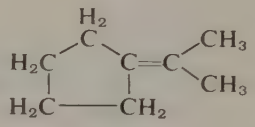
(*e*) *cis*-1,2-dimethylcyclohexane

(*f*) *n*-butane
(*g*) (±)1,2-dibromopropane
(*h*) *t*-butyl bromide

5. (*a*) Propylene will be oxidized readily by aq. $KMnO_4$, and will take up H_2 in the presence of a catalyst; cyclopropane will not.
(*b*) The cyclopentane derivative will give formaldehyde on ozonolysis.
(*c*) 1-octene will give HCHO with ozone; 4-octene will not.
(*d*) 2,4-heptadiene will take up 2 moles of hydrogen on catalytic hydrogenation; 1-methylcyclohexene will take up one mole.
(*e*) Dicyclohexyl has no double bonds; 1,11-dodecadiene will absorb bromine, can be catalytically hydrogenated, and will react with ozone.

6. (*a*) ethylene
(*b*) 2-butene
(*c*) $(CH_3)_2C{=}CH_2$
(*d*) $CH_3CH_2C(CH_3){=}CHCH_3$

(*e*) 

(*f*) 

(*g*) $CH_3CH{=}C{=}CHCH_3$

(*h*) $CH_3CH{=}C(CH_3){-}CH{=}C(CH_3){-}CH_3$

7. A = $CH_3C(=O)CH(CH_3)_2$; D = $CH_3CH_2C(OH)(CH_3)_2$

8. $CH_3CH_2CH_2CH_2OH \longrightarrow CH_3CH_2CH{=}CH_2 \longrightarrow CH_3CH_2CH(OH)CH_3$

10. Pass mixture through bromine (in an inert solvent); ethylene will be converted to 1,2-dibromoethane, and ethane will pass through. Isolate the dibromo compound, and convert it back into ethylene with zinc in alcohol.

11. Add bromine to mixture, then distill cyclohexane from higher-boiling 1,2-dibromocyclohexane.

12. One ring; five double bonds.

13. $CH_2{=}C(CH_3)CH_2CH_3 + HA \rightleftharpoons CH_3{-}C^{+}(CH_3){-}CH_2CH_3\ A^-$ $\xrightarrow{CH_2{=}C(CH_3)CH_2CH_3}$

$CH_3CH_2{-}C^{+}(CH_3){-}CH_2{-}C(CH_3){-}CH_2CH_3$ (dimer) $\xrightarrow[\text{before}]{\text{as}}$ (trimer, with loss of H^+).

14. 4.48 ml hydrogen = 0.2 millimole. For one mole hydrogen/mole compound, molecular weight = 19.6/0.2 = 98. For example,

$$\underset{\substack{0.2\ m\mathit{M}\\(19.6\ mg)}}{C_7H_{14}} + \underset{\substack{0.2\ m\mathit{M}\\(4.48\ ml)}}{H_2} \longrightarrow C_7H_{16}$$

If the compound has two double bonds, 0.1 mM compound = 19.6 mg; molecular weight = 196.

15. $(CH_3)_3CCH{=}CHC(CH_3)_3 + HBr \rightleftharpoons$

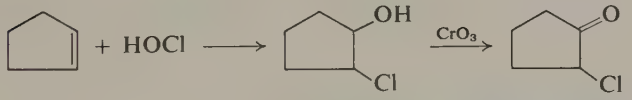
$$\{(CH_3)_3\overset{+}{C}H{-}CH_2C(CH_3)_3\}Br^- \xrightarrow{\text{rearrange}} (CH_3)_2\overset{+}{C}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2(CH_3)_3 \xrightarrow{Br^-}$$

$$(CH_3)_3\overset{\displaystyle Br}{\overset{|}{C}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2C(CH_3)_3$$

16. (*a*) $CH_3C{\equiv}CH + NH_2^- \longrightarrow CH_3C{\equiv}C{:}^-$

$$CH_3C{\equiv}C{:}^- + CH_3CH_2CH_2Br \longrightarrow CH_3C{\equiv}CCH_2CH_2CH_3$$

$$CH_3C{\equiv}CCH_2CH_2CH_3 + H(Pd) \longrightarrow \textit{cis}\text{-2-hexene}$$

(*b*) 

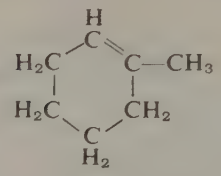
(*c*) 1. Prepare cyclic ethylene ketal from the keto ester and ethylene glycol.
2. Reduce —COOEt group with $LiAlH_4$.
3. Remove —OCH_2CH_2O— group by acid hydrolysis.

Chapter 11

1. (*a*) $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_3$; from CH_3CH_2MgBr and CH_3CH_2CHO
(*b*) $(CH_3)_2CHCH_2CH_2OH$; from $(CH_3)_2CHMgBr$ and HCHO to give isobutyl alcohol; then isobutylmagnesium bromide (via isobutyl bromide) and HCHO
(*c*) $(CH_3CH_2)_3COH$; in reverse order of steps:
(1) $CH_3CH_2COCH_2CH_3$ and CH_3CH_2MgBr;
(2) $CH_3CH_2COCH_2CH_3$ by oxidation of diethylcarbinol [see part (*a*)]
(*d*) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}CH_2CH_3$; acetone and ethylmagnesium bromide
$\underset{\displaystyle CH_3}{|}$

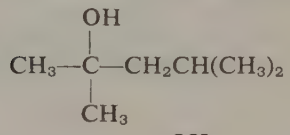
2. (*a*) $CH_3{=}{=}CHCH_3$ (*b*) $CH_2{=}C(CH_3)_2$ (*c*) $CH_3CH{=}CHCH_3$

(*d*) $(CH_3)_2C{=}CHCH_3$ (*e*)

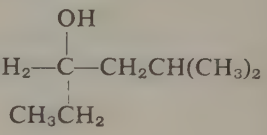


3. Products are (*a*) CH_3CH_2OH; (*b*) $CH_3CH_2CH_2OH + (CH_3)_2CHOH$; (*c*) 2-butanol; (*d*) ethanol + methanol.

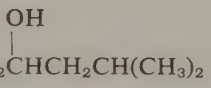
5. (*a*)



(*d*)



(*f*)



7. (*b*) acetone + $CH_3MgI \longrightarrow (CH_3)_3C{-}OH \longrightarrow (CH_3)_3C{-}Cl \longrightarrow (CH_3)_3C{-}MgCl$, and reaction of this with acetone.

Chapter 12

1. (*a*) $CH_3CH_2OCH_3$ and ethylene; (*b*) $(CH_3)_2CHOCH_3$ and $CH_2{=}CHCH_3$; (*c*) $CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CH_2CH_2CH_3$ and $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CHCH_2CH_3$ (no ether is expected); (*d*) $CH_3CH_2OCH_3$ and CH_3OCH_3

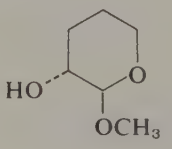
2. (*a*) $CH_3CH_2OCH_3$; (*b*) $CH_3CH{=}CH_2$; (*c*) 2-methyl-2-pentene; (*d*) CH_3OCH_3

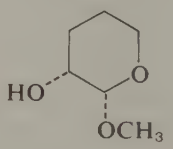
4. The product would be $CH_3CH(OCH_2CH_2CH_3)_2$.

6. The product is *t*-butyl chloride (+ acetic acid). The HCl formed in the initial stage reacts with *t*-butyl acetate.

8. By the use of $(CH_3)_3C{-}O^-K^+$ and ethyl iodide (or ethyl bromide or diethyl sulfate).

10. The products would be the two diastereomeric 2-methoxy-3-hydroxy-tetrahydropyrans:





Chapter 13

2. Reduce cyclohexanone to cyclohexanol; dehydrate to cyclohexene; hydroxylate the double bond with $KMnO_4$ or OsO_4 to give the *cis* glycol, or with a peroxy acid to give the *trans* glycol.

3. For (*a*) and (*b*), first reduce diethyl succinate with $LiAlH_4$ to give butane-1,4-diol.
   (*b*) Butane-1,4-diol + HBr ⟶ 1,4-dibromobutane; then treat the dibromo compound with methylamine.
   (*c*) First step: diethyl succinate + CH_3MgI

6. The following would not react: (*b*), (*c*).

Chapter 15

2. (*a*) same; (*b*) one would, one would not; (*c*) yes; (*d*) D-ribose.

3. The hydroxyl group in the 3 position (carbonyl group numbered 1).

5. The name L-*manno*methylose is given to L-rhamnose because C-2, C-3, C-4, and C-5 have the same configurations as those in L-mannose (and the $—CH_2OH$ of mannose is replaced by $—CH_3$ in rhamnose).

6. The glycoside is (α- or β-) methyl-D-glucofuranoside.

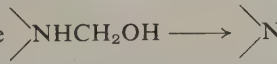
8. The oxidation occurs at the enediol grouping:

10. Sulfation (conversion of —OH groups to their sulfuric acid esters, $—OSO_2OH$) converts portions of the polysaccharide into partially poly-sulfated regions, which provide a structure containing strongly acidic $—OSO_3H$ groups similar to those in heparin. Some of these have been prepared and tested as clinical anticoagulants, but with minimal success because of undesirable side effects.

Chapter 16

3. (*a*) From 1-bromobutane by the Gabriel synthesis.
   (*b*) From 1,2-dibromoethane (Gabriel).
   (*c*) Reduce $CH_3CONHCH_3$ with $LiAlH_4$.
   (*e*) From 1,5-dibromopentane + CH_3NH_2, to give *N*-methylpiperidine; then oxidize with hydrogen peroxide.

4. This is mechanistically analogous to base-catalyzed ester interchange. (Explain.)

5. Because  + HCHO.

7. (*a*) Et_3N + $CH_2{=}CHCH_2OCH_2CH_3$ (allyldiethylamine)
   (*c*) methyl bromide + $(CH_3)_2NCN$
   (*e*) Hydrolysis (saponification) of the ester.

   General comment and hint on working out synthesis problems: It is usually best to work *backwards*, going from each compound to the one preceding it. For example, in (*c*) the final product is clearly the result of adding $(CH_3)_2CHMgBr$ to acetone. Acetone can be obtained from 2-bromopropane

by hydrolysis to the alcohol and oxidation. (*e*) Start the sequence by hydroboration of $(CH_3)_2C{=}CH_2$ to give $(CH_3)_2CHCH_2OH$.

Chapter 18

1. The negative inductive effect of the chlorine atoms of the Cl_3C— group raises the energy of the contributing structure $Cl_3C{-}\overset{+}{C}H{-}O^-$ (and reduces its relative importance in the resonance hybrid), thus reducing the single-bond character of the C=O group.

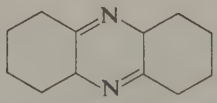
3. Quaternization of the Me_2N— group would destroy its auxochromic character, for $Me\overset{+}{N}$— has no unshared (nonbonding) electrons. Therefore, the carbonyl absorption of $Me_3\overset{+}{N}CH{=}CH{-}CHO$ would not be much different from that of $CH_2{=}CH{-}CHO$ itself.

4. The absorption at 1690 cm^{-1} is in the region of both an amide and an α,β-unsaturated ketone. Since there is no UV absorption, the unsaturated ketone can be ruled out.

5. The structures $CH_2{=}CHCH_2CH{=}CH{-}CHO$ (A) and $CH_3CH_2CH_2CH_2{-}CH_2CHO$ (B) would show these UV and IR absorption data. Note that A cannot be $CH_3CH{=}CH{-}CH{=}CH{-}CHO$, for this would have a UV maximum at a much higher wavelength.

Chapter 19

2. The product is 

3. The product is 

5. Separate the alcohol from the two ketones by means of Girard's reagent. Then separate cyclohexanone from 3-hexanone by means of sodium bisulfite (3-hexanone does form a bisulfite addition compound).

7. $$CH_3OCH{=}CH{-}\underset{\underset{\overset{+}{O}H}{\|}}{C}{-}CH_3 \longleftrightarrow CH_3\overset{+}{O}{=}CH{-}CH{=}\underset{\underset{OH}{|}}{C}{-}CH_3$$

8. A is 1-(aminomethyl)-cyclohexanol. B is cycloheptanone. Treatment of A with nitrous acid causes a pinacol-like rearrangement by way of the carbonium ion formed by decomposition (loss of N_2) from the diazonium salt.

Chapter 20

1. (*a*) Propionic acid ⟶ 3-pentanone; then reaction with $CH_2{=}P(C_6H_5)_3$. (*c*) Benzaldehyde + $BrCH_2COOEt/Zn$ (Reformatsky).

(*d*) By the use of the Wittig reagent prepared from CH_3OCH_2Cl ([$CH_3OC{=}P(C_6H_5)_3$]).
(*f*) *Via* addition of $(CH_3)_2CHMgBr$ to acetone.
(*g*) *Via* hydroboration to 1-propanol.
(*i*) *Via* 2-butanone, then diazomethane. Query: Would two products be formed, and how could they be separated?

Chapter 21

1. The following observations will serve to distinguish one compound from the other in each pair:
   (*a*) Only the methyl ketone will form a bisulfite addition compound.
   (*c*) The 1,2-diol will react with (that is, reduce) periodic acid; the other will not.
   (*e*) The 1,2-diketone will react with *o*-phenylenediamine to give a quinoxaline.
   (*g*) Either of two observations will serve: the α,β-unsaturated ketone will show a high-intensity ($\log \epsilon$ about 4) UV maximum at about 220 nm (Query: Would IR be equally useful?); or, the amine, but not the amide, would be basic and soluble in dilute aqueous HCl.
   (*i*) The α,α-dichloro compound would have an IR (C=O) band at a considerably higher frequency (higher wave number) than the compound without α-chlorine substituents. See Problem 1, Chapter 18.

2. (*a*) Addition of CH_3NH_2, then saponification of ester.
   (*c*) Hydroxylation of cyclohexene to cyclohexanol by means of B_2H_6; oxidation of cyclohexanol to cyclohexanone; addition of methylmagnesium iodide; dehydration; hydroxylation with B_2H_6.
   (*e*) Addition of methylmagnesium iodide to CH_3OCH_2COOEt gives 2-methyl-3-methoxy-2-propanol, treatment of which with H_2SO_4 (conditions for pinacol rearrangement) gives the desired aldehyde *via* the intermediate steps:

$$CH_3OCH_2\overset{+}{C}(CH_3)_2 \longrightarrow CH_3O\overset{+}{C}HCH(CH_3)_2 \xrightarrow{H_2O} CH_3OCH(OH)CH(CH_3)_2$$

   Note that $CH_3O\overset{+}{C}HCH(CH_3)_2$ is greatly stabilized by delocalization of + charge [$\longleftrightarrow CH_3\overset{+}{O}{=}CHCH(CH_3)_2$].

Chapter 22

1. (*a*) $CH_3COCH_3 + EtO^- \rightleftharpoons (CH_3C\ddot{O}CH_2)^- + EtOH$

(*c*) $CH_3C(CH_3)_2COCH_2CH_3 + EtO^- \rightleftharpoons [(CH_3)_3CC\ddot{O}CHCH_3]^- + EtOH$

(*e*) $CH_3COCH_2CH_2COCH_3 + EtO^- \rightleftharpoons$

$(CH_3COCH_2\ddot{C}HCOCH_3)^- + EtOH$

(*i*) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCOCH_2COCH\underset{\displaystyle CH_3}{\underset{|}{C}}H_3 + EtO^- \rightleftharpoons$

$[(CH_3)_2CHCO\ddot{C}HCOCH(CH_3)_2]^- + EtOH$

3. (*a*) $(H_3C)_2\underset{\displaystyle OH}{\underset{|}{C}}-CH_2COCH_3 + B:^- \rightleftharpoons (H_3C)_2\underset{\displaystyle O^-}{\underset{|}{C}}-CH_2COCH_3 \rightleftharpoons$

$(H_3C)_2C{=}O + (CH_2COCH_3)^-$

$(CH_2COCH_3)^- + BH \rightleftharpoons CH_3COCH_3 + :B^-$

(*b*) 3-hydroxybutanal in analogous manner.

4. (*a*) $CH_3CH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CHO$, from $CH_3CH_2CH_2CHO$, CH_3CHO; (*b*) from acetone, HCHO; (*c*) from CH_3CHO, HCHO; (*d*) from cyclohexanone, HCHO.

5. No resonance stabilization of $(:CH_2CH_2CHO)^-$ by delocalization of negative charge to carbonyl group.

6. (*a*) $\left(:CH_2-\underset{\displaystyle H}{\underset{|}{C}}{=}\ddot{O}: \longleftrightarrow CH_2{=}\underset{\displaystyle H}{\underset{|}{C}}-\ddot{O}:\right)^-$

(*b*) $\left(CH_3CO\ddot{C}HCOCH_3 \longleftrightarrow CH_3-\underset{\displaystyle :\ddot{O}:}{\underset{|}{C}}{=}CHCOCH_3 \longleftrightarrow CH_3COCH{=}\underset{\displaystyle :\ddot{O}:}{\underset{|}{C}}-CH_3\right)^-$

(*c*) $(CH_2{=}CH\ddot{C}HCH{=}O: \longleftrightarrow CH_2{=}CH-CH{=}CH-\ddot{O}: \longleftrightarrow$

$:CH_2-CH{=}CH-CH{=}O)^-$

(*d*) $(CH_2{=}CH\ddot{C}HCH{=}CH_2 \longleftrightarrow :CH_2-CH{=}CH-CH{=}CH_2 \longleftrightarrow$

$CH_2{=}CH-CH{=}CH-CH_2:)^-$

(*e*) $(CH_2{=}CH-CH{=}\overset{+}{O}H \longleftrightarrow \overset{+}{C}H_2-CH{=}CH-OH)$

7. (*b*) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COCH_3$ (*d*) $(CH_3)_2\underset{\displaystyle CH_2OH}{\underset{|}{C}}CHO$

(*e*) $CH_3COCH(CHOHCH_2CH_3)COCH_3$ [the HOCHCH₂CH₃ group is drawn above the central CH] (followed by dehydration)

(*f*) $CH_3CH(OH)CH_2NO_2$

8. $CH_2{=}CHCH_2CHO + B:^- \rightleftharpoons$

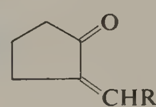
$(CH_2{=}CH\ddot{C}HCHO \longleftrightarrow :CH_2CH{=}CHCHO)^-$

Condensation now occurs at γ carbon atom, which attacks acetaldehyde.

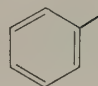
9. $CH_3COC(CH_3)_2COCH_3 + OEt^- \rightleftharpoons CH_3{-}C(O^-)(OEt){-}C(CH_3)_2{-}COCH_3 \longrightarrow$

$CH_3{-}C({=}O)OEt + (:C(CH_3)_2COCH_3)^-$

10. (*a*) $CH_3COCH{=}CHR$

(*b*) 

(*c*) $CH_3C({=}CHR)COCH_2CH_3$ or $CH_3C({=}CHR)COC({=}CHR)CH_3$ [the =CHR and =RCH groups are drawn above]

(*d*) $(CH_3)_3CCOCH{=}CHR$; in these, R = 

12. $CH_3CO\bar{C}HCOCH_3 \longleftrightarrow CH_3C(O^-){=}CHCOCH_3 \longleftrightarrow CH_3COCH{=}C(O^-){-}CH_3$;

$CH_3CO\bar{C}HCH_2COCH_3 \longleftrightarrow CH_3C(O^-){=}CHCH_2COCH_3$; in the case of the 1,4-diketone the second carbonyl group is "insulated" by the intervening $-CH_2-$ and does not participate in the negative-charge delocalization as it does in the case of the 1,3-diketone.

16. Compound A is $CH_3CO{-}O{-}CH(CH_3)CH_2COCH_3$. Treatment with KOH causes a β elimination of the acetoxy group:

$$A \xrightarrow[-H^+]{OH^-} CH_3COO{-}CH(CH_3){-}\ddot{\bar{C}}HCOCH_3 \longrightarrow$$

$$CH_3COO^- + CH_3CH{=}CHCOCH_3$$

17. Pulegone $\xrightarrow{OH^-}$ acetone + 3-methylcyclohexanone (reverse aldol), neither of which shows UV max at 252 nm.

Chapter 23

3. (*a*) $RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$
(*b*) $RCOOH + NH_3 \rightleftharpoons RCOO^- + NH_4^+$
(*c*) $RCOOH + EtNH_2 \rightleftharpoons RCOO^- + EtNH_3^+$
(*d*) $RCOOH + EtO^- \rightleftharpoons RCOOH + EtOH$
(*e*) $RCOOH + EtOH(H_2SO_4) \rightleftharpoons RCOOEt + H_2O$
(*f*) $RCOOH + Me_3N \rightleftharpoons RCOO^- + Me_3NH^+$ (R = CH_3CH_2—)

6. (*a*) $RCOCl + EtOH \longrightarrow RCOOEt + HCl$
(*b*) $RCOCl + (CH_3)_2CHCH_2OH \longrightarrow RCOOCH_2CH(CH_3)_2 + HCl$
(*c*) $RCOCl + CH_3COO^-Na^+ \longrightarrow RCOOCOCH_3 + Cl^- + Na^+$
(*d*) $RCOCl + H_2O \longrightarrow RCOOH + HCl$
(*e*) $RCOCl + NH_2NH_2 \longrightarrow RCONHNHCOR + 2HCl$
(*f*) $RCOCl + HONH_2 \longrightarrow RCONHOH + HCl$
(*g*) $RCOCl + MeNHEt \longrightarrow RCON\begin{matrix}Me\\Et\end{matrix} + HCl$

NOTE: In *e*, *f*, and *g* the HCl formed would react with the basic amine to give the corresponding salt.

7. (*a*) *n*BuBr + KCN $\longrightarrow$ *n*BuCN, then hydrolysis, (*b*) CH_3COCl + sodium acetate (see 6*c*); (*c*) see 6*g*, then reduce $CH_3CH_2CONH_2$ with $LiAlH_4$; (*d*) $BrCH_2CH_2Br$ + KCN (see 6*a*); (*e*) saponify with NaOH.

8. *a*, *b*, and *d*.

9. (*a*) Remove the *n*-butyric acid with $NaHCO_3$; remove pentanal with sodium bisulfite; remove di-*n*-butyl ether with H_3PO_4; octane remains.
(*c*) 2-hexanone will form a bisulfite addition compound, 3-hexanone will not.

10. acetone + $CH_3MgBr \longrightarrow$ *t*-butyl alcohol $\longrightarrow$ *t*-butyl chloride $\longrightarrow$ Grignard reagent $\xrightarrow{CO_2}$ trimethylacetic acid.

12. The tropical plants, which are not subject to freezing climatic conditions, would be expected to have the higher saturated/unsaturated ratio.

14. No. Oxidation of 3-methylcyclohexanone would give a mixture of α- and β-methyladipic acids.

15. Acetic acid, acetic anhydride, and methoxyacetic anhydride, in that order (look up boiling points).

Chapter 24

1. Products are

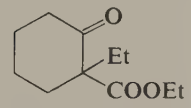
(*a*) $CH_3COCH(CH_3)COOEt$

(*b*) $CH_3CH_2CH(CH_3)CH(COOEt)_2$

(*c*) $CH_3COCH_2CH(COOEt)_2$

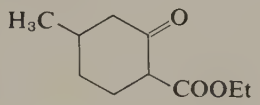
(*e*) $CH_3COCH(CH_2COOEt)COOMe$

(*d*)



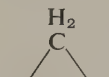
2. (*a*) *Via* *n*-butyl bromide and acetoacetic ester.
(*c*) *Via* diethyl ethylmalonate and $BrCH_2COOEt$.

(*d*) Alkylate



with EtBr.

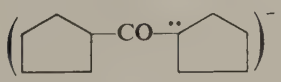
(*e*) Via $LiAlH_4$ reduction of



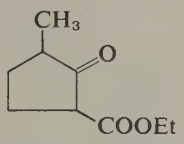
which can be prepared *via* $BrCH_2CH_2Br$ and malonic ester.

(*g*) $HOCH_2C(CH_3)_2CH_2OH$, by reduction of $(CH_3)_2C(COOEt)_2$.
(How could this diol be prepared with the use of an aldol condensation?)

3. (*a*) $(\ddot{C}H_2CHO)^-$
(*b*) $(CH_3CO\ddot{C}H_2)^-$
(*c*) $[(CH_3)_3CCO\ddot{C}H_2]^-$
(*d*) $(CH_3CO\ddot{C}HCOCH_3)^-$
(*e*) $[(CH_3CO)_3\ddot{C}]^-$
(*f*) $[\ddot{C}H(COOMe)_2]^-$
(*g*) $[CH_3\ddot{C}(COOMe)_2]^-$
(*h*) $[\ddot{C}(COOEt)_3]^-$
(*i*)

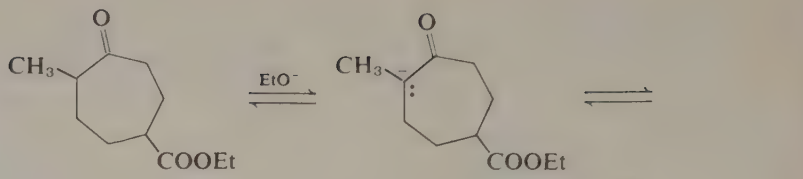


5. $EtOOCCH(CH_3)CH_2CH_2CH_2COOEt \xrightarrow{NaOEt}$

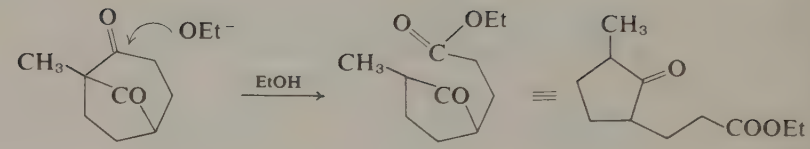


6. $CH_3CH{=}C(NR_2)CH_2CH_3 + CH_2{=}CHCOOMe \xrightarrow[\text{(hydrol.)}]{} CH_3CHCOCH_2CH_3$ with CH_2CH_2COOMe on the CH

7. (*a*)



(*b*)



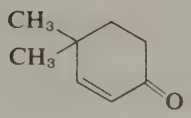
Chapter 25

1. (*a*) $(EtOOC)_2CHCH_2CH_2COOEt$

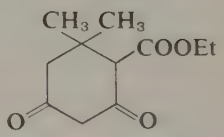
(*c*) $(CH_3)_2CCH_2CH_2CN$ (CHO)

(*e*) $EtOOCCHCH(COOEt)_2$ (CH_2COOEt)

2. (*a*)



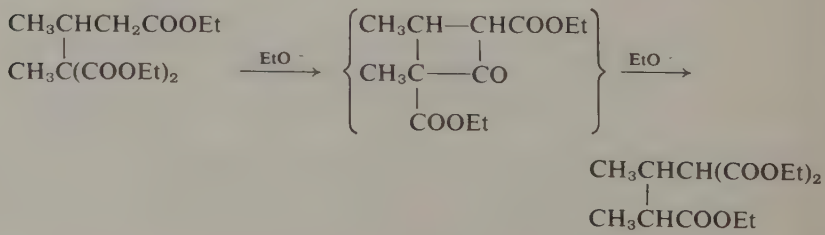
(*c*)



3. The "normal" initial addition product is

CH_3CHCH_2COOEt
$CH_3C(COOEt)_2$

In the presence of NaOEt, this undergoes a Dieckmann ring closure and subsequent ring reopening:



4. (*a*) See Section 25-4.

(*c*) *Via* $C_6H_5CH_2CN \xrightarrow[NaOEt]{CH_3COOEt} C_6H_5\underset{\displaystyle COCH_3}{\underset{|}{CH}}CN$

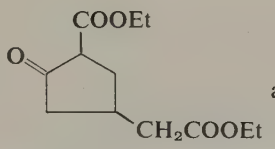
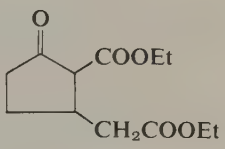
then methylate the α carbon atom, hydrolyze —CN to —COOH, decarboxylate.

(*e*) *Via* product of Dieckmann ring closure of $CH_3N(CH_2CH_2COOEt)_2$; then add $CH_2{=}CHCOCH_3$, saponify, decarboxylate.

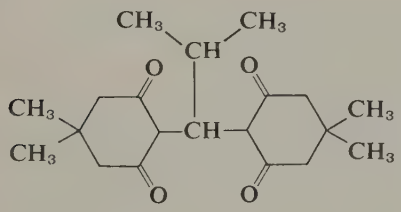
(*g*) $CH_3CONHCH(COOEt)_2$ is a malonic ester with a replaceable α hydrogen. A Michael addition to $CH_2{=}CHCOOEt$ is the first step.

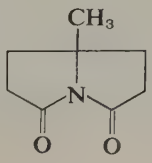
(*i*) See examples in Section 25-1; for example, Equations (1), (2), and (3).

Chapter 27

4. The products would be  and 

5. The initial step is protonation of the carbon-carbon double bond to give $CH_3\overset{+}{C}HCH_2CH_2COOH$ and $\overset{+}{C}H_2CH_2CH_2CH_2COOH$, with the former predominating. Attack of —COOH on the carbonium center closes the lactone ring.

7. (*b*) 

8. Compound B is 

9. See Section 27-10.

Chapter 28

1. (*a*) 2, 3, and 4 positions; (*b*) 3 and 4 positions (Br,Br = 1,2); (*c*) four possible (all positions different); (*d*) only one; (*e*) two possible: 2 and 4 (Cl,Cl = 1,3).

2. 1,2,3,4; 1,2,4,5; 1,2,3,5. There are three tetramethylbromobenzenes (one from each of the three hydrocarbons).

3. HINT: (*a*) Disregard conformational isomers; (*b*) since the electrons are not delocalized in a planar symmetrical orbital (as in benzene) two 1,2-dibromo compounds are theoretically possible.

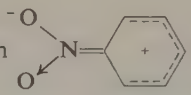
4. 1,3-dimethyl-4-bromobenzene.

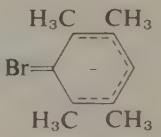
5. *p*-xylene can give only one mononitro compound; ethylbenzene can give three.

6. (*a*) Substituent enters at position 2; (*b*) substituent can enter at two positions; *ortho* to CH_3 and *ortho* to CH_2CH_3.

7. (*a*) Ethylbenzene; (*b*) *sec*-butylbenzene; (*c*) *t*-butylbenzene; (*d*) allylbenzene; (*e*) *t*-butylbenzene; (*f*) *sec*-butylbenzene.

Chapter 29

2. The contribution of the form  to the structure of nitrobenzene is not as large as the contribution of the dipolar form in the case of *p*-nitrodimethylaniline; thus steric inhibition of its contribution does not cause so large a change in dipole moment.

3. There is little steric interference with the contribution 

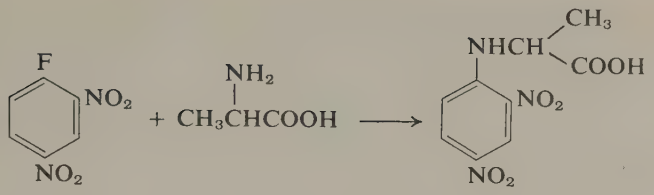
4. (*a*) *Meta*; (*b*) *ortho* to NHAc; (*c*) *ortho* to OMe; (*d*) *ortho* to $CH_2CH_2NO_2$; (*e*) *ortho* to OMe; (*f*) *ortho* to CH_3; (*g*) *ortho* to OMe; (*h*) *ortho* to NHAc; (*i*) *ortho* to CN; (*j*) *ortho* to NH_2.

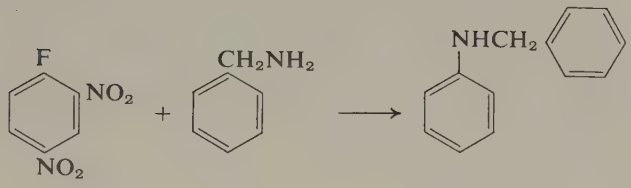
6. (*a*) benzene ⟶ bromobenzene ⟶ *p*-nitrobromobenzene
   (*b*) toluene ⟶ *p*-nitrotoluene ⟶ 2-bromo-4-nitrotoluene
   (*c*) benzene ⟶ nitrobenzene ⟶ *m*-bromonitrobenzene
   (*d*) benzene ⟶ bromobenzene ⟶ *p*-bromoacetophenone
   (*e*) *p*-toluidine ⟶ *p*-acetotoluidide (*N*-acetyl-*p*-toluidine) ⟶ 3-bromo-4-acetylaminotoluene ⟶ 3-bromo-4-aminotoluene.

7. Because upon electrophilic demand of the attacking reagent the —CH=CH— bond can supply electrons to the ring.

Chapter 30

1. (*a*) Nitrate bromobenzene, reduce NO_2 to NH_2.
   (*b*) Nitrate acetanilide, hydrolyze $NHCOCH_3$ to NH_2.
   (*c*) Nitrate phenetole.
   (*d*) Nitrate phenyl acetate, reduce NO_2 to NH_2 (catalytically).
   (*e*) Nitrate anisole, reduce NO_2 to NH_2.
   (*f*) Dinitrate anisole; better, treat 2,4-dinitrochlorobenzene with NaOMe to replace Cl by OMe.

2. (*a*) 

(*c*) 

3. Products are (*a*) 2,6-dimethyl-4-nitro-*N*-methylaniline; (*b*) 2-methoxy-3-nitrotoluene; (*c*) *p*-nitrophenylhydrazine; (*d*) *p*-nitrosoaniline; (*e*) 2-bromo-4-nitrodiphenylamine.

4. Greater stability of $C_6H_5CH_2^+$ than $C_6H_{13}CH_2^+$; *p*-methoxybenzyl chloride would be more reactive because *p*-OCH_3 participates in delocalization of + charge. Show how it does so.

5. Prepare 4-chlorobutyl benzenesulfonate, treat this with benzylmagnesium chloride.

6. (*a*) Benzene ⟶ bromobenzene ⟶ phenylmagnesium bromide ⟶ benzoic acid ⟶ cyanobenzene (benzonitrile) ⟶ benzylamine.
   (*b*) Toluene ⟶ benzyl chloride ⟶ benzyl cyanide ⟶ phenylacetic acid.
   (*c*) Toluene ⟶ *p*-methylacetophenone ⟶ *p*-toluic acid ⟶ benzene-1,4- dicarboxylic acid (terephthalic acid).
   (*d*) Benzene ⟶ bromobenzene ⟶ phenylmagnesium bromide; allow to react with diethyl carbonate.
   (*e*) Bromobenzene ⟶ toluene (*via* Wurtz-Fittig) ⟶ *p*-bromotoluene ⟶ *p*-xylene (Wurtz-Fittig).

7. *Via* Ullmann reactions with appropriate bromo or iodo compounds.
   [NOTE: Syntheses can nearly always be accomplished by more than one route. The above are suggested methods, but others can be devised.]

Chapter 31

1. Entering nitro group goes (*a*) *para*; (*b*) *ortho* to either methyl; (*c*) *ortho* to CH_3; (*d*) *para*; (*e*) *para*; (*f*) *ortho* to —$NHCOCH_3$; (*g*) position 4; (*h*) *ortho* to CH_3; (*i*) *meta*; (*j*) *ortho* to CH_3; (*k*) position 4.

2. (*a*) Aniline ⟶ acetanilide ⟶ *p*-nitroacetanilide; hydrolyze.
   (*b*) Acetanilide ⟶ *p*-bromoacetanilide ⟶ 4-bromo-2-nitroacetanilide ⟶ 4-bromo-2-nitroaniline; oxidize —NH_2 to —NO_2 (see text).

(*c*) Toluene ⟶ *o*-nitrotoluene (separated from *p*-compound) ⟶ *o*-*N*-acetyl toluidine ⟶ 2-acetylamino-5-nitrotoluene; hydrolyze to $-NH_2$, oxidize $-NH_2$ to $-NO_2$.
(*d*) ammonolysis (with alcoholic NH_3) of 2,4-dinitrochlorobenzene.

3. Displacement of Br^- by nucleophilic attack of $CH_3CH_2COO^-$.

4. Displacement of Br^- from Aryl—$COCH_2Br$.

5. (*a*) Prepare 2,4-dinitrotoluene; (*b*) prepare *p*-nitrosodimethylaniline; (*c*) condense these as in Section 30-4; (*d*) hydrolyze Schiff's base.

6. Condense with Aryl—NO to give Aryl—$N{=}C(COOEt)_2$; hydrolyze.

9. Condensation of aniline with *p*-nitrosoanisole.

Chapter 32

1. Products are (*a*) *N*-nitroso-*N*-methylaniline; (*b*) *N*-nitroso-di-*n*-butylamine; (*c*) no new product; (*d*) *p*-chlorobenzenediazonium salt; (*e*) diazonium salt; (*f*) *p*-nitroso-*N*,*N*-diethylaniline.

2. (*a*) Anisole ⟶ *p*-nitroanisole ⟶ amine; diazotize; replace with —CN.
(*b*) Nitrobenzene ⟶ *m*-bromonitrobenzene ⟶ amine; diazotize; replace with Br.
(*c*) Aniline ⟶ 2,4,6-tribromoaniline ⟶ remove $-NH_2$ *via* diazotization, H_3PO_2.
(*d*) Nitrobenzene ⟶ *m*-bromonitrobenzene ⟶ *m*-bromoaniline ⟶ *m*-bromoacetanilide; nitrate; reduce.
(*e*) Toluene ⟶ *o*-nitrotoluene; reduce, diazotize, replace by —Cl.
(*f*) *m*-dinitrobenzene ⟶ *m*-nitroaniline; diazotize, replace by OH.
(*g*) Anisole ⟶ *p*-bromoanisole ⟶ Grignard reagent ⟶ *p*-methoxybenzoic acid; demethylate with HBr.
(*h*) *m*-dibromobenzene (as in *b*) ⟶ 2,4-dibromonitrobenzene; reduce.
(*i*) *p*-chloronitrobenzene ⟶ *p*-chloroaniline ⟶ *p*-chloroacetanilide; nitrate; reduce; hydrolyze.

3. *c*, *d*, *f*, *g*, *j*.

4. (*a*) From aniline *via* benzonitrile (replacement of N_2^+ by CN).
(*b*) Replacement of N_2^+ by OH; methylation.
(*c*) Coupling of diazotized aniline with phenol.
(*d*) From *p*-bromoaniline, replacement of N_2^+ by Br.
(*e*) From (*c*) followed by reduction with $Na_2S_2O_4$.

5. (*a*) *N*-methyl-*o*-toluidine + HONO ⟶ *N*-nitroso compound (neutral).
(*b*) *m*-toluidine ⟶ diazonium salt (forms dye with a phenol).
(*c*) The amino compound is soluble in dilute aqueous acid.
(*d*) The salt has ionic bromine; detect with $AgNO_3$.
(*e*) Phenol is acidic, soluble in dilute alkali.
(*f*) The phenol is acidic.
(*g*) The benzyl bromide has an active halogen ($AgNO_3$).

6. By selective solubility in dilute aqueous acid and alkali.

7. Convert to isophthalic (1,3-) acid. This is a known reference compound.

10. *p*-hydroxybenzyl alcohol (or products derived from it).

11. The two *ortho*-methyl groups provide a steric inhibition of the resonance delocalization that, in *N*,*N*-dimethylaniline, permits participation of the amino nitrogen atom in charge delocalization in the transition state of the electrophilic attack upon the ring.

Chapter 33

1. $h > f > b > g > d > c > a > e > i$

2. (*a*) *via p*-bromoaniline
   (*b*) *via* sulfonation of benzene
   (*c*) *via* Kolbe synthesis of salicylic acid
   (*d*) as in (*c*)
   (*e*) *via p*-nitroanisole
   (*f*) *via p*-nitro-*n*-butylbenzene; or *via p*-hydroxybutyrophenone
   (*g*) Reimer-Tiemann reaction on *p*-cresol
   (*h*) *via* 3,4-dimethoxyacetophenone [Friedel-Crafts on catechol dimethyl ether (veratrole)]

4. Compound A can be *p*-hydroxybenzyl alcohol; compound B would then be *p*-methoxybenzyl alcohol, and the acid would be *p*-methoxybenzoic acid.

6. The glucoside is arbutin, that is, the monoglucoside of hydroquinone; the phenol D is *p*-methoxyphenol; E is *p*-dimethoxybenzene.

7. Picein is the glucoside of *p*-hydroxyacetophenone.

Chapter 34

1. Products are

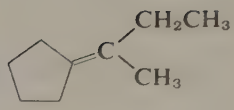
(*a*) $(CH_3)_2C{=}C(CH_3)(CH_2CH_3)$

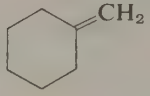
$CH_2{=}C(CH_3)CH(CH_3)CH_2CH_3$

$(CH_3)_2CHC(CH_3){=}CHCH_3$

(*b*) mixture of $CH_3CH_2C(CH_3){=}CH_2$ and $CH_3CH_2CH{=}CHCH_3$

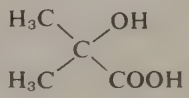
(*c*) 1,2-dimethylcyclopentene

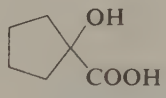
(*d*) 1-methyl-2-ethylcyclohexene, perhaps some 

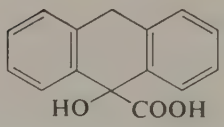
(*e*)  and 

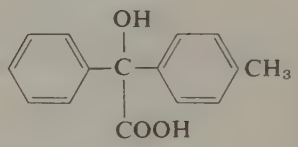
2. Methanol, dimethyl ether; methyl ethyl ether.

3. Products are:

(*a*) 

(*b*) 

(*c*) 

(*d*) 

4. 2,6-dimethyl-1,4-dihydroxybenzene.

5. By oxidation with a peracid; $ArCOCH_3 \longrightarrow ArOCOCH_3$.

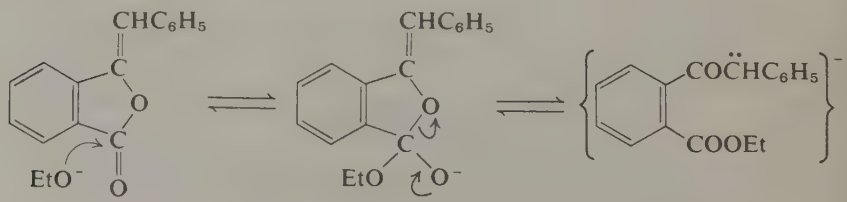
6. Succinic acid ⟶ 1,4-butane-diol ⟶ adipic acid (*via* dibromide, dinitrile) ⟶ cyclopentanone ⟶ lactone of 5-hydroxypentanoic acid (*via* peracid oxidation).

7. (*a*) Can introduce $—NH_2$ by first preparing the acid (that is, benzoic acid ⟶ aniline).

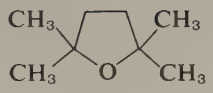
8. (*a*) *via* Beckmann rearrangement
   (*b*) Beckmann rearrangement; $LiAlH_4$ reduction
   (*c*) adipic acid ⟶ cyclopentanone ⟶ 2-piperidone ⟶ piperidine by $LiAlH_4$ reduction
   (*d*) benzoic acid ⟶ phenylacetic acid ⟶ hydrocinnamic acid (Arndt-Eistert reaction)

9. By (1) Schmidt reaction, leading to cyclic lactam of 6-aminohexanoic acid; (2) reaction of —NH—CO— grouping with HN_3.

10. Reaction starts by following step:

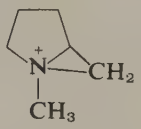


Chapter 35

1. Product is 

2. Product is pinacolone.

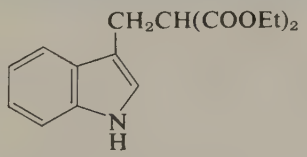
3. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

4. Proceeds *via* cyclic imonium ion: 

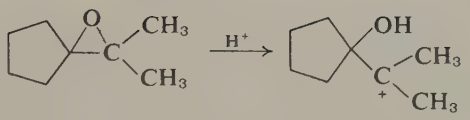
5. Products are (*a*) 2-ethoxypyridine; (*b*) 2-hydrazinopyridine; or 1,2-dipyridylhydrazine; (*c*) 2-methoxy-3-bromopyridine; (*d*) *N*-ethyl-2-pyridone; (*e*) 2-aminoquinoline.

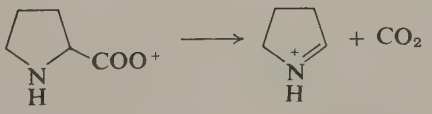
6. Proceeds *via* 3,4-dimethoxyphenethylamine (by reduction of the nitrile), then Bischler-Napieralski reaction; finally, dehydrogenation (heat with Pd-black).

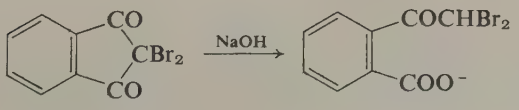
7. Prepare gramine from indole by means of the Mannich reaction. Gramine can be used as an alkylating agent; for example, it reacts with the sodium derivative of ethyl malonate to give the following indole derivative:



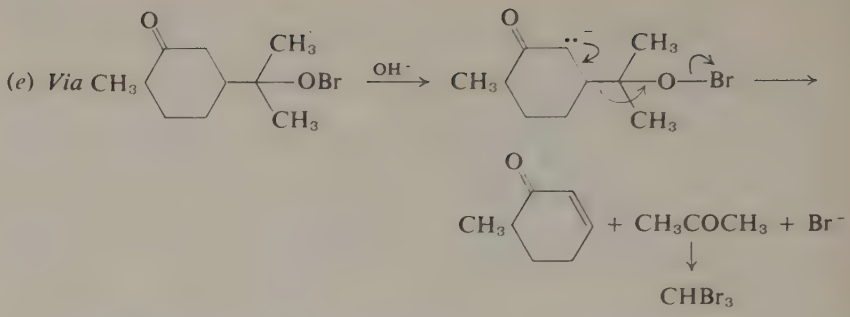
Chapter 36

1. (*a*) *Via* 

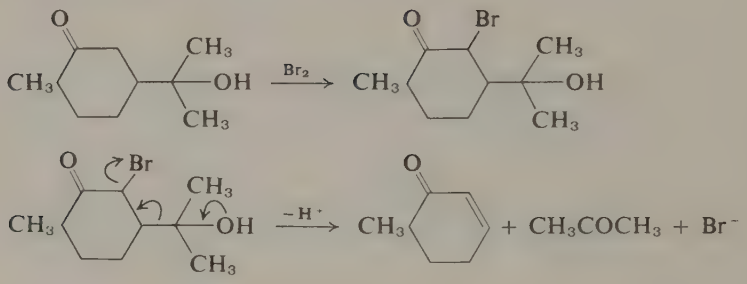
(*b*) *Via* 

(*d*) *Via* 

(e) *Via*



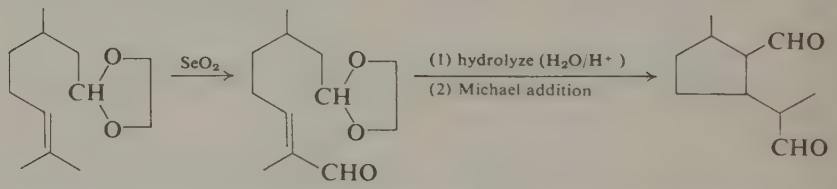
or alternatively,



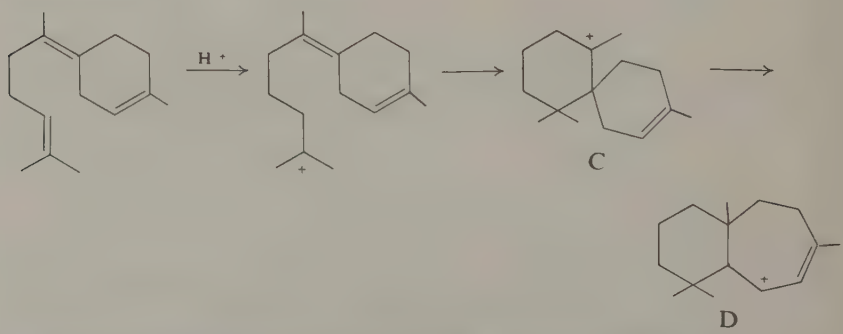
Chapter 38

1. First alkylate acetoacetic ester with the halide to give α-prenylacetoacetic ester; then saponify and decarboxylate.

3.



5. By way of C and D, the final step being loss of a proton and hydration of the double bond:



6. Lycopene would give acetone on ozonolysis; β-carotene would not.

Chapter 39

1. Using $^{14}CH_3$-methionine, the methyl groups on the C-C-C units would be labeled if the acetate-malonate pathway with subsequent *C*-methylation of the polyketide intermediate were followed. However, if the macrolide carbon skeleton were formed from propionate (C-C-C) units that were in turn derived from acetate by *C*-methylation, this result would be ambiguous. In the actual experiment, propionic acid labeled 1-^{14}C-3-$^{3}H_3$C- was used; all of the tritium label was found in the *C*-methyl groups and the ^{14}C in the carbon atoms of the macrolide ring.

3. The CH_3O— methyl group would be labeled from methionine. The ring and the acetyl group would be labeled according to the "regular" linear condensation of acetate units.

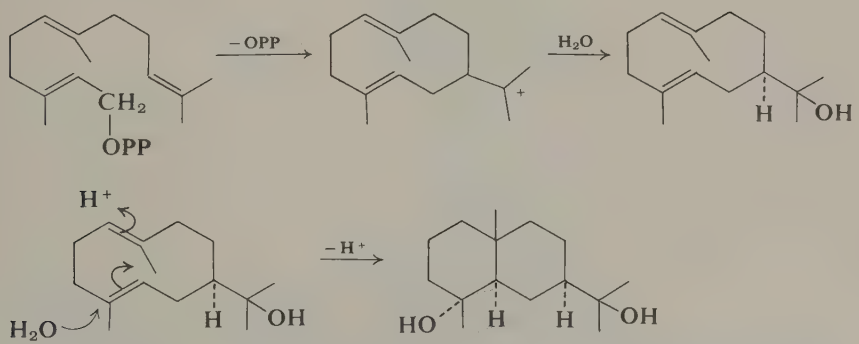
4. From nicotinic acid CoA ester + 2 malonate.

5. (*a*) Oxidize with $KMnO_4$, determine radioactivity of the benzoic acid and CO_2. If the benzoic acid is radioactive, perform Schmidt or Curtius reaction and determine whether the aniline or CO_2 formed is radioactive. (*b*) If radioactivity is not in the ring, but is in the benzoic acid, the label is at C-3. Remaining problem: if the radioactivity is not in the benzoic acid, what kind of degradation experiments could you perform to determine whether it is at C-2 or C-1?

$$C_6H_5\overset{3}{C}H{=}\overset{2}{C}H{-}\overset{1}{C}OOH$$

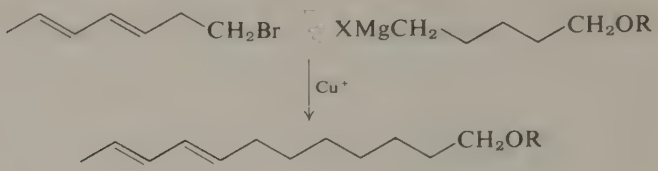
Chapter 40

2. The following sequence can be postulated (from farnesol):

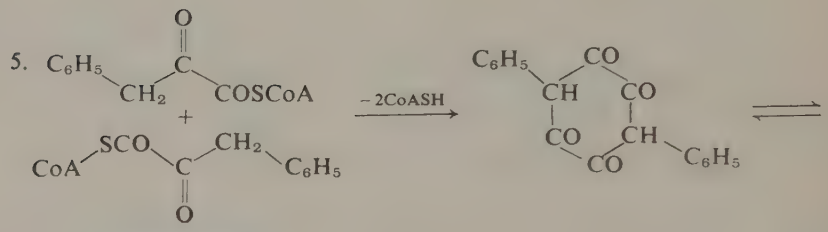


3. A unique feature of this synthesis is a coupling reaction between a Grignard reagent and a primary alkyl halide in the presence of cuprous copper, Cu^+.

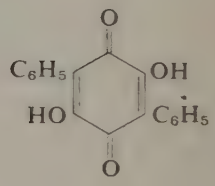
The final step is the following (R = tetrahydropyranyl, which is ultimately hydrolyzed to give the alcohol):



5.



2 pyruvyl-SCoA
(from prephenic acid)



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