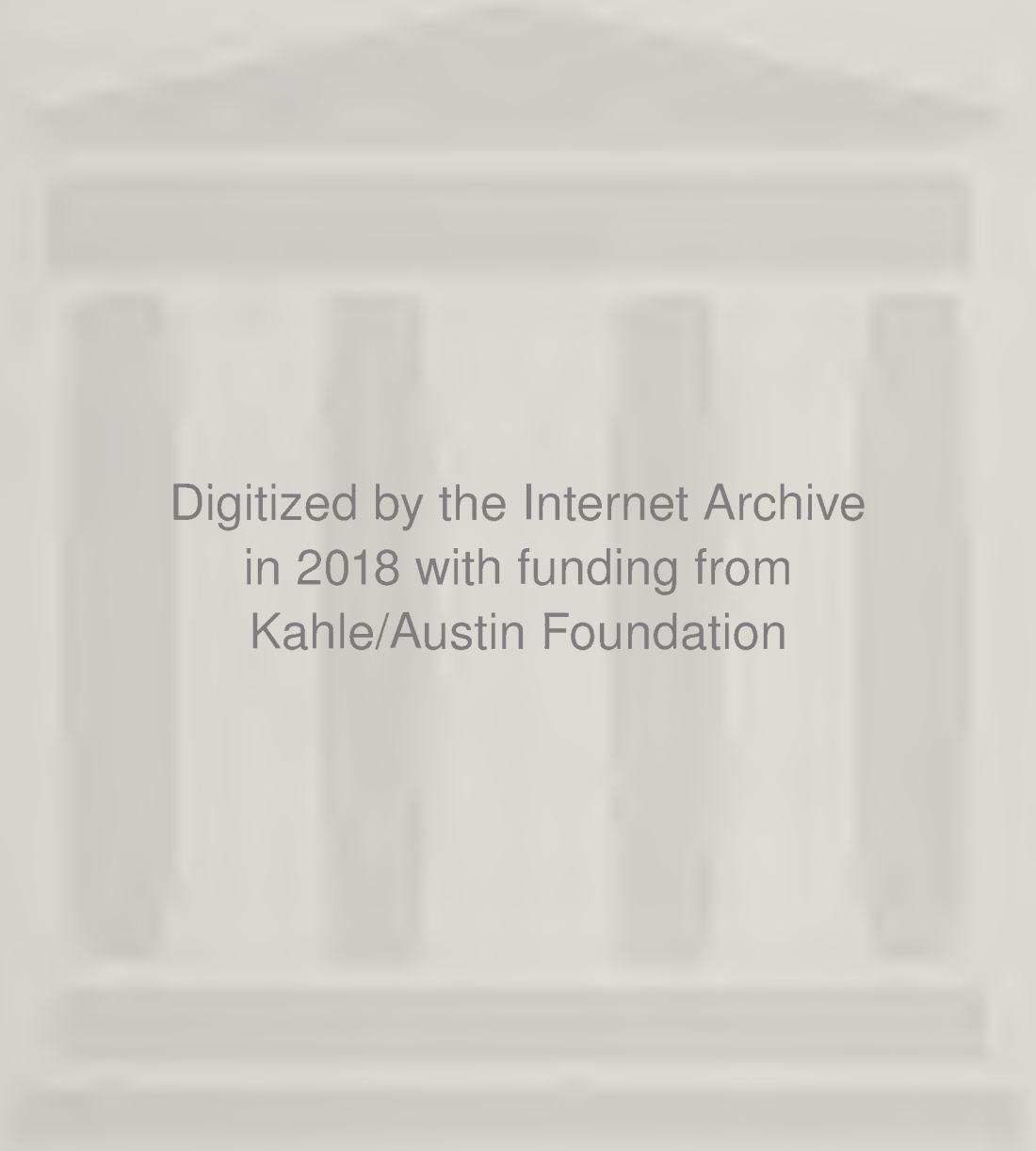
EXPERIMENTAL ORGANIC CHEMISTRY

Clark F. Most, JR.



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PREFACE

This book acquaints students with all basic laboratory procedures, presented in four major parts: (I) Techniques, (II) Experiments, (III) Organic Qualitative Analysis, and Appendixes.

TECHNIQUES

The 20-chapter Techniques section acquaints the student with all common organic techniques, and has a relatively simple illustrative experiment with each. Students will occasionally find underlined plays on words which refer to some part of the subject matter at hand. This is not only a matter of interest and perhaps humor, but one of pedagogy as well. It helps train the research-oriented student to look for relationships that are not always immediately apparent.

EXPERIMENTS

The Experiments section introduces more complex experiments than those in the Techniques section. The experiments commonly involve synthetic procedures followed by workup and analysis requiring more than one technique. The experiments are arranged largely by compound class, but there are also sections on famous name reactions, redox, kinetics, acidity and neutralization, and polymers. There are 50 major experiments in addition to those in the Techniques and Organic Qualitative Analysis sections. Basically, each experiment is in the following format: introduction, theory and discussion, techniques, experimental part, writing the discussion, prelaboratory and postlaboratory exercises.

ORGANIC QUALITATIVE ANALYSIS

This part of the book encompasses most of the wet analytical techniques that are required for analysis of major functional groups. It can be used as a mini course on organic wet analysis for characterization and/or identification of a variety of tabulated unknowns, or it can be used as a tool to help identify products obtained in the Techniques and Experiments sections.

The section on qualitative organic analysis has been keyed to each experiment so that the instructor can easily assign wet analytical methods as an adjunct to the experiment.

APPENDIXES

There are three appendixes. Appendix A includes the less-referred-to techniques: sublimation, density determination, and molecular weight determinations. Appendix B is a pronunciation guide, and Appendix C presents a compilation of chemical hazards.

GENERAL APPROACH

Presentations of theory and technique have been presented *separately* so that students do not have to search through theoretical discussions in order to find details of techniques. Each experiment presents enough theory and technique so that students are able to *fully comprehend* reaction and procedure. Attempt has been made to write procedures with such care that the instructions are complete and easy to follow—easy enough so that a good share of prelaboratory lectures are obviated, thereby saving precious laboratory time and curtailing the many procedural questions students often have. A set of prelaboratory exercises accompanying each experiment help the students to carefully consider what they are going to do in the laboratory before beginning work. The writer has been using prelaboratory exercises for about 10 years and has found this approach extremely helpful in promoting understanding and recall. It also saves laboratory time by requiring the students' prior organization of thought process.

Whenever topics are presented which are generally found in detail in lecture textbooks, students are referred to these sources. However, the theory and discussion sections in this book emphasize electron transfer pathways and present fuller discussions of each experiment or technique than are found in many lecture textbooks and in most other laboratory textbooks. The writer believes that it is better to make possible a full understanding of seventy experiments than a half-understanding of one hundred.

Because for most students one of the most difficult areas of laboratory work involves writing a good discussion of results, each experiment includes suggestions for the same.

Students are led into more independent development of procedures by Experiment 37 (which requires that the students write their own procedures by analogy), Part XIX (which discusses synthetic sequences), and the techniques on searching the chemical literature and report writing.

NOMENCLATURE

The common practice of organic laboratory books of indiscriminately mixing common and systematic nomenclature is confusing for students and is not a sound educational technique. *This book uses that nomenclature that seems to be most commonly employed,* but with parenthetical references to the other method. Whenever possible, the IUPAC system has been given preference.

PRONUNCIATION GUIDE

Pronunciation is one of the most neglected areas of chemical study. Many students hesitate in or feel foolish about using words that they do not know how to pronounce. Because proper pronunciation is an important part of chemical communication, Appendix B contains an alphabetized pronunciation guide to many of the chemical and chemically related words used in this book.

SPECTROSCOPY

The IR and NMR techniques do not repeat much of the theoretical detail generally found in lecture textbooks, but enlarge on aspects of a topic which are necessary for student understanding of laboratory processes. Procedural details have been made as complete as practicable.

COMPUTERS

Computer usage is increasingly important in the chemical industry, in medicine, in colleges, and in other areas. To start acquainting students with the chemistry-computer interface, several experiments have been included which utilize computer analysis of experimental results.

MASS SPECTROMETRY

Mass spectrometry is not normally included in organic laboratory books because the equipment is too expensive. However, this book presents an introduction to mass spectrometric analysis via microcomputer simulations.

The mass spectrometry simulation permits for the first time the teaching of mass spectrometry to all students in the undergraduate laboratory. The mass spectrometry program contains 17 different unknown alcohols, aldehydes, and ketones arranged as 36 unknown samples. Some of these unknowns are programmed as GLC samples and require instrument control settings which differ from those used under standard conditions. The students must learn what control setting to use in order to obtain meaningful spectra. They can adjust the controls to maximize or minimize the size of the molecular ion (M) peaks or the ($M + 1$) peaks. The writer has tried to make the results of the simulation as realistic as possible: The sizes of the peaks actually change relative to the control panel settings, and at high ionizing currents, one observes small peaks due to pump oil. Very complete information about unknowns is provided in the Instructor's Manual, including mechanisms of fragmentations.

LABORATORY NOTE-KEEPING

The Laboratory Notebook Technique is the most comprehensive to be found in any organic laboratory book. If the instructor chooses to follow through with the most rigorous procedures discussed, students learn record-keeping techniques that will be acceptable to both university and chemical industry, and will stand up in controversial patent disputes. Also in this section is a review of the various calculations an organic laboratory student must make.

LABORATORY SAFETY

This book treats every experiment as an adjunct in safety, makes available in Appendix C the chemical hazards of the chemicals used in this book, and calls attention to every likely operational hazard. Particularly hazardous chemicals, like benzene, have been avoided. Safety considerations are so much more complete than those found in other organic laboratory books that this text might indeed set a new standard for the same.

CONSERVATION OF CHEMICALS

The cost of organics is an increasingly important consideration. In most cases, the laboratory instructions in this book call for one-quarter to one-half of the amounts of chemicals characteristically required by similar macroscale laboratory textbooks. This book has a built-in program and specific instructions to students for conserving materials. Solvents are recycled, and the products of many processes can be used in later experiments. The technique on process economics emphasizes the necessity of conservation and cost effectiveness.

PROCESS ECONOMICS

A cost analysis of chemical process is the subject of Technique 20. This analysis provides the student with a basis for understanding economics of the chemical industry and is accompanied by a computer program which drastically reduces the time required for analysis.

USABLE PRODUCTS

To further add interest to laboratory work, a number of experiments have been devised that lead to usable products. None of these experiments was chosen solely for its product value. Each relates to a theory and/or technique in the study of organic chemistry laboratory.

CONTENTS

Orientation and Organization
Laboratory Safety
Basic Laboratory Equipment and Techniques

INTRODUCTION

ORIENTATION AND ORGANIZATION

Organic chemistry laboratory, with its unique body of information, should prove to be one of the most enjoyable experiences during your undergraduate tenure. I hope that you will find it interesting, useful, and intriguing. I am sure that you will find it technically challenging and requiring careful thought, self-discipline, and work.

Organic laboratory and lecture complement each other. Your lecture course supplies fundamental theory about molecular and electronic structure, chemical reactions, and their mechanisms. In the laboratory you will put this knowledge into practice and learn supplementary theoretical concepts and mechanisms when necessary to help you more fully understand the chemical process in progress.

In the lecture course there is considerable emphasis on chemical reactions. In the equations accompanying such reactions we are shown a single molecule colliding with one other. But in the reality of the laboratory we should recognize that millions of such molecules are simultaneously colliding, not only with each other as shown in the textbook equation, but also with other species present in the mixture and with reactive parts of substrate molecules other than those parts that permit formation of the primary product. These multitudes of collisions often lead to numerous products besides the one expected. Such materials are referred to as **byproducts.** Because byproducts are so common in organic reactions, a great deal of time must often be devoted to separating product from byproducts, and thus separations techniques are very important to the practicing organic chemist.

The goal of this book is to help you understand organic laboratory processes and develop the basic techniques associated with them. Using this book, you have the opportunity to learn about all of the fundamental separation and identification techniques, instrumentation, economics, literature searches, record keeping, report writing, and laboratory safety.

ORGANIZATION OF THIS BOOK

This book has four major parts: Techniques, Experiments, Organic Qualitative Analysis, and Appendixes.

Part I includes the major techniques, and is the heart of a laboratory course. It acquaints you with the fundamental laboratory techniques of organic chemistry. It also provides discussions of the underlying theory associated with the techniques. Theory and technical process descriptions are separate, as much as possible, so that you can concentrate on each aspect and assimilate information as you study, and so that you can find information quickly and easily. If you want to become acquainted with the description of some physical operation, you will not have to search through a mixture of theory and technique to find it. Immediately following the description and discussion of each technique or topic are one or two illustrative experiments.

Part II, following the Techniques section, contains an additional group of experiments which your instructor might assign in place of, or in addition to, those immediately following each technique. The experiments give you opportunities to apply the techniques and to enhance your understanding of chemical processes. To aid your understanding

and enlarge your ability to predict the outcome of chemical reactions, there is an emphasis on reaction mechanisms. In general, the experiments in this section tend to be more complex than those in the techniques section, employing a greater number of techniques simultaneously or in succession.

Part III contains fundamentals of organic qualitative analysis, replete with its array of classic organic reactions and the joys of puzzle solving.

The Appendixes contain important information to which you must refer from time to time. The compilation of chemical safety data is of paramount importance.

Two special features of the text are its concentration on laboratory safety and conservation. One section of this introductory chapter is on laboratory safety, and every technique and experiment has an outline of procedural hazards. Appendix C lists chemical hazards for every chemical used in this book. Each experiment has instructions for conserving raw laboratory materials, especially organics. You will see that you can recycle solvents and use the products of many experiments in later experiments.

Using the Book Effectively

This book has many features that can help you learn more effectively. One is the set of prelaboratory exercises which accompanies each technique or experiment. These exercises as assigned by your instructor will help you enter the laboratory with confidence. They will promote understanding and recall. And they will help conserve your laboratory time because you will know better what to do, why you do it, and when.

A second aid is the specific section number reference that you will find at the beginning of each experiment. Each reference is to a technique with which you must be familiar to do your lab work efficiently, safely, and confidently.

Appendix B, a pronunciation guide, is another aid. The guide lists chemically related words that might be new to you or that you might only dimly recall. When you know how to pronounce a word and feel confident using it, you communicate more precisely than you can if you say, "that stuff" or "that thing."

This book uses a mix of common and IUPAC nomenclature, the name used depending on what appears to be the more usual name. As an aid to learning and searching the literature it also provides parenthetical references to the other nomenclature method. A word enclosed in parentheses is a common name unless it is preceded by the designation IUPAC.

The triangles (△) in the experimental sections can help you to plan your time. A single triangle (△) suggests a pretty good place to suspend lab work if really necessary; a double triangle (△△) suggests a very good stopping point. As you gain experience, you will need to rely on triangles less and will be able to define your own stopping places.

Computers today are widely used in business and industry, and the chemical industry is no exception. You cannot work as a chemist very long and not find some way in which a computer can assist you. Because of the almost universal need for computers in the modern scientific world, this book correlates data analysis in seven experiments with use of a microcomputer. In addition, the techniques of mass spectrometry are introduced by computer simulation.

LABORATORY EFFICIENCY

Organic laboratory usually requires a lot of work in a short period, which should suggest that you will need to work efficiently. To conserve time and work safely, you must be prepared for the laboratory period. You must be ready to go to work as soon as you arrive. You must understand what you are going to do and why you are doing it. Reading instructions without comprehension as from a cookbook trains one to be an unthinking technician, not a chemist, and furthermore "cookbooking" can be hazardous.

You cannot expect to be efficient if your brain is trying to figure out the procedure while your hands are working with a piece of equipment and your eyes are constantly darting back and forth from the "cookbook" to the equipment. There will also be times

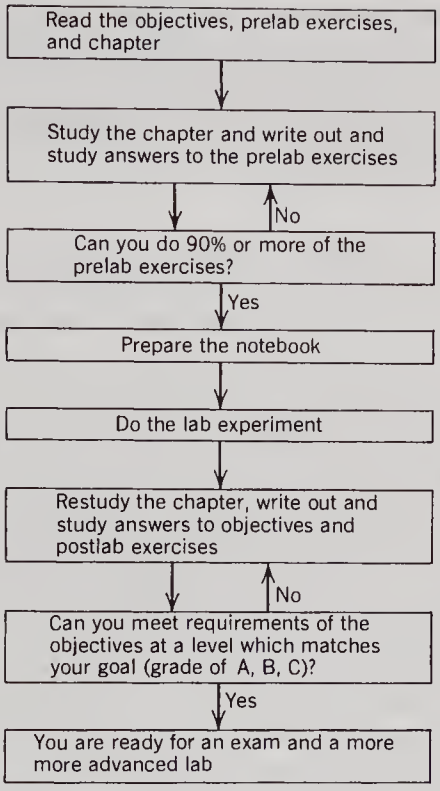

FIGURE 0.1 Flow diagram for Learning and Laboratory Preparation.

when you will need to have more than one thing going at once—finishing one experiment while beginning another or monitoring a process while washing glassware. It will be essential to plan and to use your time carefully. In addition your lab text, your own advance preparation and reference to flow diagrams and outlines will help you be efficient.

This book should help you become more efficient and orderly in the chemistry laboratory. Figure 0.1 is a methodological approach to learning laboratory procedure. For best results, follow this flow diagram.

Students who do not have a definite, organized plan for their laboratory work will not be able to finish on time and will find themselves spending extra hours beyond their designated laboratory period. The following suggestions will help you conserve your valuable laboratory time:

Organization of Thought Process

The following several things should be done *before* you enter the laboratory:

1. Read the experiment and necessary techniques. Picture mentally the sequence of various operational procedures.
2. Make a flow diagram to which you can refer as you work.
3. Complete the preliminary work in your laboratory notebook.
4. Make required stoichiometric, concentration, and other calculations.
5. Make a rough schedule of operations so that you are at no time simply sitting "waiting for the pot to boil." You can prepare for the next activity, finish up an old experiment, wash dishes, and so on, during periods of waiting for reactions to go to completion or for phases to separate in a separation funnel.

Organization of Work Area

1. Keep your drawer and/or cabinets in order. Have a set location for each piece of equipment, and keep your equipment clean and in place so you can always find it readily.
2. When you are ready to work, lay out in an orderly fashion the equipment for the

activity you are about to commence. Place your laboratory notebook and small objects on clean sheets of paper to keep them uncontaminated.

3. When you have finished your work, wash all of your dishes and put them away; clean your work area with a wet paper towel, dish cloth, or sponge; and lock your drawers and/or cabinets.

Courteous Performance

The way students conduct themselves relative to one another is not only a matter of sensitivity for others' needs and welfare but is also a matter of efficiency. Taking the following simple, thoughtful steps will help to keep the lab running smoothly:

1. When using laboratory reagents, use them in the location assigned for their use. Do not carry them away to your own work area. Keep the reagents clean by pouring from their containers rather than dipping into them. When you are done with a reagent bottle, cap it, wipe it clean, and return it to its assigned place.
2. Clean up after yourself. If you spill a chemical, whether it be a community work area or your own work area, clean it up immediately. Because only you know for certain what chemical was used and its toxicity, it is incumbent on you to see that the work area is uncontaminated for the next person to use.
3. Quiet conversation and humor has its place in the laboratory. But please keep the noise level of your work area down. Loud talk, laughter, and the sound of your radio might not only be annoying to others but be a hazard as well. It is important to be able to hear the essential sounds that go on in a laboratory and to be undistracted during serious work.
4. Let your neighbors know what work you plan to do if your experiment varies from that of those around you. It would be hazardous to light a burner, for example, when others are working with flammable solvents.
5. Return all community property to its assigned location when you terminate your work for the day.

LABORATORY SAFETY

Laboratory safety is the most important single topic for a novice chemist. Although chemistry is an innately hazardous occupation, the safety record of the chemical industry is envious. In 1963 the industry had 3.32 disabling injuries per million hours of work, whereas the average for all industries was 6.12. The chemical industry has a consistently low accident rate because chemists are aware of the hazardous nature of chemistry and promote safety consciousness.

Accident prevention is more complex than writing or reading a manual of safety rules. The weakest link in the safety process is the individual who becomes complacent. You have probably heard, "Familiarity breeds contempt," but familiarity with laboratory procedures is essential. It is necessary, as you become familiar with the various procedures, that you accord them the respect they deserve.

Unsafe physical conditions or unsafe personal acts cause all accidents. Unsafe conditions account for about 15% of accidents. This means that 85% result from personal failures to be adequately informed and to observe safety rules. The way to minimize accidents is to know safety precautions before you do laboratory work.

Remember: Accidents are not intentional. They happen when you do not expect them; and if you have a serious accident, you might never fully recover.

LABORATORY ATTIRE

Wear simple clothing. Shirts and blouses with loose-fitting sleeves might get caught on a piece of apparatus or machinery. Because it is too difficult to remove spills from cloth top shoes, wear hard top shoes that will also help to protect you from dropped objects. You will probably be prohibited from wearing sandals in your laboratory. A laboratory coat or apron helps protect you and your clothing. It is wise to wear a pair of rubber kitchen gloves, especially when you are working with the more dangerous, toxic or corrosive chemicals. If you have long hair, wear a net or tie your hair back behind your head and shoulders so there is no danger of its falling into a flame or reaction vessel and so that you have clear peripheral vision.

Always wear eye protection *whenever* you are in the laboratory. Even when you are not working there is hazard, for someone else in the lab might have an accident. As minimum defense, wear shatterproof glasses, preferably with side shields. Shatterproof safety goggles are even better and are required by law in some states. Although goggles can be uncomfortable, and although they may steam up, goggles give better splash protection than glasses. When goggles become too irritating, we can step outside the laboratory for a few minutes. Rubbing the inside of the lens with a fresh slice of raw potato will help reduce fogging, as will certain commercial preparations. Visitors in the laboratory should, of course, also wear eye protection.

One more precaution: If you have any choice, leave contact lenses at home. Contacts pose an extra hazard in the laboratory; if a chemical gets in your eyes, it may become trapped behind the contact lens, or the chemical might stick the lens to your eye.

PERSONAL HABITS AND HOUSEKEEPING

- You must not eat, drink, or smoke in the laboratory; you should never eat ice from the laboratory ice chest.
- You must never taste or smell a chemical unless your instructor tells you to. If you want to determine the odor, you should inhale only a small amount of vapor, and then only into your nose, not your lungs. The correct way to smell a substance is to moisten a stopper and gradually bring it toward your nose with your hand.
- You should never hold a container at or above face level while observing and/or stirring its contents.
- You should wash your hands carefully before using restroom facilities and when leaving the laboratory.
- You should avoid working with haste and impatience. Adequate prelaboratory preparation is essential.
- You should never work alone. Someone familiar with emergency procedures for the assigned laboratory should be in the room with you.
- You should avoid horseplay. A few seconds of foolish trifling can easily result in personal injury.
- You should always follow safety precautions in setting up and doing a job.

Good housekeeping and having equipment and chemicals in good condition and in their proper places is vital to any safety program. A messy laboratory breeds accidents. Avoid laying flask or bottle caps and stoppers on the bench top and contaminating both. Replace the cap or stopper on the correct container after using it; then wipe the container free of chemical that might have run down its side. Clean the bench top and floor promptly after spills and when you are finished with your work. Only you know what chemical was spilled, and only you are sure of its toxicity; hence it is your responsibility to clean it up.

Maintain adequate aisles for daily work and emergency exit by keeping stools as close to the bench as possible and drawers and cabinet doors shut.

FIRES, EXPLOSIONS, AND IMPLOSIONS

Fires

Fire is an ever-present hazard because many organic solvents are volatile and flammable. In general you should keep flames well away from organic liquids. (Section 0.5 discusses methods of using flames and other heating equipment.) Also you must keep equipment with electrical switches (variacs, vacuum pumps, etc.) as far as possible from your work area because using any ordinary electrical switch causes a spark. If you work in a hood, keep the switches outside, and avoid plugging or unplugging electrical devices near flammable liquids because plugging and unplugging create sparks.

Never pour organic liquids down a drain or into a trough that empties into a sink. Because vapors can escape from a sink or trough, and because they may hover along a bench top, vapors are a potential fire hazard even after you have disposed of the chemicals.

Your instructor will advise you whether flame permit areas are designated in the lab or whether flames are allowed on certain days. You would of course avoid make-up work using flammable solvents on a day when flames are in general use as they might be for experiments in which water is the solvent or high boiling liquids are distilled. You can readily understand now why smoking is always prohibited in the laboratory.

Flash point is a useful indicator that tells how flammable a liquid might be. The **flash point** is the lowest temperature at which a liquid emits sufficient vapors to ignite in the presence of air when an open flame is passed near the surface of the liquid. The lower the flash point, the more dangerous the liquid. Appendix C lists the flash points for liquids used in this book.

Extinguishing Fires

If the vapors from a vessel ignite, do not panic! You can usually put them out by gently placing a watchglass, glass plate, beaker, or clipboard over the opening of the container to smother the flame. Extinguish any flame nearby and correct the cause of the fire before proceeding.

If a bench top fire occurs, extinguish it with a fire extinguisher with which you are familiar. Use the correct type of extinguisher for your particular fire and use it properly. Although your instructor will probably demonstrate use of fire extinguishers in your laboratory, a few words about the type of extinguisher to use are in order: (1) The lower the flash point of a substance, the less effective water will be; (2) aqueous system extinguishers should not be used on fires originating from electrical discharges (hydrogen and oxygen gases may be formed); (3) the blast from carbon dioxide extinguishers tends to blow burning papers about.

If your clothing or hair catch on fire, try not to run because running will make the fire burn faster. Try not to breathe the hot combustion vapors. Call for a fire blanket and in the meantime roll on the floor. If the safety shower is near, use it. In all cases, notify the instructor and others around you at the first sign of fire to allow them to get out of the way or to assist you. You will want to *know the exact locations* of the safety shower, fire blanket, and extinguishers. You should also be familiar with evacuation plans in case of a serious fire or accident.

Explosions

An **explosion** is the violent expansion of the volume of a substance. Explosions in the laboratory usually result (1) when a large amount of vapor from a volatile, flammable solvent ignites suddenly with the correct amount of air; (2) when a compound capable of auto-oxidation-reduction reactions (like trinitrotoluene, trinitrophenol, trinitratopropane) is shocked or heated; (3) when compounds (like peroxides and diazonium salts) that readily decompose into more stable compounds are heated; (4) when an exothermic reaction progresses so rapidly that the extreme overheating causes vaporization and explosion.

You should take special care to avoid using volatile, flammable solvents near a flame or where a spark can be generated by any electrical device (like an electric stirring motor or an electric switch). Distilling to dryness is also a dangerous practice because of the possible presence of peroxides or other explosive materials in the dry residue in the flask. If you think a process is potentially explosive, work behind a safety shield and use only small quantities of the reactants. Appendix C lists explosion hazards for chemicals used in this book.

Implosions

An **implosion** is a violent inward collapse caused by the sudden movement of fragmented glassware toward the center of an evacuated system. An implosion is dangerous because when all the fragments reach the center, they can violently rebound from each other and fly outward again. The hot liquids and corrosive chemicals that might be in the collapsed vessel rebound with the flying fragments. Implosions can occur when a structurally unsound or improperly shaped piece of glassware is subjected to vacuum. Carefully choose glassware to be used in an evacuated system for appropriateness of design. Some glassware is intended for use in evacuated systems, and some is not. For example, the thin walls of Erlenmeyer flasks are not intended to withstand evacuation, but the thick walls of suction flasks or the spherical walls of round-bottom flasks are. Carefully inspect glassware to be used in an evacuated system for flaws. Always set up evacuated systems behind a safety shield.

CHEMICALS AND EQUIPMENT

The most important thing to remember about chemicals, laboratory equipment, and machinery is that they cannot think. Thinking is *your* responsibility. Knowing about safety and thinking enough to avoid accidents is a better defense than first aid.

Chemical Toxicity

Chemical toxicities vary; you need to know which chemicals are dangerous and to what extent. Before beginning any experiment, you should be acquainted with the hazards of the chemicals you will be working with. Appendix C lists the known toxicities for chemicals used in this book.

Knowing toxicities can help you avoid oral and percutaneous poisoning. Practicing the cardinal rule of the laboratory—no eating or drinking—makes it unlikely that you will be poisoned orally. Pipetting is the only other way in which you might get something in your mouth. But as a careful chemist you *never pipet by mouth;* you use a rubber bulb for suction. Knowing about chemical toxicity can help you avoid poisoning by percutaneous (through intact skin) absorption or through skin abrasions. Some chemicals, like phenol (benzenol), benzene, aniline (benzenamine), and nitrobenzene can be rapidly absorbed percutaneously, even as vapor. You will want to use Appendix C faithfully.

Naturally, you will try to avoid contact with laboratory chemicals. You will want to keep them in designated containers with lids securely fastened and in their appointed places. To minimize spills during transport, carry the chemicals in a pail to and from the stockroom or when moving them across the laboratory.

Dispose of chemicals in an authorized manner only. Throughout this book, you will have instructions for disposal of organic chemicals and information about recovery containers. In most cases, water-soluble wastes can be discarded into a sink along with cold running water. Special containers are usually designated for solid inorganic wastes and broken glass. You will want to inquire about disposal in your laboratory.

Equipment and Machinery

It is a good practice to use equipment to do the job for which it was designed. If improvising becomes necessary, you should have your instructor check your setup. Inspect your equipment frequently and repair or replace defective items. Moving parts on machinery, such as belts on a vacuum pump, should be covered with guards. Report all abnormal conditions to your instructor. You can minimize operational hazards as well as chemical hazards if you envision them in advance and if you develop and adhere to safe operating procedures. This book lists operational hazards associated with techniques and experiments.

FIRST AID

A milligram of prevention is worth a kilogram of cure. However, when accidents do happen, rapid treatment—first aid—can make the difference between minor and serious injury. Remember, however, that first aid is only *first* aid. All injuries sustained in a chemical laboratory might require expert medical attention in addition to first aid. Some chemistry departments have a policy that all injuries be treated by the college health service or hospital emergency room. Your instructor will advise you as to what your chemistry department's rules are.

Chemicals in Eyes

If a chemical gets in your eyes, you must get to the eyewash station as quickly as you can. If you do not have a standard eyewash station in your laboratory, use a short length of flexible hose attached to a sink or spigot. Turn the hose upward toward your eyes, and turn on only enough water to get it readily into your eyes. Excess pressure is not only uncomfortable but can damage eye tissue.

Victims may need help in getting to the eyewash station and in *holding their eyes open.* A crucial point about eye washing is that the irrigation should begin at the earliest possible moment after the accident because the first seconds are the most important. In some cases, no amount of washing can save your eyes if you delay even a little.

Irrigate the eyes a minimum of 15 min for acids and most other chemicals, and at least 30 min for bases. Someone should keep track of the time since you are likely to underestimate it. Do not use neutralizers in the eyes.

Remember, leave contact lenses at home. However, if you do get chemicals in your eyes while wearing contacts, remove them as quickly as possible and irrigate your eyes. Soft lenses are especially dangerous because they can absorb and retain many organic chemicals. Do not put soft lenses back in your eyes unless you *know* they are no longer contaminated.

Spills on Clothing and Body

Treat spills on clothing and skin with copious water washing. You should be familiar with the location of the safety shower and the best route to it from your bench area. Turn the shower on full for 15 min for most chemicals, but 30 min for bases. Remove all contaminated clothing. When showering is required, your instructor will promptly clear the room of all laboratory personnel. But if you cannot have privacy, be safe rather than bashful. Serious chemical burns can result from contact with some acids and bases.

In some laboratories acid and base neutralization solutions are kept on hand. A solution for neutralizing bases consists of 1 or 2% aqueous weak acid like acetic, boric, or citric acids. A similar preparation for treating acids usually consists of 2 or 3% aqueous sodium bicarbonate. If you use a neutralization solution, administer it after an initial few minutes of showering, and then continue the shower.

Suitable treatment for accidents with other noxious chemicals, especially in cases involving percutaneous (through the skin) absorption, depends on the chemical. Your stockroom probably has a first aid book or chart on poisons. Internal poisoning requires treatment by a physician.

Cuts and Thermal Burns

Stop bleeding by compression and/or use of pressure points. All cuts should be examined by college health service personnel to determine if glass is imbedded in the tissue.

First-degree thermal burns (red skin) are best treated by application of cold water, preferably with ice. Do not apply salves. Large-area first-degree burns and any second- or third-degree burns (blisters and charring or cooking) require the service of a physician.

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BASIC LABORATORY EQUIPMENT AND TECHNIQUES

In organic chemistry laboratory you will routinely use many basic items of laboratory equipment and become familiar with a number of simple techniques. This section will acquaint you with such preparatory information. Some of the equipment will be community property; other equipment will be assigned to you and you will be directly responsible for it.

0.1 COMMUNITY PROPERTY

Community property is equipment and supplies available to everyone in the laboratory. In this category are likely to be vacuum pumps, water aspirators, voltage controllers or rheostats (Variacs), heating mantles, hot plates, steam baths, ringstands, clamps, stock reagents, and so forth. It is very important that you return each of these items, properly cleaned, to its assigned place after each use so that it will be readily available to others. Your instructor will show you the locations of community items.

0.2 GLASSWARE AND OTHER PERSONAL ITEMS

You will regularly use various pieces of glassware and must know how to care for them. Figure 0.2 illustrates some equipment with which you might be familiar.

Erlenmeyer flasks are used for titrations, for crystallizations, for preparations in which the contents must be swirled, and in reactions that will be set aside for a while. The shape and narrow neck make containment easy, facilitate removal of solids, reduce evaporation, and decrease the amount of dirt likely to fall in.

Round-bottom flasks are used for mixtures that must be heated for a period of time. They are designed to fit the rounded cavity of heating mantles or to set in a steam bath ring. Round-bottom flasks, also called boiling flasks, commonly have one, two, or three necks and come in a variety of sizes. To make them stand upright on a bench top, you can set them on cork rings or beakers.

Beakers are used for general mixing and for heating mixtures when a large surface area is desirable. They are easy to pour from and easy to clean.

Funnels are of several types. The glass conical funnel is used to avoid spills when adding liquids to containers and for gravity filtering of solids from liquids (Technique 4). The stemless funnel is used when solids might crystallize in the stem during filtration (Technique 5). The powder funnel is used for adding solids to containers. The porcelain Hirsch and Büchner funnels are used for vacuum filtration separations of solids from liquids (Technique 5). A separatory funnel is used to separate mixtures of immiscible liquids (Technique 6) or used as a dropping funnel to slowly add a liquid into a reaction vessel.

The condenser is used to condense vapors to the liquid state. It is used upright

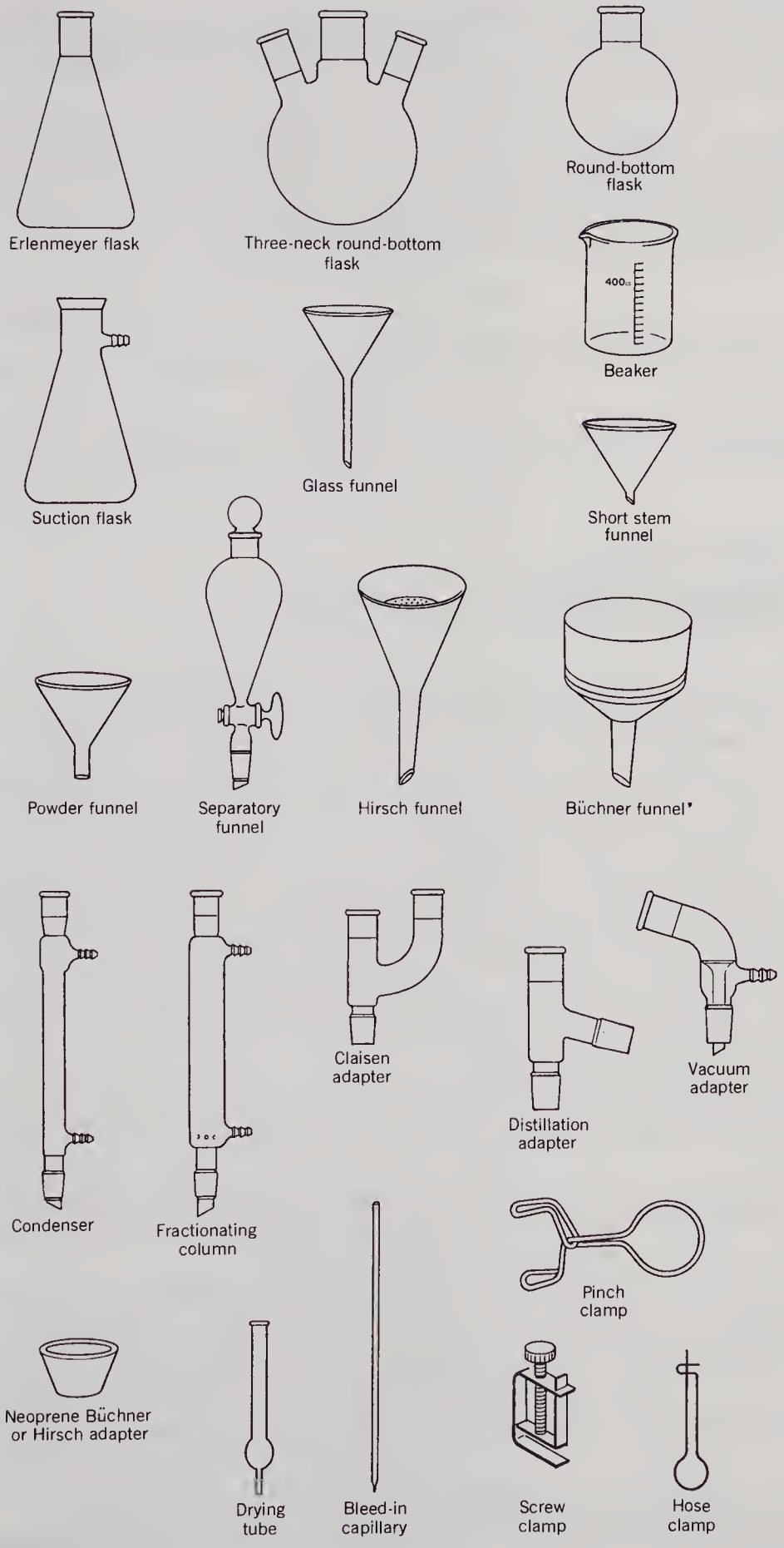


FIGURE 0.2 Laboratory equipment.

during reflux (as in Section 0.5) or slanted horizontally during distillation (Technique 7).

A fractionating column is similar in general shape to the condenser, but usually has glass prongs at the bottom to support packing (described in Technique 7 on fractional distillation).

The various adapters are used to adapt the glassware to specific purposes like distillation or evacuation. The neoprene adapter makes a tight joint between a suction flask and a Hirsch or Büchner funnel (a bored rubber stopper is a substitute). The Claisen adapter is used for steam distillations (Technique 7), as a convenience for adding reagents, or other specialized purposes.

The suction flask, or filter flask, collects the filtrate during vacuum filtrations. Such flasks can also be conveniently used as liquid traps (Section 0.14 or Technique 4).

The drying tube is for drying gases or keeping moisture out of reaction mixtures (Technique 2).

The bleed-in capillary, or ebulliator, is used to introduce a fine stream of air bubbles during vacuum distillation.

The pinch clamp is used when you want to let liquid or gas intermittently through a hose, or to maintain a hose either all the way open or closed. The screw clamp can be used for heavier hose, and can be adjusted to keep a hose closed, partly open, or completely open. The hose clamps secure hoses to nipples.

0.3 ASSEMBLY AND CARE OF GLASSWARE

Most laboratories use standard taper glassware with ground glass joints which make the glassware quick to assemble and disassemble, make tight joints, and are easy to clean. However, standard taper glassware is expensive, its joints tend to stick together, and its assemblages are very rigid and must not be stressed.

Before you set up an apparatus, make certain that all ground glass surfaces are clean. Chemical "dirt" will prevent the joints from fitting properly; they will be leaky. Besides that, during subsequent heating the chemicals might melt and stick ("freeze") the joints together. Clean ground glass joints fit so well that they are sometimes difficult to get apart. However, gentle twisting will usually suffice, especially if the equipment is disassembled when it is still hot. Some chemists prefer to use a very *thin* coat of stopcock grease on joints before assembling the apparatus to make them come apart easily.

Actually, there are just three situations in which you must use stopcock grease: (1) when strongly basic solutions are involved in the experiment; (2) when the joints are to be part of an evacuated system; and (3) when one joint is designed to rotate in the other.

In the first instance, strongly basic solutions like those of NaOH attack the hydroxyl groups on one glass joint, creating anions that can form bonds with the mate joint. When enough bonds form, the two parts cannot be separated, and the joint is said to be "frozen." Stopcock grease coats the joints so that bonds do not form.

When a system is to be evacuated with an oil vacuum pump, stopcock grease makes the joints tight enough so that very low pressures are attainable. Greasing is not necessary at water aspirator pressures.

Finally, since ground glass surfaces do not move easily against each other, greasing is always required for movable parts like stopcocks.

Whenever you apply grease, use only enough to make the assembled joints appear nonopaque. Put a couple of thin longitudinal smears of lubricant on the male joint, put the joints together, and then twist them to distribute the grease evenly. With too much stopcock grease, residues will get into the reaction mixtures.

Hydrocarbon greases and silicone greases are available. For ordinary uses hydrocarbon greases are as good as silicone and are easier to remove with solvents like hexane or carbon tetrachloride (tetrachloromethane).

If a joint freezes, you can try tapping it very *gently* with a wooden object. Or you can try heating *gently* and rotating the female joint over a steam bath, periodically twisting

and/or tapping. You should try to heat the female joint so it expands faster than the male. If you suspect that joints are frozen by presence of an organic chemical, try soaking them in hexane, acetone (propanone), alcohol (ethanol), or other solvents for the suspected chemical. If these tactics fail, ask for help.

As you assemble the ground glass components of an apparatus, be careful not to put stress on the various parts by forcing them into position. Securely support the apparatus by clamps in a way that reduces joint stress and prevents parts from falling off. You must not rely on friction to hold the parts together. The diagrams throughout this book will help you decide where to support various parts of an apparatus.

Tube and Stopper Assemblies

If your laboratory is not equipped with standard taper glassware or if you do not have all of the ground glass parts for a particular apparatus, you will use tube and stopper assemblies.

In such cases, wherever a ground glass joint appears on a standard taper diagram you will substitute bored rubber stoppers or corks to fasten the two pieces together.

Cleaning Glassware

Clean glassware as soon after use as possible because that is when it is easiest to clean. The longer it stands, the more opportunity there is for corrosive tars and other materials to attack the glass and consequently make it more difficult to clean. Caustic chemicals left in glass containers will etch the glass, making thorough cleaning more difficult in the future; severe etching will make the glass opaque.

As soon as you dissemble an apparatus, wipe all stopcock grease from the joints to prevent grease from getting into the flask or on a bottle brush (and from there all over everything!). After wiping the joints, rinse them with hexane, chloroform, or acetone. Not all glassware needs to be scrubbed. Glassware that contained water-soluble materials may have only to be rinsed and set aside to dry. Glassware that has held only volatile liquids needs only to be allowed to air dry. For dirtier glassware, you can use either organic solvents or soap and water. Organic solvents will often expedite cleaning up, but are more expensive than soap and water. To cut costs, the philosophy of your laboratory might be to try aqueous scrubbing first. Soap and water will very often be quite satisfactory, but a scouring powder like Ajax or Old Dutch is better. Bring a scouring powder to put in your drawer if your chemistry department does not supply it.

If your laboratory provides organic cleaning solvents, proceed as follows. Select a solvent that you think is capable of dissolving the residue. The most common solvent is technical or recovery grade acetone (propanone). Add a *small* amount of the solvent to the dirty container; then allow it to stand with occasional swirling. Next, pour the liquid into a recovery container for that solvent. Repeat the process if necessary. Scrubbing with a test tube brush might be necessary, and finally a soap and water scrubbing might be needed.

Wash grade acetone can usually be used several times before it must be redistilled. Conservation, cost, and time spent distilling suggest that the solvent be used to its fullest capacity before purifying or discarding.

Some reactions will leave glassware coated with residues that cannot be removed as described above. In such cases, *remove the bulk of the residue;* then add 5 or 10 ml of ethanol to the glassware, followed by two or three KOH pellets. Warm the mixture gently on a steam bath and allow it to stand about 15 min (or longer if necessary) with occasional stirring. Then proceed with cleaning as described above.

Hot alcoholic KOH is extremely caustic and can cause severe chemical burns. Use rubber gloves and a safety shield!

Another cleaning solution is chromic acid which should be used only as a last resort and upon advice of your laboratory instructor. It consists of 35 mL of saturated aqueous $K_2Cr_2O_7$ or $Na_2Cr_2O_7$ dissolved in 1 liter of concentrated sulfuric acid. First remove as much as possible of the residue in the soiled glassware.

If you prepare your own chromic acid cleaning solution, be sure to add the sulfuric acid to the dichromate solution, not vice versa. Proceed slowly with stirring. The reaction is very exothermic and could cause spattering or even cracking of glassware. Wear rubber gloves and work behind a shield when preparing the solution.

Using a small quantity of the solution, swirl it in the glassware for about 5 min; then discard it into a designated waste container or pour down the drain along with plenty of water. *Ask your instructor which to do.* If your glassware is not clean after this treatment, the residue will probably not be a problem in future laboratory work.

Chromate cleaning solutions can quickly produce chemical burns. They are powerful oxidizers and can cause explosions in contact with some tarry residues and easily oxidized compounds. They are carcinogens. Use rubber gloves and a safety shield!

The most convenient way to dry water-wet glassware is to turn it upside down to drain thoroughly and allow it to air dry. If you must use the piece soon after rinsing, you can hasten drying by using a final rinse with hot water, or by oven drying. Another way to dry water-wet glassware quickly is to rinse it with about 10 ml of clean, wash grade acetone. Put the acetone rinse in its assigned recovery container, and then pass a *gentle* stream of clean air into the glassware or set the glassware aside to dry. (Air from lab air lines often contains oil vapors which could contaminate glassware.) Here again, if the glassware is warm, it will dry more quickly.

Because acetone is flammable you must never work near a flame or heat the glassware with a flame to evaporate the acetone.

0.4 STIRRING

Chemical reactions proceed more rapidly and thoroughly when the component chemicals of the mixtures are continually mixed or stirred. We shall now discuss the simpler methods of stirring which you are likely to use.

The simplest and easiest stirring method is swirling. Hold the container (usually a flask) in your hand and rotate it in a somewhat conical fashion so that the bottom of the flask is moving in a wider circle than the top. You can get a more violent agitation by shaking the flask from side to side.

Swirling is not always satisfactory for viscous liquids, for solids, or for heavy suspensions. In such cases you can use a stirring rod.

For long-term stirring of nonviscous mixtures, an electrically operated magnetic stirring device is convenient (Figure 0.3). The stirring bar is usually a Teflon-coated bar magnet, but a paper clip makes a good stirrer if it does not react with the materials to be stirred. Put a stirring bar into the flask along with the mixture and set the flask on the stirring device; then adjust the speed of the bar. The proper technique is to increase the rotation speed gradually until you get the desired mixing speed. If the speed is too high, the bar will vibrate instead of rotating properly. In that case, or if the bar suddenly stops rotating and starts to vibrate or flop wildly around in the flask, turn the motor off and start it again slowly. A magnetic stirrer operates satisfactorily in conjunction with a heating mantle.

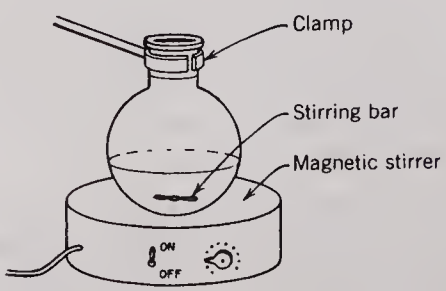


FIGURE 0.3 Magnetic stirring.

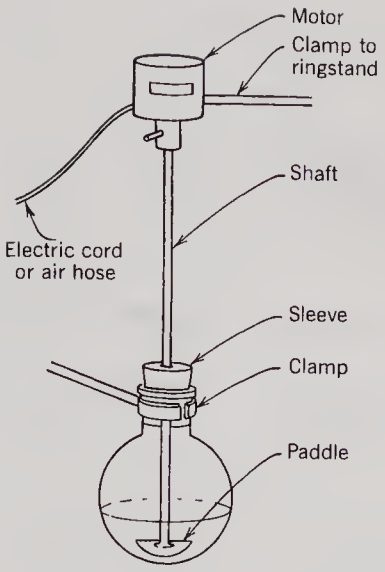


FIGURE 0.4 Paddle stirring.

For viscous liquids or heavy suspension use a motor-driven stirring paddle. The paddle is attached to a vertical shaft which is turned by a motor mounted above the reaction vessel, as shown in Figure 0.4. The shaft is usually held in place by a sleeve attached to the reaction vessel by a ground glass connection. You can use either an electric or an air-powered motor and adjust the speed of stirring by rheostat or air pressure, respectively.

Electric stirring motors generate sparks. Using volatile, flammable solvents around electric motors is inadvisable.

0.5 HEATING AND COOLING

Temperature control of a reaction mixture is important for two reasons. First, as temperature increases, the reaction rate increases exponentially in accord with the following equation:

$$\text{rate} = ke^{-(\Delta G^*/RT)} \qquad (0\text{-}1)$$

ΔG^* is the free energy of activation, R is the gas content, T is the Kelvin temperature, and k is a constant associated with the reaction. Increasing T decreases the value of the negative exponent; hence the rate increases. Running the reaction at a reasonable rate requires careful temperature control for, as you recall, reaction rate roughly doubles with each 10 C° rise in temperature.

The second reason for controlling temperature is that as the temperature of a reaction medium increases, the rates of side reactions often increase faster than that of the main reaction because the free energies of the side reactions are often higher than that of the main reaction. The main reaction makes the desired product; side reactions occur along with the main reaction but make unwanted by-products.

Exothermic reactions in particular need especially careful temperature control to prevent the previously noted problems and to ensure safety.

Heating with Flames

The easiest method of heating is with a Bunsen burner (Figure 0.5). In general, you should use flames only for aqueous solutions or those with very high flash points (at least 100 °C). If you use a burner, place a piece of wire gauze between the flame and the flask being heated. The gauze distributes the heat more evenly.

Avoid using open flames in the presence of volatile, flammable mixtures. Before

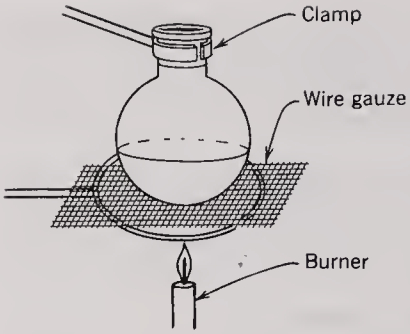


FIGURE 0.5 Heating with Bunsen burner.

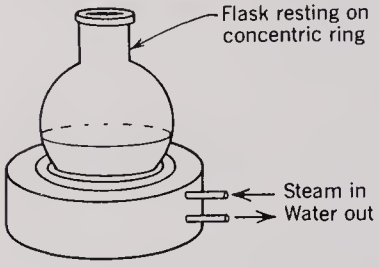


FIGURE 0.6 Heating with steam bath.

you use a burner, check with your instructor about flame-permit days or areas. Never leave a lit Bunsen burner unattended.

Steam Cones or Baths

Heating with a steam bath, shown in Figure 0.6, is convenient and safer than using a flame. It is appropriate when you are heating a solution to less than 100 °C. Condensation of steam in the laboratory might be a problem, especially if the condensate runs into your reaction mixture.

The steam bath, or cone, consists of a chamber into which steam is introduced, and a top of removable concentric rings. The apparatus is best used with round-bottom flasks that set down into the rings and may be supported by them.

To use a steam bath, first connect the steam line to the steam inlet with a rubber hose; likewise connect the water outlet to a drain. With the flask securely clamped to a ringstand, lower the flask into the steam bath so that the desired amount of heating is attained. For transferring larger amounts of heat from steam to flask, remove concentric rings so that the flask can be set well into the bath or cone and so that all of the lower half of the flask is immersed in steam. Steam should issue slowly and evenly from between the inner ring and flask and should not be puffing from between concentric rings. For transferring smaller amounts of heat remove fewer rings and suspend the flask so that steam bathes less of its surface. Heat flat-bottom containers by setting them on the bath or cone surface and removing enough rings to bathe the bottom of the flask to the desired extent: the greater the desired heat transfer the more rings you remove.

To avoid steam burns, turn off the steam source before placing flasks on or removing them from the steam bath.

Hot Water Bath

The water bath is a very simple method of heating either liquid or solid in a flask or beaker. Simply suspend or set the flask to be heated in a larger container (a large beaker, large Petri dish, etc.) of hot water. Use a fairly large container to minimize temperature changes. You can keep the bath at about the right temperature by adding more hot water as necessary or by setting the large container on a hot plate or steam bath.

Heating Mantles

Heating mantles (Figure 0.7), insulated jackets with electrical resistance wiring inside, provide a constant, easily controlled, relatively safe heat source for heating liquids. They

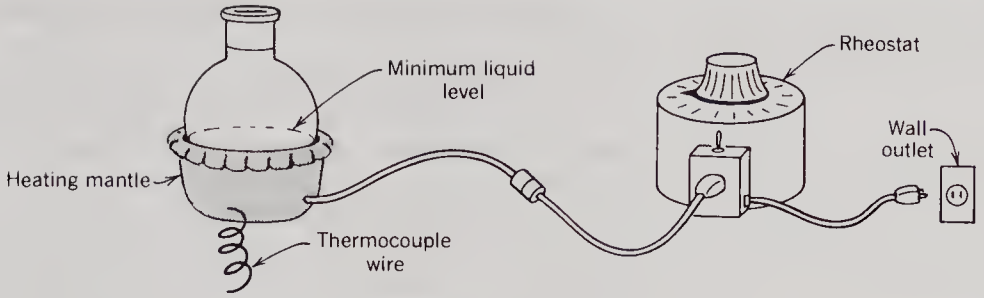


FIGURE 0.7 Heating with heating mantle.

are specifically designed for round-bottom flasks and come in a variety of sizes to match flask sizes.

The heating mantle has some disadvantages: It is expensive; it may produce hot spots on a flask; it is slow to heat and to cool; it requires a thermocouple to ascertain its temperature; during distillations the contents of the flask are often well below the top of the mantle and decomposition is therefore more likely.

If you use a heating mantle, be sure to match flask and mantle sizes to avoid overheating the mantle. Plug the mantle into a rheostat and use the rheostat voltage settings to control mantle temperature. *Never plug a mantle directly into a wall socket* or you might burn out the heating elements. For the same reason, do not turn on the current to the mantle unless a flask *containing liquid* is in the mantle. To avoid spoiling a mantle or producing potentially dangerous conditions, you must be careful not to spill chemicals into the mantle.

Always set the mantle on a ring connected to ringstand, on a lab jack, or on some other stand so you can quickly remove the mantle from the flask. Rapid removal is sometimes necessary to avoid overheating flask contents, to prevent a runaway reaction, or to allow for subsequent rapid cooling with a water bath. Remember that the high heat capacity of the mantle does not permit rapid cooling of the flask and contents by simply turning off the electricity or lowering the voltage setting.

Spills in a heating mantle can produce a fire or noxious fumes.

Hot Plates

A hot plate is an electrically heated plate, the temperature of which is controlled by an internal rheostat. A hot plate can be used to directly heat a flat-bottom reaction vessel, to heat a water bath, or to heat an oil bath. Some hot plates also contain magnetic stirring motors.

Avoid pouring flammable solvents into containers sitting on a hot plate. Remove the container first.

Oil Baths

An oil bath is a dish of oil used for heating (Figure 0.8). The dish can be of Pyrex glass or porcelain. A porcelain casserole is convenient because it is less fragile than glass and has a handle, but it is also more expensive. The bath is kept free of temperature gradients

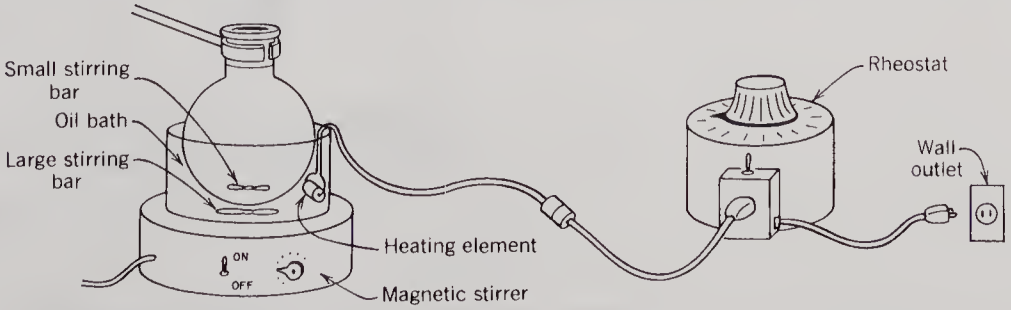


FIGURE 0.8 Heating with oil bath.

by magnetic stirring and the temperature is monitored with a thermometer in the bath oil.

An oil stable at temperatures up to about 200 °C is used for the bath. High-viscosity mineral oil, silicone oils, and polyethylene glycols including carbon waxes are commonly used. The polyethylene glycols have the advantage of being water soluble, which facilitates cleaning up.

The oil is usually heated by immersing in it a small electrical resistance heating element, very often a coil of nichrome wire lying around the inside perimeter of the bath. An inexpensive heating element can be made from a 5-W, 125-ohm resistor by soldering the lead wires to an electrical cord. The extent of heating is controlled with a variable transformer like that used for a heating mantle. The bath can also be heated with a hot plate or Bunsen burner.

To avoid electrical shock when using an unmodified variac or using a rheostat as a variable resistor, you must be very careful not to touch any electrically uninsulated parts, including the heating element.

Heating an oil bath with a burner is a fire hazard.

If an oil bath begins to smoke, stop heating immediately. The oil might be near its flash point. Used, darkened oils are most dangerous.

The smoke from overheated oils is likely to contain carcinogens and must not be breathed.

Never use bath oil that has had water spilled into it; avoid spilling water into hot bath oil. The resulting spattering can cause severe burns since the oil may be much hotter than boiling water.

Advantages of an oil bath are severalfold: (1) No hot spots are produced, therefore decomposition of reactants is lessened; (2) temperature of the bath can be determined with a thermometer in the bath; (3) the bath can be made hotter very rapidly by increasing the rheostat voltage; (4) the contents of the flask are easily visible; (5) the bath can be lowered to keep the contents of a distilling flask no lower than the bath level. Some disadvantages are the mess of cleaning up oily surfaces, the greater fire hazard, and storing of the oil baths.

Sand Baths

Transfer of heat from the surface of a hot plate or hot plate-magnetic stirrer to a reaction vessel can often be conveniently accomplished using a metal or glass dish (like a Petri or recrystallizing dish) containing a shallow layer of sand.

Set the reaction flask into the dish so that it rests on the bottom of the dish and clamp it in place. Pour in the sand so that it flows into contact with all parts of the reaction

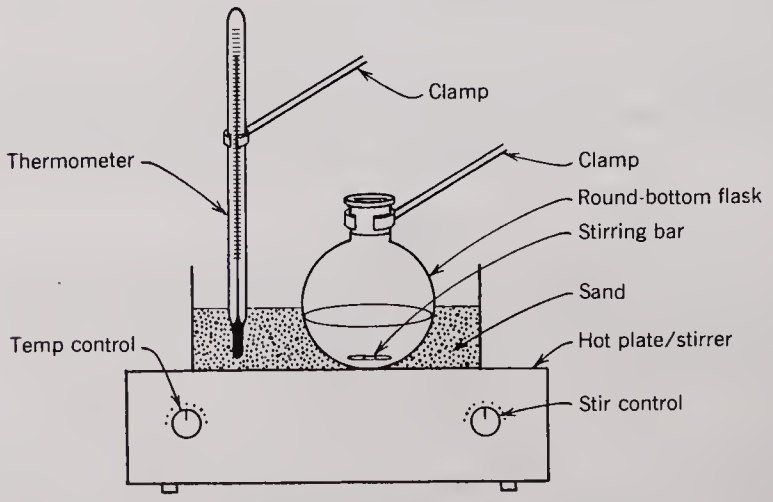


FIGURE 0.9 Sand bath with hot plate and reaction flask.

vessel (Figure 0.9) to a height even with the level to which it will be filled with the reactant mixture. Monitor the temperature of the system by imbedding a thermometer in the sand near the reaction vessel.

Because sand has a low conductivity, sand baths attain a uniform temperature slowly and are slow to cool. Therefore they are best used with small flasks (up to about 50 mL). You can help to maintain a uniform temperature by covering the sand-containing dish with aluminum foil. To obtain best heat control and to *prevent damage to the heating element* of the hot plate, use minimum amounts of sand, especially when the required temperature is greater than 150 °C. Because sand cools slowly, you must remove the flask from the sand in order to end a heating process. You can do this most easily by removing the elevating block and lowering the hot plate and sand bath.

When lowering the hot plate and sand bath, remember that they might be very hot.

Take care not to spill flammable liquids into a hot sand bath.

Reflux

There are many occasions when it is necessary to heat a reaction mixture at a constant temperature for a protracted time. The simplest way to do this is to use for the mixture a solvent with a boiling point near the desired temperature and allow the mixture to boil. In such a procedure you must prevent loss of solvent by evaporation. This is accomplished by a reflux apparatus, in which a condenser is vertically attached to a boiling flask, as shown in Figure 0.10.

The principle of reflux is that the solvent vapors rise into the condenser where they come into contact with the condenser walls, which are cooled by water circulating through the condenser jacket. The vapors condense to liquid as the molecules give up their energy to the cold walls, and the liquid runs back into the flask. The word "reflux" comes from the prefix "re" (back) and "fluxus" (a flow) and literally means "flow back."

A reflux apparatus is used in conjunction with one of the previously discussed heating methods. Always set the heating device on a ring connected to a ringstand, on a lab jack, or on some other stand so you can quickly remove the heat source if necessary.

Choose as a "pot" a flask of a size such that during the reflux it will be about half full. Put boiling chips (next section) and the reaction mixture into the flask and clamp it to the ringstand. Lower the flask into the cold heating device.

Attach rubber hoses to the condenser nipples, securing them to the condenser and spigot with hose clamps or wire. Introduce cold water into the *bottom* of the condenser jacket and allow it to run out the top. Keep the flow rate just fast enough to keep the condenser jacket cold. For low-boiling liquids this might require no more than a series of discrete drops from the end of the drain hose. Check the flow rate from time to time

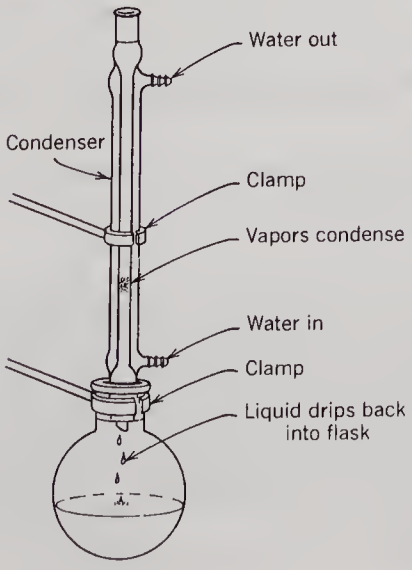


FIGURE 0.10 Condensing with a reflux condenser.

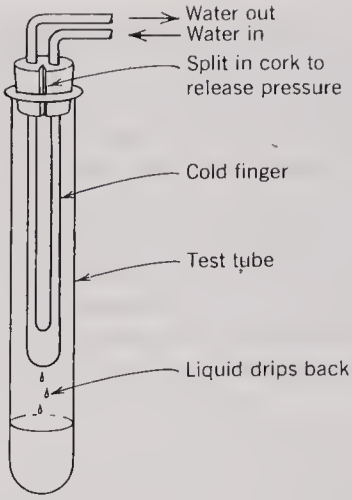


FIGURE 0.11 Condensing with a cold finger.

to ensure that the laboratory water pressure has not changed. An occasional check is especially important when many condensers and/or water aspirators are in use. If the apparatus is to be operated when you are not in attendance, you can increase the flow rate slightly in order to ensure that water pressure will be adequate. The problems with a too fast flow rate are (1) the danger that excess pressure will blow the hose off and cause water to be sprayed about, and (2) poor conservation of water resources. On the other hand, too slow a flow rate will not cool the condenser walls enough to produce condensation of vapors in the lower half of the condenser. In such a case some vapors might escape to the atmosphere.

Never stopper the top end of the reflux condenser. When using any apparatus that is not set up for vacuum, be sure that there is an opening to the atmosphere. Otherwise pressure of vapors inside might blow the apparatus apart.

Heat the reaction mixture to boiling, producing a steady stream of bubbles from the boiling chips. As vapor rises up the condenser and condenses back to the liquid state you will observe a condensate ring, below which liquid flows back into the pot. By controlling heat input, maintain the height of the condensate ring at no more than halfway up the condenser. Otherwise some solvent might be lost to the atmosphere.

When the heating period is over, lower the heat source and turn it off. Shut off the condenser water.

There are many types of condensers. Another kind that you might use in your first year of organic chemistry is the *cold finger* (Figure 0.11). A cold finger is used for refluxing small amounts of liquids or in sublimations (described in Appendix A). The principle of the cold finger is the same as for the tube condenser described previously. Liquid condenses on the outside of the finger and drips back into the boiling liquid. It is important to leave an opening to the atmosphere (the split cork in Figure 0.11) to prevent pressure buildups in the boiling flask or test tube. When using a cold finger, introduce water into the upper nipple and take it off the lower nipple.

To prevent accidental spraying and flooding, use hose clamps on condenser hoses. Avoid high water pressures.

Boiling Chips

Boiling chips are chips of an inert porous material which produce many tiny bubbles in a boiling solution. The proliferation of small bubbles makes the liquid boil smoothly.

A boiling chip produces bubbles because of sharp edges and corners that provide nucleation sites (sites that initiate bubble formation) and because the air in the many small pores of the chip mixes with vapors of the liquid as it is heated. The vapors expand and, picking up more vapor from the hot liquid around the chips, become a steady stream of tiny vapor bubbles, which help to keep the liquid from superheating around hot spots in the flask.

If superheating occurs, vapor pressure builds up, and then is suddenly released, creating a very large vapor bubble all at once. The bubble rushes to the surface and blows liquid about, perhaps out of the flask. This sort of boiling action is known as **bumping.** Use boiling chips whenever a liquid is to be boiled. The number depends on the amount of liquid, but usually two or three will do. They must be added *before* heating is begun because adding the chip to a possibly superheated liquid could cause a sudden boiling over. Whenever you allow a liquid to cool and then reheat it, you must add new boiling chips. This is because as the liquid cools, vapors within the pores condense to liquid and there is no longer any air or vapor to begin new bubble formation.

A handy substitute for boiling chips is a magnetic stirring bar rotating rapidly enough to cause bubble formation. The bubbles then act in the same way as those from the pores of boiling chips.

Never add boiling chips to an already heated liquid. The sudden boiling might be very violent.

Methods of Cooling

In an experiment it might be necessary to control an exothermic reaction, to keep a reaction temperature low, to cause precipitation of a solid, and so on. Such actions require cooling.

The simplest way to cool a container is to immerse it in a beaker of cold water or hold it under a tap.

To obtain temperatures below room temperature down to 0 °C, you can use an ice-water bath. Mix small chunks of ice with just enough water to ensure good contact with the flask walls. Crushed ice is more efficient than ice cubes, and in some climates, you can use snow in the winter as a conservation measure.

For temperatures down to −10 °C, you can use a mixture of crushed ice or snow and NaCl in a weight ratio of about 3:1. Insulating the ice bath container—for example, by wrapping it in a towel—will prolong its usefulness.

For temperatures down to about −78 °C, you can use a bath consisting of dry ice (solid CO_2) in a solvent like acetone (propanone) or isopropyl alcohol (2-propanol). Prepare the bath in a well-insulated container like a Dewar flask or a container enclosed in polystyrene foam. With a tongs slowly add small chunks of dry ice to the liquid. Too rapid addition will cause frothing as the solid CO_2 sublimes. You can control the temperature, measured by an alcohol thermometer, by stirring, and adding dry ice until you get the desired temperature. Add an occasional chunk to maintain that temperature.

When using a Dewar flask, keep it inside a shield. Avoid bumping it. Such flasks have evacuated chambers: therefore implosion is possible.

Use insulated gloves or tongs when handling dry ice because its −78 °C temperature can easily freeze living tissues.

0.6 EVAPORATING AND CONCENTRATING LIQUIDS

It is often necessary to concentrate a solution by removing some of the liquid or to evaporate a solvent to recover a solid or nonvolatile liquid.

Approach removal of solvent to dryness with caution because some organic compounds are unstable or tend to form peroxides when in contact with air. Ethers, often used as solvents, notably fall into the latter category. Exercise special care in their removal. The problem is that because the peroxides are less volatile than the ethers, the peroxides are concentrated as the ether evaporates. When the last of the ether distills away, the temperature of the residue rises, perhaps to a point at which the peroxide detonates. Evaporate ether solutions to dryness only on a steam bath or at a temperature less than 100 °C under vacuum with a well-stirred oil bath so that hot spots on the flask do not develop.

Ordinarily, evaporation to dryness involves two steps: (1) distillation to remove as

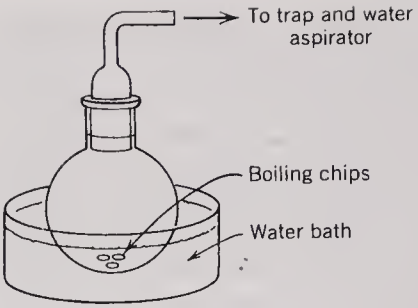


FIGURE 0.12 Vacuum removal of solvent.

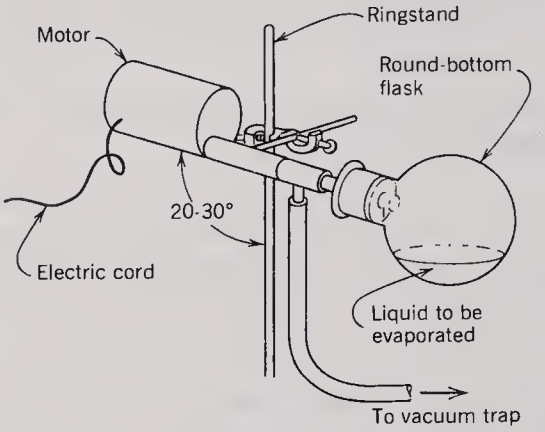


FIGURE 0.13 Rotary evaporator.

much liquid as possible without causing any decomposition, then (2) evaporation of the rest of the solvent under vacuum.

Work behind a shield whenever evaporating a liquid to dryness.

Concentration or Evaporation by Distillation

We generally use distillation whenever large amounts of solvents are involved or when solvents are to be recovered for future use. A simple distillation apparatus is discussed in Technique 7.

Open Dish Evaporation

Sometimes it might be advisable or convenient to put the liquid in a beaker or evaporating dish, set it on a hot plate or steam bath, and allow the vapors to escape into the air. We often use this technique for aqueous solutions where recovery of solvent is not important. For nonaqueous solutions, use of a hood is ordinarily advisable. If time is not critical, you can simply set the open dish in a hood with the fan on and allow evaporation at room temperature.

Employ open dish evaporation of solvents (other than water) in a hood.

Evaporation from a Flask

You can make evaporation from a flask occur by introducing a gentle stream of air into a flask of boiling liquid. The air blows vapors out and continually shifts the equilibrium in the direction of evaporation. The glass tube conducting the air into the flask should be about 1 to 2 cm above the liquid.

You can also accomplish evaporation from a flask by applying vacuum in an apparatus like that shown in Figure 0.12. The vacuum is most readily supplied by a water aspirator.

A rotary evaporator (Figure 0.13) provides a more sophisticated means of vacuum evaporation. First turn on the vacuum, then, using a *small* amount of stopcock grease, attach the flask containing the liquid to be evaporated, and turn on the electric motor. The continual rotation of the flask wets the sides and provides a greater surface from which evaporation can occur. Always release the vacuum by disconnecting the vacuum

hose or by opening a vacuum release stopcock before turning off the aspirator or pump. Otherwise vacuum will suck water into your flask if you are using a water aspirator.

Check your glassware before using it in an evacuated system. Put a safety shield between yourself and the apparatus.

0.7 CONTROLLING AND TRAPPING GASES

In many reactions gases are evolved as by-products. When these gases are toxic, it is best to run reactions in a hood. If a hood is not available or if the volume of air removal is not sufficient, you can sometimes use traps to prevent vapors from escaping into the laboratory.

Traps are commonly used for water-soluble gases. Figure 0.14 is a simple gas trap, a funnel inverted over a beaker of water, for trapping gases like HCl or NH_3. The funnel should not touch the water because a change in pressure might suck water into the reaction mixture. The trap water works more efficiently if it contains an acid or base to trap base or acid, respectively. Stirring the trap water magnetically also increases efficiency. Traps of this sort are not feasible for reactions that evolve gas in large amounts or at a rapid rate.

Figure 0.15 shows another simple trap. Any column-like structure (condenser, fractionating column, vacuum adapter, large bore tubing) is fit with a two-hole stopper through which two sections of glass tubing are inserted. You introduce the reaction gases into one tube and water from tap or condenser into the other. Gas and water mix in the column and are flushed down the drain. A trap of this type is better suited for a reaction that produces large amounts of gases.

If gases are readily evolved in a reaction, take care to ensure that the reaction vessel is large enough to prevent frothing over. Careful temperature control might be required.

Use a hood for reactions producing noxious gases.

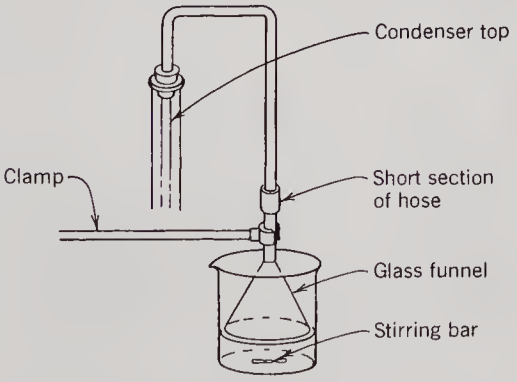


FIGURE 0.14 Glass funnel gas trap.

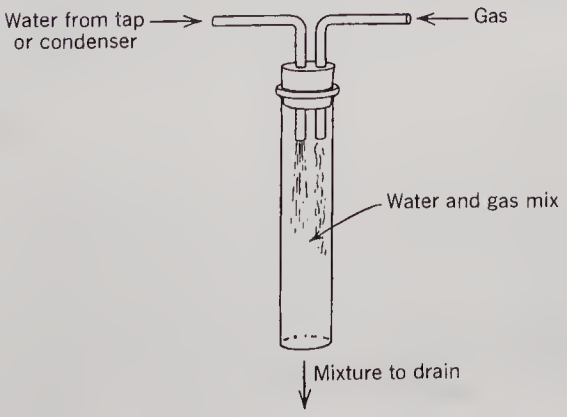


FIGURE 0.15 Column-type gas trap.

0.8 ADDING CHEMICALS TO REACTION VESSELS

In many reactions, you must put all reagents into the reaction vessel before the reaction is made to commence. In other cases, you add one or more reagents in small amounts as the reaction progresses.

Adding Solids

Before a reaction begins, you can conveniently add to a flask through a powder funnel (Figure 0.16). Or you can put the solid on a strip of paper, roll it to make a tube smaller than the flask neck, insert it slightly into the neck, and move it to a vertical position.

To add a solid to a boiling solution, pour a small amount down the length of the condenser. If particles stick in the condenser, they might be washed down by reflux, or you might have to push them down with a glass rod or wash them down with a small amount of reaction solvent.

You can also add solids from a second flask attached to a neck of the reaction vessel by a length of large-diameter, thin-wall hose. A pinch clamp prevents vapors from dampening the solid in the flask or from escaping from the flask between additions. The flask can contain a large amount to be shaken into the reaction vessel in increments. Or you can put preweighed amounts in several flasks and exchange flasks after each addition.

Adding Liquids

Before the reaction commences, you can easily add liquids to a reaction flask by pouring them through a long stem, glass funnel.

When it is desirable to add liquids to a flask during a reaction, it is most convenient to use an addition (dropping) funnel, which has a pressure equalizing tube along its side. Please see Figure 0.17. In most cases, you can probably substitute a separatory funnel. If a separatory funnel is used, you will have to occasionally equilibrate the pressure by

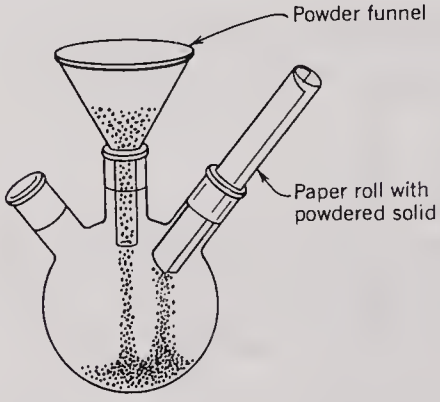


FIGURE 0.16 Adding solids through powder funnel or paper roll.

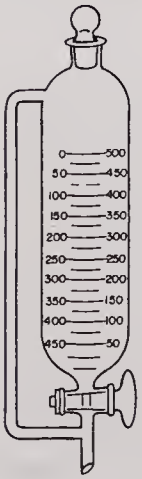


FIGURE 0.17 Dropping funnel.

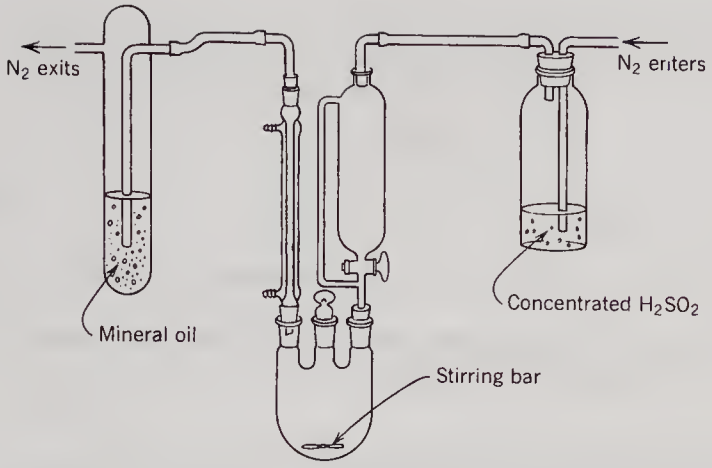


FIGURE 0.18 Apparatus for using inert atmosphere.

briefly opening both the reaction flask and the separatory funnel. You will probably have to adjust the stopcock slightly from time to time because as the height of liquid in the funnel decreases, the rate of addition decreases.

When adding liquid from a dropping funnel, take care not to add too much at once when the reaction is exothermic. This is especially easy to do when the temperature is low and nothing seems to be happening.

Adding Gases We usually add gases to a reaction mixture with a tube that extends below the surface of the reaction mixture. Do not extend the tube so far down, however, that it can be broken by a stirrer, which is generally necessary in order to promote dissolution of the gas. Do not waste gas by adding it any faster than dissolution allows.

If it is likely that pressure changes would allow liquid to back up in the addition tube, (1) extend the tube down into the vortex of the rapidly stirred solution, but not below the surface, or (2) use a liquid trap of the sort shown in Technique 4 for vacuum filtration.

0.9 INERT ATMOSPHERE

We use inert atmospheres for reactions (notably the Grignard reaction) that work best when there is no oxygen or water vapor present above the reaction mixture.

We usually use dry nitrogen gas as an inert atmosphere. We can introduce it using the apparatus shown in Figure 0.18. At first the flow rate is high and we remove the stopper from the addition funnel to flush out the air present; later we reduce it so that only a *slight* pressure is involved. The nitrogen gas bubbles through concentrated sulfuric acid to dry the gas thoroughly. The oil trap shown in the figure prevents air from entering but allows nitrogen to bubble through.

0.10 MORTAR AND PESTLE

Solid reagents that need to be pulverized are most commonly ground in a mortar with a pestle. Mortars are usually made of porcelain and have heavy walls so they do not break easily (Figure 0.19).

You simply put the substance to be pulverized into the mortar and grind it by rotary motions with the pestle. For efficient grinding, the mortar should be only filled about one-quarter full. The harder the solid to be ground, the less of it you should put in the mortar.

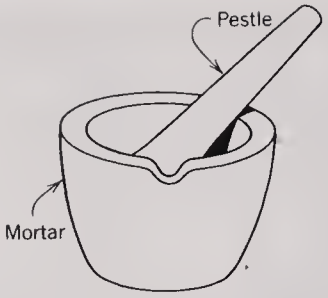


FIGURE 0.19 Mortar and pestle.

Sometimes a gentle vertical-motion pounding of a solid is necessary before you can commence grinding.

0.11 TESTING pH WITH INDICATOR PAPER

We often need to test solutions for pH. When using litmus paper or indicator paper, remember that you want to test the *aqueous* phase in a multiphase system. Get a drop of the liquid on a stirring rod, then touch the rod to a piece of paper. The paper should be lying on a clean watch glass, not on the bench top. Never dip the test paper into the solution to be tested!

0.12 STORING PRODUCTS AND INTERMEDIATES

The products of your labor deserve a container worthy of your efforts. If you have vials of several different sizes available, choose one whose capacity is not much larger than the volume of your product.

Put a light-sensitive product in a dark container or wrap the vial with dark-colored paper or aluminum foil.

If a solid chemical is air-sensitive, put it into a vial with loose cap, place the vial in a vacuum desiccator, and evacuate the desiccator. Then introduce dry nitrogen gas into the desiccator, open the desiccator, and tighten the cap on the vial. Another way to treat an air-sensitive sample is to put it in a 20-cm length large-diameter tube with one end sealed. Draw a vacuum on the tube. Then while it is still attached to the vacuum hose, melt the tube at an appropriate distance to form the sample. The tube will collapse in the vacuum and seal at the point of melting, storing the sample in a vacuum. Ask your instructor for assistance the first time you try this.

Remember to keep a safety shield between you and evacuated equipment.

Take care that the caps or cap liners of vials containing liquids do not dissolve in the liquid.

Corks and rubber stoppers often make good caps. However, many a student has stored a liquid in a vial with a rubber stopper, only to find the next week that the vial was empty because the liquid had dissolved in the stopper, diffused through, and evaporated from its surface! A cork or stopper should extend about one-third of its length into the vial.

0.13 LABELING

Every product, whether a final product or an intermediate, must be properly labeled. A label should include at least the following: the name of the product, the name of the student, and an identifying code that refers the reader of the label to a notebook and page. An example is NF-1-27, which means Nancee Folkestad, notebook number one,

page 27. The date of a preparation usually appears on the label. Your laboratory instructor might also ask you to include other information, such as yield, appropriate physical properties, and experiment number.

0.14 EXPERIMENTAL PART

The first day of laboratory you will be assigned drawers and/or cabinets in which you store your equipment.

You will probably need to bring from home safety goggles, laboratory coat or apron, scouring powder, and a dish cloth or sponge. Store these items with the rest of your equipment.

After checking all glassware to see that it is present and free of chips, cracks, or stars (many small cracks radiating from a central point), take note of (1) *locations of safety equipment:* eyewash station, shower, fire extinguisher, neutralizer solutions (if any), and exits nearest your work area; (2) *locations of work equipment:* balances, hoods, ovens, ringstands and clamps, hoses, reagent shelves, liquid and solid recovery or disposal containers.

There are two practical pieces of equipment you will use many times during your tenure in the organic laboratory and which you might have time to construct during this first lab period.

Construction of flat-bottom stirrer. Cut a 20-cm section of soft glass rod. Fire polish one end; then heat the other end in the burner flame until it is soft enough to form a 1-cm disc when the rod is pressed vertically onto an unpainted ringstand base. This rod will be useful for stirring, crushing solids for melting point determinations, removing crystals from Erlenmeyer flasks, pressing crystals in a Hirsch or Büchner funnel, and many other purposes.

Construction of vacuum filtration trap. Please refer to the right-hand part of the apparatus in Figure 4.6. Obtain a two-hole rubber stopper that will fit one of your 250-ml (or larger) suction flasks. Cut and fire polish two 10-cm sections of 8-mm soft glass tubing. Insert them into the rubber stopper, one one-half of the way and the other one-quarter of the way through. To the latter tube attach a 5-cm section of vacuum hose. The screw clamp on this hose permits controlling the extent of evaculation and releasing vacuum at the end of a vacuum process.

Use glycerine lubricant and a pad in your palm when inserting the glass tubing into the rubber stopper. Grasp the tube about 2 cm from the end to be inserted; then insert it gently with a rotary motion while you press it in. **Ask for assistance if you have not done this before.**

PART I

THE TECHNIQUES

TECHNIQUE 1

THE LABORATORY NOTEBOOK

A **notebook** is a bound assembly of blank, numbered pages for recording the progress of scientific work or ideas. The laboratory notebook is your means of communicating to yourself and others what you do in the laboratory. It serves several functions: (1) it is a place for information that you will need during lab work; (2) it is a place for a permanent record of experiment and results; (3) it is a place for an analysis and discussion of results. The notebook record you keep should be so thoroughly and clearly written that any of your peers could understand and exactly reproduce the experiments you performed.

A laboratory notebook can also double as an irrefutable record of when certain carefully written ideas, perhaps patentable, occurred to you.

If you were a professor, physician, or practicing chemist doing research, your notebook would have to pass the scrutiny of peer reviewers or perhaps a patent attorney. Although you are not now a professional researcher, this is an opportune time to learn how to keep such records. The following description of how to keep a notebook is based on a construction that would pass critical review. Your instructor will advise you which aspects of such record keeping are most important for you in this course.

1.1 GENERAL INSTRUCTIONS

Your laboratory instructor will advise you whether the notebook will be (1) regularly handed in for grading, (2) subject to spot checks during laboratory periods, or (3) for your own use. Some instructors collect carbon copies of all notebook pages used during the laboratory period. Your instructor will also tell you whether you are to write your entire report in the notebook or use the notebook primarily to provide a data base from which to prepare a separate handwritten or typed report. In the latter case, you should refer to Technique 19 on report writing.

The Notekeeping Hardware

A bound notebook with sewed pages consecutively numbered should be used for laboratory work. Loose leaf or spiral notebooks are unsatisfactory. The fundamental reason for using bound, numbered pages is that, with proper notekeeping, a permanent, unalterable record is produced. The best notebooks are those with hard covers and stitched pages of high quality, buffered paper that will last for 100 years or more. Such notebooks might cost as much as $100.00. But a satisfactory student model organic chemistry notebook with reasonably hard cover and stitched pages can be purchased for as little as $4.00 or $5.00.

Notebook pages are available in a variety of styles: lines, grids, alternating pages of lines and grids, pages with or without margins, and pages with printed matter at the top and bottom. The less expensive student notebook pages generally have lines with a left margin of about one inch or have a grid on every page. The grid style has the advantages of facilitating the preparation of graphs and tables.

Research notebooks at universities and industrial notebooks have numbered pages, but inexpensive student notebooks might not. If you have one without, you must number

all of the pages before using it. Put a page number in the upper outside corner of each page (including reverse sides of pages), starting with the first page and proceeding to the end of the book. Make the number legible and enclose it in a circle so that it will not be mistaken for any other entry.

Because the record should be unalterable you must record all information in the notebook with permanent ink. Pencil or erasable ink is never acceptable, and water-soluble inks will smear if the writing gets wet. A black ball-point pen with a fine point works best.

The Record Keeping Process

Write your notebook legibly, grammatically, and in a patterned and logical manner. You should write neatly, express your thoughts clearly, and provide a detailed account of your work. The kind of notebook you keep is a reflection on your interest in your work, your character, and capabilities. Remember that a corporate recruiter might ask to see your organic chemistry notebook; or that your organic chemistry instructor might base part of his or her recommendation of you on your notebook.

Make your notebook records as you work; do not write them later from memory or transcribe them from notes made on paper towels, filter paper, scrap paper, and so on. Such scraps are easily lost or you could make an error in transcription. Some students do not like to record as they work because their notebooks get messy looking. However, as desirable as neatness is, it is more important to have accurate and complete notes than neat ones. Besides, you will improve with practice. If you make an error in recording, strike out the error with a single line of ink, but leave it readable because information you momentarily believe is incorrect might be found to be correct. Never delete part of your record, and never tear out pages.

In scientific writing, particulary in the journals, we find that reports are written in passive past tense, and that first person statements are avoided. For example, we would not write, "I added 3 g of KOH to the mixture" but rather, "Three g of KOH were added to the mixture." However, it is becoming increasingly common to use the first person and active voice, particularly in notebook writing. There are at least two advantages to this approach: first, sentences can often be more concise, and second, it is obvious who is speaking and describing the procedure and results. Some instructors prefer that you use the past tense and passive voice during recordkeeping because it may sound a bit more objective and professional, and because it is good practice for writing in the language of the journals. Other instructors might prefer that you write in the first person until you get to the discussion section (described in Section 1.2). Be sure to ask about your instructor's preference.

Record *all* weights and other measurements directly into the notebook along with labels such as g and ml. You will have a somewhat neater and more organized notebook if for each experiment you put all such measurements on one or two separate pages reserved for that purpose. You can also put all calculations like determinations of limiting reagents, reagent amounts, and percent yield on these pages. Section 1.4 in this chapter discusses several kinds of calculations you will need to make in your notebook.

Use every page in sequence, *leaving no blank pages.* If you do not complete one experiment before beginning another, do not leave intervening blank pages for its completion. On the right-hand side of the page, just above the signatures, write "Continued on page ____." Commence work for the interrupted experiment on the top of a new page which begins with the inscription, "Continued from page ____." Figure 1.1 illustrates these concepts.

Never remove a page from your notebook, never add a page to your notebook, and never extend the size of a notebook page. Like leaving blank pages, such practices leave the authenticity of the notebook open to doubt.

Good recordkeeping requires that you *never* write in margins. Marginal notations suggest that information might be added out of calendar order, thereby decreasing the credibility of the entire notebook. Margins are often ruled only 10 mm from the edge of the page to discourage the writer from this practice but to allow sufficient room for microfilming.

Synthesis of 4-Bromobenzenol
12/5/80

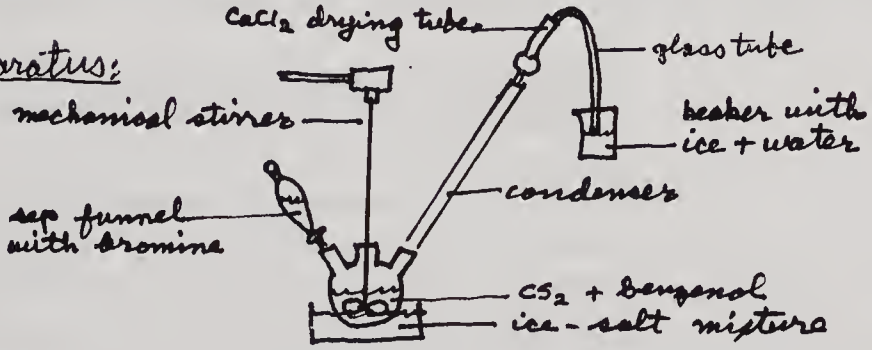
Purpose: To prepare 4-bromobenzenol from benzenol and molecular bromine.

Materials:

Compound	amt.	m w	moles	d	b p	m p
benzenol	10.0g	94.11	.106	1.07^{20}	182	43
bromine	5.96ml	159.8	.107	3.12^{20}		—
Dithiozomethane	15ml	76.14	—	1.26^{20}	46	—
4-bromobenzenol	—	173.02	—	1.84^{15}	238	66.4
2-bromobenzenol	—	173.02	—	1.49^{20}	194	5.6
2,4-dibromobenzenol	—	251.92	—	—	238	40
water	100ml		—	1.0	100°	0°

(Data from Handbook of Chemistry and Physics, 53rd. ed., R.C. West, Ed., Cleveland, O., 1972-1973)

Apparatus:



Procedure: The method was that of R. Adams and C. Marvel, Organic Syntheses, Coll. Vol. 1, 2nd. ed., H. Gilman and A. Blatt, Eds., John Wiley & Sons, Inc., New York, 1932, p. 128. The materials are scaled down to 1/100 except for ice and water, which is scaled down to 1/10. A 100 ml reaction flask is used rather than 5 l. Addn of Br_2 over 15 min.

Signature: Al Keene 3/7/86

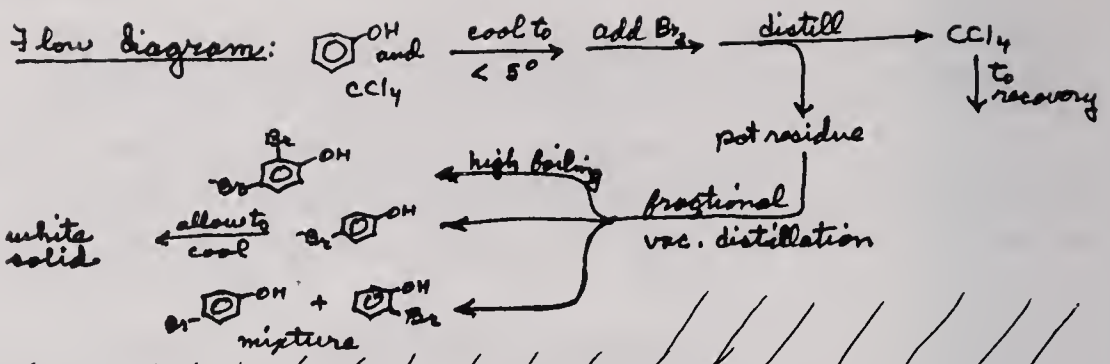
Read and Understood by: Mala Thion 3/8/86

FIGURE 1.1 Laboratory notebook.

According to common industrial research practice, you should cross out any part of a notebook page on which you do not write. This rule applies to any space one *full line or greater in area.* The rule lends credibility to recorded work by ensuring that no data can ever be entered out of calendar order.

Common industrial research practice also requires that the notebook be dated and signed at the bottom of each page, and that it be witnessed. Many patent disputes have been won on the basis of proper dating and witnessing. (There are about 1000 patent disputes in the United States each year.) At the end of each laboratory period and when

Flow diagram:



Safety Precautions: Chemical Hazards:

Benzenol - Dangerous! Tox rating 3; is absorbed through skin readily. Moderate fire hazard.

Bromine - Tox rating 2-3. Eye and resp. tract irritant. TLV 0.1 ppm. Moderate fire hazard.

Dithioxomethane - Tox rating 3. Powerful CNS depressant. Easily absorbed through skin. Fire hazard dangerous.

(Continue to list chemical and procedural hazards)

Observations and Results: Each time bromine was added the pot mixture turned brownish, then slowly become colorless. At the end of the 15 min. reaction period the mixture was slightly yellow and remained so even after another 10 min. Only 3 ml of the CS_2 was recovered during simple distillation.

During vacuum distillation the condenser started to plug up with product. I had to introduce warm water into the condenser in order to melt the product. I traced the problem to loss of vacuum where the vacuum hose was attached to the receiver.

4-bromobenzenol solidified white. m.p. = 62-64°C.

Signature: al Keene 3/9/86

Read and understood by: Stu Dent 3/9/86

you reach the end of a page, sign and date the page as shown in Figure 1.1. Oftentimes the signature follows the inscription "Recorded by." Furthermore, you should have your report read and witnessed by someone who is technically competent to understand what you have written. If your instructor requires witnessing, the witness will probably be another member of your organic class. Obtain the witness' signature and date of signing within a few days and no longer than a month after the work is done. The signature of

Literature m.p. = 66.4° (lit. source noted under materials)
The yield was 7.4 g; the % yield 40%.

Discussion of Results. The yield was much lower than that reported by Adams and Marvel. This might have been due to having lost too much solvent (CS_2) during the reaction, thereby preventing adequate contact between the reactants. The solvent was 70% gone at the end of the reaction, probably as a result of its high volatility and ease of being removed by entrainment with HBr. The final product obtained was of reasonable purity as indicated by its melting point range of 62-64°, as compared to the literature value of 66.4°. The somewhat lower melting point and 2° range might be due to incomplete separation from 2-bromobenzenol byproduct.

(Post laboratory exercises can be put here)

Signature: Al Keene 3/10/86
Read and understood by: Norma Lee Good 3/12/86

the witness should follow the inscription, "Read and understood by" or "Work observed by," depending on what the witness actually did. In most instances "Read and understood by" will be most appropriate. The primary function of witnessing is to certify that understandable work was performed on or by a certain date.

When you are working in a laboratory, always reserve space for your notebook on the lab bench. First put the notebook in place and *then* set up your equipment. If you are right-handed, put the notebook on the right side of the laboratory equipment; if you are left-handed, put the notebook on the left. Protect the notebook from operations that might soil it. Use hose clamps on all water and steam connections so that you do not periodically soak the notebook.

1.2 FORMAT

There is no single correct laboratory notebook format. However, certain basic items described in the following discussion are generally included. Your laboratory instructor will advise you to what extent you must adhere to the following format and will give you instructions for variations. As you study the format, you should refer to the sample notebook pages that accompany it.

Front Matter

The **front matter** of a laboratory notebook includes the title on the spine and/or cover, the identification and signout page, instructions page, table of contents, the preface, and perhaps a table of abbreviations.

Exterior Identification

On the outside of the front cover, neatly print the title of the book and your name, something small and simple like

ORGANIC LABORATORY

Book One

Stu Dent

Instead of Book One, you might want to use your code number for the book, like SD01, which contains the initials of Stu Dent along with an indication that this is book 01.

Ask your instructor's preference for the location of title and student name. Some instructors prefer that the student's name be at the upper right-hand corner. It is also helpful for your own use to have the title on the spine of the book so that when it is shelved you can readily identify it. Because most laboratory notebooks have dark covers, use white typewriter correction fluid for lettering or to paint a white background on which you can print dark letters.

Identification and Signout Page

The first page of the notebook should contain solely identification information: notebook number, name of user, address of user or organization issuing the book, usual location of the book, date that the book was put into service, and an example of the user's signature.

This page also indicates when the book is filled or when its use is discontinued.

Figure 1.2 illustrates an example of an identification and signout page.

Instructions Page

Page 2 (or more pages if necessary) contains the specific instructions of the company you work for or of your laboratory instructor regarding your use of the notebook. Title the page "Instructions." Write here a summary of the notekeeping procedures and format you are to follow. If your instructor provides a sheet of written instructions, paste or tape them securely on this page. If you use tape, tape the full length of all edges.

Table of Contents

Title the page "Table of Contents" and set it up with three columns: date, subject, and page. Each time you begin a new experiment, enter the date begun, its title, and the page number on which it starts. Space for 30 to 40 entries should be sufficient.

Preface

The preface is a brief description of the writer and the reason for the notebook. Its purpose is to acquaint future readers of the notebook with basic information regarding your work. Write a couple of paragraphs describing

1. Who you are; what your area of specialization is, and your job title and status (unless you are doing a special project, your title is probably "organic chemistry student").
2. For whom you are working, and that person's area of specialization.
3. What the goal of your work is. If you are doing a special project, note the status of the project to date.
4. The location of the work performance and where records and samples will be stored.
5. Who or what organization funds or sponsors the work, including name and address.

Use "Preface" as the title for this page.

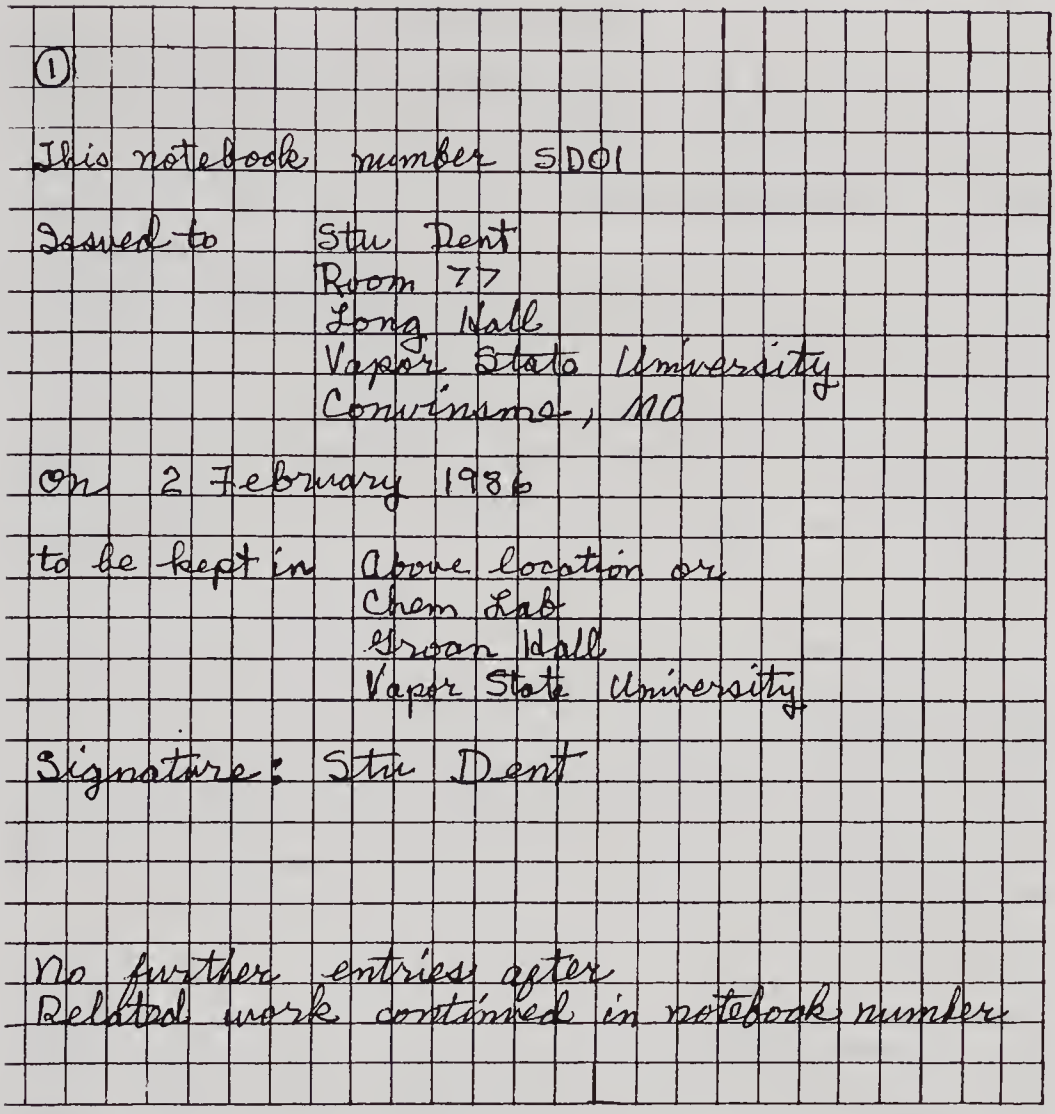


FIGURE 1.2 Identification and signout page.

The preface is often omitted, but you can see how informative it is for someone who wants to follow up on your work.

Table of Abbreviations

This page contains often-used abbreviations, symbols, and code numbers that are found throughout the book. You might prefer to put this on the inside back cover of the book. If you do not need this section, omit it.

Experimental Section Format

Although there is some latitude in the format of the experimental section of your notebooks, there are a number of elements that must be included, usually in the following order: name and number of the experiment, date, purpose, procedure, observations and results, discussion, and conclusion. As you study each of the following elements, please refer to Figure 1.1.

To conserve laboratory time and to familiarize yourself with the experiment, complete all entries through procedure before coming to lab, record observations and results while you are working in the laboratory, and write the discussion and conclusion after you conclude the laboratory work. Table 1.1 is a laboratory report checklist to help you proceed correctly and record in your notebook all necessary items. Use the table to check off items as you do the work.

Name of Experiment

Begin each experiment on a new page. Write the name of the experiment and its number, if any or if required by your laboratory instructor, at the top of the page.

TABLE 1-1 Laboratory Notebook Checklist

Item	*Lab Report Number*																													
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*
Write directly in notebook																														
Use ink																														
Separate page for measurement and calculations																														
Format items 1 through 7 entered in notebook																														
Procedure adequately described and referenced																														
List make and model of each instrument used																														
List physical conditions under which each instrument was used																														
Fasten in spectra, charts, etc. with glue or tape																														
Adequately identify spectra, etc.																														
List literature values of physical constants																														
List literature references																														
Report yield in g																														
Report % yield, mass % recovery																														
Discussion section completed																														
Postlab exercise completed																														
Report signed and dated																														
Report witnessed, dated																														
Product labeled and turned in (Please see Section 1.22)																														

Writing the Date

Write the date at the top of the page near the outside margin. Make the date end at the right margin of right-hand pages and begin at the left margin of left-handed pages. This location makes it easy to locate work performed within a particular time period as you flip the pages. Some instructors prefer that you date the top of each page, whereas others require only that you write the date each time you begin work on a new day. Be sure to ask about your instructor's preference.

If you do not complete your experiment in one day and return to the laboratory to finish it another day, write the date at the appropriate margin and at the location on the page where work commenced anew.

In some laboratory work it is important to record time of day as well as the date.

Several **date formats** are in current use, but the form that is most clearly unmistakable is, for example, either Mar. 10, 1986 or 10 Mar. 1986. The American date, 3/10/86, could be mistaken for the European form 10/3/86, both of which mean March 10, 1986. European formats also include 10.3.86 and 10.III.86. Ask if your instructor has a preference.

Purpose or Introduction

Write a statement of the reason for performing the experiment. Ordinarily, this statement will be quite brief, as shown in Figure 1.2. However, for a novel experiment of considerable importance like your senior research project, you might want to expand the purpose to an **introductory statement** which begins with the purpose and then notes related work, literature references, results of previous work, and potential benefits of performing the current experimentation.

Include chemical equations and reaction mechanisms, if any, in this section.

Procedure

Begin this section with the title "Procedure." Outline carefully the procedure you expect to follow. If the procedure is readily available in the chemical literature or in your laboratory textbook, you can replace the procedure with a statement such as, "The procedure was that described by C. Most, Jr., *Organic Laboratory Textbook,* John Wiley & Sons, 1986, p. 341, with modifications as noted below." The last phrase refers the reader to procedure alterations that you found necessary as your work progressed. Even if you outline your procedure, you should always cite the literature for the method used unless you are totally devising your own procedure.

You can make the procedure easy to follow by making a flow diagram (Section 1.3) or numbered list of experimental steps.

Prepare a list of the reagents along with both mole and mass (or volume) quantities to be used. Include here appropriate physical properties of reagents and solvents such as boiling point, density, and solubility properties. For example, you must know the density of a solvent into which you plan to extract your product from water so that you know whether the upper or lower phase contains the product. You can most conveniently arrange this information in tabular form as shown in Figure 1.1.

You can save writing many words of description by making a good **line drawing** of equipment of special design. Unusual labware or labware combinations, and novel mechanical devices are examples of the sorts of equipment for which you would make sketches. You do not need to draw commonly used apparati because you can assume that other chemists will have a mental image of them when they are mentioned.

Write a summary of **procedural and chemical hazards.** This is especially important when the reference material is found only outside the laboratory. Even if the safety data is available in the laboratory, advantages in having data recorded in your notebook are that you can refer to it *quickly,* and that you are more likely to remember it if you write it.

Observations and Results

Begin this section with the titled "Observations and Results." In this section you record what you are doing and observing. If someone else helps you or performs part of the work, be sure to note this. *Record all observations and data immediately,* directly into your notebook. Record *all* observations that are likely to be useful, remembering that it is better to record too much than too little. Record here yields, percent recoveries, percent yields, physical and chemical properties that you determined, and anything else that results from your work. Record along with the properties literature values and references.

Data can often be best presented in graphic form. When you make a graph, be sure that it includes a title and labeled axes with numerical quantities clearly indicated. *Use graph paper.* Do not make your own ruled lines. Make a note on or near the graph telling where the data came from.

Some experiments require accumulation of data in the forms of spectra from strip chart recorders, computer printouts, and perhaps photographs. Whether or not you should attach these sheets to your notebook pages depends on their size, the number of them you are likely to accumulate, and the directions given you by your instructor.

In general, if there are to be many insertions or if a sheet is much larger than a single notebook page it should probably be stored somewhere other than in the notebook. However, it might be acceptable to attach the sheet on one page and fold it so that when the notebook is opened the sheet lies across the opposite page. In no event should the inserted sheet extend outside of the book when it is closed. If an oversize sheet is attached to a notebook page, it should be securely fastened in with glue or tape and never be removed. If the sheet is stored separately, both book and sheet should be cross-referenced. For example, the notebook would say, "IR-33 of limonene is stored in the instrument room of the chemistry department at Vapor State U."; it would then list the important spectral peaks, the conditions of analysis, usually found on the chart paper, and other pertinent findings. The spectral chart would contain the usual information plus a reference to the notebook and page describing the spectrum and should be dated, signed, and witnessed just like any other laboratory work.

For attaching paper inserts to the notebook, tape is more satisfactory than glue. Use a transparent mending tape of as high a quality as your records warrant. For student purposes, the drug store variety is probably satisfactory, although it will eventually discolor and become loose. Archival quality tape is available for records likely to be of great importance.

Lay the sheet to be attached on the notebook page and hold it firmly in place. Affix your signature along one side so that it overlaps both the notebook page and the sheet attached thereto. Next, without moving the sheet, tape it in place on all four sides.

When you use instruments, record the make and model of each instrument, along with the appropriate physical conditions under which you used the instrument.

Discussion of Results

Begin this section with the title "Discussion," "Evaluation of Data," or some other similar title. Write this section after you have completed the experimental work. This very important part of the experiment should include such items as what *you* actually accomplished or learned, criticisms of your own procedure or the literature procedure, speculations as to why yields were low or physical properties were not as expected, formulation of empirical rules gleaned from the data, and evaluation of spectral data and physical properties that establish the identity and purity of your product. Although the discussion centers on your results, it is quite appropriate to relate your results to those of other scientists. Do not make your discussion a reiteration of the data obtained.

Conclusion

The title of this section is, of course, "Conclusion." In it you summarize the goal of the project, what you did, and what you discovered. The conclusion tells whether the goal

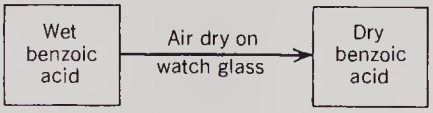
was attained and whether the basic hypothesis was proven correct, and what should have been done differently to obtain better results.

1.3 FLOW DIAGRAMS

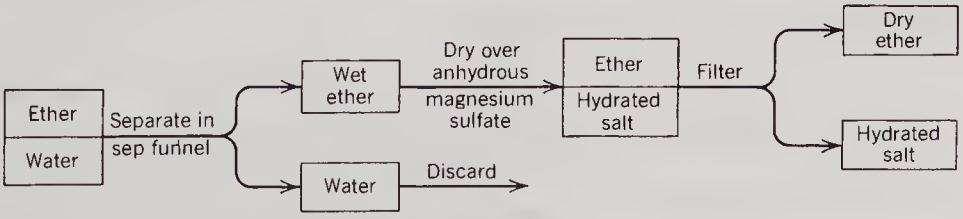
Flow diagrams are outlines of procedure. They very quickly let you see what your plan of attack is to be. The flow diagram is analogous to a sentence with a subject and a verb: the mixture or substance to be worked on is like the subject, and the action words describing what to do are like the verb.

Flow diagrams are written in a manner similar to that of writing sequential organic reactions in which organic substances are written between arrows and the reagents over the arrows.

Perhaps the best way to describe writing flow diagrams is to explain an example or two. Suppose you want to dry a water-wet sample of benzoic acid. You would simply write



Notice that the substances worked on are put in boxes and the instructions, or actions taken involving the substances, are put over the arrow. Suppose that you want to separate ether from water and obtain it in dry form. Since ether and water are only partly miscible, two phases are present. The two phases are separated most conveniently in a separatory funnel and then an anhydrous salt is used to dry the ether. The flow diagram is as follows.



Notice that a double box is used to represent the initial two-phase system and that the phase of lesser density is put on top.

1.4 CALCULATIONS

For any experimental procedure, certain calculations are almost always necessary. The following is a reminder of some applicable principles from your first-year chemistry.

Significant Figures

Keep in mind the rules about significant figures. Those rules, summarized below, apply in organic chemistry every bit as much as they did in general chemistry!

1. All nonzero figures are significant. For example, 32.674 has five significant figures.
2. Zeros are significant if they are between nonzero figures. 30024 has five significant figures and 10.2 has three.
3. Zeros are significant if they follow a nonzero figure to the right of a decimal point. Therefore, 0.200 contains three significant figures.
4. Zeros to the right of a decimal point are not significant when their only function is to indicate the magnitude of the measurement. For example, in 0.00213 the zeros to

the right of the decimal only indicate that no measurement was made in the tenths and hundredths positions. The number contains three significant figures.

5. Zeros are not significant when no decimal point is shown and zeros follow nonzero figures. Thus 40,000 has one significant figure.
6. When no decimal point is shown and zeros follow nonzero figures, zeros can be indicated as significant if a line appears above the significant zeros. Thus $\overline{40,000}$ has three significant figures.
7. Any number derived from a definition has an infinite number of significant figures. For example, there are exactly 1000 ml in a liter; and there are exactly 12 eggs in a dozen. All numbers used as coefficients in stoichiometry have an infinite number of significant figures.
8. In a sum or difference there can be no significant figures farther to the right than is found in the least precise measurement used. You can find the cutoff point for significant figures in the sum or difference by drawing a vertical line just to the right of the last significant figure in the least precise measurement. The following examples illustrate these points:

$$\begin{array}{r} 3.4\,|\,2 \\ 0.0\,|\,01 \\ +10.2\,| \\ \hline 13.6\,|\,21 \end{array}$$

rounded to 13.6 because the least precise measurement (10.2) has but one figure to the right of the decimal.

$$\begin{array}{r} 70,2\,|\,00 \\ 3\,|\,42 \\ +1.7\,|\,20.0 \\ \hline 72,2\,|\,52.0 \end{array}$$

rounded to 72,300 because the two zeros of the least precise measurement (70,200) are not signficant.

$$\begin{array}{r} 8.2\,|\,1 \\ -1.1\,| \\ \hline 7.1\,|\,1 \end{array}$$

rounded to 7.1 because 1.1 is the least precise measurement.

9. There can be no more significant figures in a product or quotient than there are in the measurement with the fewest significant figures:

   (4.224)(3.1) = 13.0944 rounded to 13 because the measurement with fewest significant figures (3.1) has only two.

   7.52/8.672 = 0.867 because the measurement with the fewest significant figures (7.52) has only three.

Using Density to Calculate Volume from Mass

When measuring liquids, it is often more convenient to use volume than mass. Given the mass amount of a reagent, you can convert to volume by using the density of the liquid (you can find densities of substances in a handbook of chemistry and physics). The relationship to use is

$$\text{volume} = \frac{\text{mass}}{\text{density}}$$

For example, if the amount of reagent to use is 3.00 g and its density is 0.86 g/ml, the volume is

$$\text{volume} = 3.00\ \text{g}\left(\frac{\text{ml}}{0.86\ \text{g}}\right) = 3.5\ \text{ml}$$

To calculate mass from volume, the reverse procedure is used:

$$\text{mass} = \text{volume} \times \text{density}$$

Reagents and Yields

The limiting reagent is the reagent that limits the amount of product which can be formed in a reaction. All other reagents are present in excess of the amount needed to react with the limiting reagent, which of course gets used up completely. A limiting reagent is often present in organic reactions. In accord with the balanced equation for a reaction, the limiting reagent will determine the **theoretical yield** (maximum possible yield). For example, consider the reaction of 1-propanol with phosphorus trichloride to produce 1-chloropropane according to the balanced chemical equation

$$\underset{\text{mol wt = 60.0 g}}{3CH_3CH_2CH_2OH} + PCl_3 \longrightarrow \underset{\text{mol wt = 78.5 g}}{3CH_3CH_2CH_2Cl} + H_3PO_3$$

Let us assume that 0.90 mole of 1-propanol is treated with 0.40 mole of phosphorus trichloride. In order to identify the limiting reagent and find the theoretical yield, you will need to do the stoichiometric problem twice, once with each reagent:

$$0.40 \text{ mole } PCl_3 \left(\frac{3 \text{ moles PrCl}}{1 \text{ mole } PCl_3}\right) = 1.2 \text{ moles PrCl}$$

$$0.90 \text{ mole PrOH} \left(\frac{3 \text{ moles PrCl}}{3 \text{ moles PrOH}}\right) = 0.90 \text{ mole PrCl}$$

In the examples, PrOH and PrCl represent the 1-propanol and 1-chloropropane, respectively. According to the balanced chemical sequation, each mole of phosphorus trichloride will produce 3 moles of 1-chloropropane; the ratio factor $PrCl/PCl_3$ in the factor-label equation allows us to determine that 1.2 moles of 1-chloropropane can be produced from 0.40 mole of phosphorus trichloride. However, the other factor label equation shows us that only 0.90 mole of 1-chloropropane can be prepared from 0.90 mole of 1-propanol. Therefore, 1-propanol is the reagent that limits the amount of product that can be prepared. 1-Propanol is the limiting reagent and phosphorus trichloride is present in excess.

We can now find, by the following factor-label equation, the number of grams of 1-propanol to use in the reaction:

$$0.90 \text{ mole PrOH} \left(\frac{60.0 \text{ g PrOH}}{\text{mole PrOH}}\right) = 54 \text{ g PrOH}$$

You can find the molecular mass of 1-propanol (60.0 g/mole) in a handbook or by summing the atomic masses.

We can also calculate the theoretical yield in grams using the limiting reagent as the starting material:

$$\text{g limiting reagent} \xrightarrow{(1)} \text{moles limiting reagent} \xrightarrow{(2)} \text{moles product} \xrightarrow{(3)} \text{g product}$$

Step 1 employs the molecular mass of the limiting reagent to change the grams to moles; step 2 involves the stoichiometric ratio of product to limiting reagent as found in the balanced chemical equation; and step 3 uses the molecular mass of product to change moles to grams. The conversion of 54 g of 1-propanol to 1-chloropropane is therefore given by

$$54 \text{ g PrOH} \left(\frac{\text{mole PrOH}}{60.0 \text{ g PrOH}}\right) \left(\frac{3 \text{ moles PrCl}}{3 \text{ moles PrOH}}\right) \left(\frac{78.5 \text{ g PrCl}}{\text{mole PrCl}}\right) = 71 \text{ g PrCl}$$

The *actual yield* of product is unlikely to match the theoretical yield. The lower actual yield is due to such factors as experimental errors and side reactions yielding other organic products. We usually find the actual yield by measuring the mass of product on a balance.

The *percent yield* is the ratio of actual yield to theoretical yield multiplied by 100:

$$\frac{\text{actual yield (100)}}{\text{theoretical yield}} = \% \text{ yield}$$

If 56.0 g of 1-chloropropane were actually obtained from the reaction of the 1-propanol with the phosphorus trichloride, you would find the percent yield as follows:

$$\frac{(56.0\text{ g})(100)}{(71\text{ g})} = 79\%$$

When a natural product is isolated, the term *percent yield* is often not used. In such cases the *mass percent recovery* is reported. It is calculated in accord with the equation

$$\frac{(\text{mass of isolated substance})(100)}{(\text{mass of material started with})} = \text{mass \% recovery}$$

For example, if 1.5 g of limonene were isolated from 250 g of orange peel, the mass percent recovery would be

$$\frac{(1.5\text{ g limonene})(100)}{(250\text{ g orange peel})} = 0.0060\%$$

Percent by Mass Solutions

Aqueous solutions of reagents are commonly used in organic chemistry. You can often use stock solutions, but sometimes you will have to prepare your own. In preparing relatively dilute solution concentrations of one or two significant figures, make the approximation that the density of water is 1 g/ml and that the final mass of solution equals the final volume. The number of grams of reagent to use is given by

$$\text{g reagent} = \frac{(\text{percent required})(\text{total volume of solution needed})}{(100)}$$

and the amount of water by

$$\text{ml water} = (\text{total volume of solution needed}) - (\text{g reagent})$$

Suppose that you need 50 ml of 10% NaOH solution. Because only one significant figure is involved and it is a dilute solution, use the above equation to give

$$\frac{(10)(50\text{ g})}{(100)} = 5\text{ g NaOH}$$

$$50\text{ ml} - 5\text{g} = 45\text{ ml water}$$

Dilution to Obtain a Required Molarity

You probably recall that molarity (M) is the number of moles of solute per liter of solution. Sometimes in the organic laboratory you will need to dilute a solution of given molarity to obtain a less concentrated solution. Use the following equation to determine the dilution:

$$V_1M_1 = V_2M_2$$

In this equation V_1 and V_2 are the initial and final volumes, and M_1 and M_2 are the initial and final molarities. Suppose you have 6.0M solution of hydrochloric acid, but need 45 ml of 2.0M hydrochloric acid. The volume of 6.0M solution to use is given by

$$V_1 = \frac{V_2M_2}{M_1} = \frac{(45\text{ ml})(2.0M)}{(6.0M)} = 15\text{ ml}$$

The procedure then, is to start with the 15 ml of 6.0M HCl in a graduated cylinder; then add enough water to bring the volume to 45 ml.

1.5 EXPERIMENTAL PART

In 1828 the German chemist Friedrich Woehler inadvertently became the founder of synthetic organic chemistry by preparing the organic compound urea from an isocyanate

considered to be inorganic. His intention was to bring about a double replacement reaction in aqueous medium between ammonium chloride and silver isocyanate:

$$AgNCO + NH_4Cl \longrightarrow AgCl + NH_4NCO$$

He filtered off the precipitated silver chloride, then evaporated the filtrate, finding to his great surprise crystals of urea.

Given that Woehler started with 0.1 mole each of reactants and isolated 0.06 mole of urea (mp 133 °C) in an equilibrium mixture with ammonium cyanate (not isocyanate!), write as complete a laboratory report as you can, imagining that you are he and have just discovered your amazing results. Include in your notebook all of the essentials of notebook reporting your instructor requires, using proper format and including as insightful a discussion as you can.

1.6 EXERCISES

Postlaboratory

1. Make a list of additional information you would like to have had in order to write a more complete report of Woehler's work.

REFERENCE

1. Kanare, H. M. *Writing the Laboratory Notebook;* American Chemical Society: Washington, DC, 1985. This reference lists suppliers of laboratory notebooks, archival mending tape and glue, and pens and inks.

TECHNIQUE 2

DRYING SOLIDS, LIQUIDS, AND GASES

When we talk about drying a substance we do not necessarily mean that it is wet with water. It might be wet with some other liquid. However, the removal of water is of special interest because many reaction products are water wet from prior separation procedures. And sometimes it is necessary to remove water from reagents or solvents before a reaction commences.

2.1 DRYING SOLIDS

Discussion of Drying Solids

The underlying principle in drying solids is to enhance liquid molecule evaporation, which we can do in two ways: (1) by increasing the ability of the molecules to escape from the surface of the wetted solid and (2) by decreasing the tendency to return to the wetted surface.

Escape from the solid surface requires energy. The more energy the molecules have, the more readily they can overcome the intermolecular forces that hold them together and to the surface of the solid. High temperatures are effective for drying solids more rapidly and more completely.

Both *rate* of drying and *completeness*, or *extent*, of drying are important. The extent of drying is how dry the solid gets, and is a function of the equilibrium vapor pressure.

When molecules evaporate within a closed container, an equilibrium is established wherein the rates of evaporation and return are equal. At equilibrium the vapor pressure of the molecules above the wet surface is equal to the pressure of the evaporating molecules at the surface as they try to escape. At equilibrium the rate of evaporation is equal to the rate of condensation and there is no further net loss of molecules from the wet solid. Decreasing the vapor pressure in the vapor phase therefore shifts the equilibrium toward evaporation. Decrease is accomplished by vacuum and/or by presence of a desiccant (drying agent).

Techniques of Drying Solids

If there is only a small amount of solid, drying is most easily accomplished by letting the solid dry in the filter that was used in separating it during filtration (Technique 4).

Another way you can dry a solid is to spread it on a watch glass or filter paper and allow it to air dry. Extra damp product can be put between two pieces of filter paper and pressed, then allowed to air dry. The thinner the layer, the faster it will dry.

Always use a hood for evaporation of noxious solvents.

You can dry samples more quickly by putting them on a watch glass or in a large beaker in an oven at a temperature *below their melting point*, or in general at a temperature of no higher than 110 °C. Higher temperatures might cause decomposition or oxidation in the air. It is important to remember that impure solids melt below the melting point of the pure solid (Technique 3). You should not oven dry samples that readily sublime because of their tendency to evaporate directly from the solid state. Air circulation to carry away vapors is essential for drying samples; forced air circulation is most efficient. If your oven has only a small opening to the atmosphere, you might want to leave the door open a bit, especially at first if the sample is large and very damp. A vacuum oven will increase the extent of drying. Labeling, of course, is very important when using community ovens!

Check the flash points of compounds before oven drying them.

Application of heat from an infrared lamp or even an ordinary light bulb will dry solids faster and more thoroughly than air drying. The same precautions as for using ovens regarding melting, decomposing, and subliming samples apply.

A vacuum desiccator, shown in Figure 2.1, is sometimes used for drying water-wet samples. In this apparatus, vacuum helps evaporate water, which then becomes trapped by the desiccant. The use of a desiccator might be especially important in humid climates. Vacuum is not essential in the desiccator, but it improves the rate of drying by increasing the diffusion of water molecules from solid to desiccant (a discussion of desiccants is found in Section 2.2). Calcium sulfate (Drierite) is probably the most commonly used desiccant. Because its hydrated form has a water vapor pressure of only 0.001 torr, it dries quite completely. It is also available in indicator form in which the calcium sulfate is dyed by blue anhydrous cobalt(II) chloride, which turns pink when hydrated. Only a

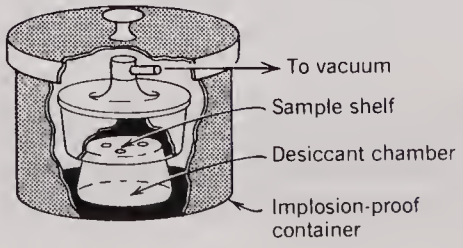


FIGURE 2.1 Cutaway section of vacuum desiccator.

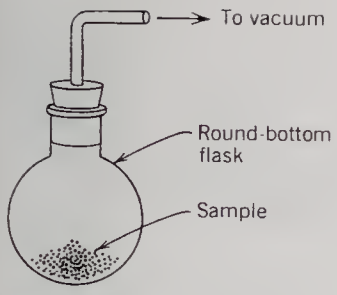


FIGURE 2.2 Vacuum drying apparatus.

little of the indicator desiccant need be mixed with a larger amount of the less expensive untreated calcium sulfate. You can also use concentrated sulfuric acid, which also provides a 0.001-torr water vapor pressure. Calcium chloride is also commonly used, and has a water vapor pressure of 0.04 torr for its hydrated form. Put the desiccant in the lower chamber of the desiccator, and the sample in a beaker or watch glass on the sample shelf.

A desiccator must be put in an implosion-proof container if high vacuum is employed.

Place a shield between yourself and any evacuated system.

The simple drying apparatus in Figure 2.2 consists of a round-bottom flask that contains the sample and is connected to an evacuating source. The flask is heated on a steam bath, or over a light bulb such that the melting point of the sample is not exceeded.

Do not excessively heat flasks under high vacuum as the softened glass might implode.

Solids wetted by solvents other than water are ordinarily left to air dry. But if the solvent has a high boiling point and drying is very slow, three approaches can be used: (1) Dry the wet solid in an oven *if* the temperature is kept well below flash points and below the melting point of the wetted solid. (2) Rinse the wet solid with a lower boiling liquid in which the solid is insoluble but which is miscible with the higher boiling liquid. (3) Use a vacuum method of drying.

2.2 DRYING LIQUIDS

Discussion of Drying Agents

Most extractions involve water as one of the solvents. It is inevitable that some water will be transferred into the organic phase because of imperfections in technique, partial miscibility of the organic phase and water, or both.

You remove water from the organic layer by using a desiccant, an anhydrous inorganic salt which hydrates on contact with water or its vapors. The reason that water is removed from the organic solvent by the anhydrous salt is that the salt attracts water more than does the solvent. The solvent-water interactions are of the dipole-induced dipole or dipole-dipole type, whereas the desiccant water interactions are of the much stronger ion-dipole variety.

The ideal drying agent for a given application should be insoluble in the organic solvent, should not react with solute or solvent, and should quickly and completely absorb large quantities of water.

The amount of water that can be taken up by a given weight of salt is referred to as the drying agent's **capacity**. Its capability to dry a solution completely is called **intensity, efficiency,** or **completeness.**

Let us look at equation 2-1, which illustrates the use of an anhydrous salt, DA, to remove water from a liquid:

$$H_2O + \text{liquid} + DA \rightleftharpoons DA \cdot (H_2O) + \text{liquid} \qquad (2\text{-}1)$$

Notice that this is an equilibrium process. High intensity is a function of an equilibrium far in the direction of hydration. Various drying agents have different degrees of intensity. For example, anhydrous sodium sulfate and magnesium sulfate both have high capacities, but magnesium sulfate has a higher intensity. Table 2.1 lists a number of common drying agents along with their pertinent properties.

A few comments about the common drying agents will help you select an appropriate one. Magnesium sulfate might react with strong organic bases since it is a Lewis acid. Do not leave it in long contact with any compound whose reactions are catalyzed by Lewis acids. It also reacts very exothermically with water and might cause the solvent

TABLE 2.1 Drying Agents and Their Properties

Anhydrous Forms	*Hydrated*	*Capacity*	*Intensity*	*Speed of Drying*
Magnesium sulfate, $MgSO_4$	$MgSO_4 \cdot 7H_2O$	High	Medium High	Rapid
Sodium sulfate, Na_2SO_4	$Na_2SO_4 \cdot 7H_2O$ $Na_2SO_4 \cdot 10H_2O$	High	Low	Slow–Medium
Calcium chloride, $CaCl_2$	$CaCl_2 \cdot 2H_2O$ $CaCl_2 \cdot 6H_2O$	High	High	Rapid
Calcium sulfate, $CaSO_4$ (Drierite)	$CaSO_4 \cdot \frac{1}{2}H_2O$ $CaSO_4 \cdot 2H_2O$	Low	High	Rapid
Potassium carbonate, K_2CO_3	$K_2CO_3 \cdot 1\frac{1}{2}H_2O$ $K_2CO_3 \cdot 2H_2O$	Medium	Medium	Medium

Adapted from Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry;* Wiley: New York, 1980, p. 97. Used with permission of John Wiley & Sons, Inc.

to heat up and perhaps boil if added too quickly. Calcium chloride combines with oxygen and nitrogen compounds like alcohols, phenols, aldehydes, ketones, some esters, amines, amino acids, and amides. Since potassium carbonate is more strongly basic, it is useful for drying solutions of basic organics, but is unsuitable for drying acidic compounds like carboxylic acids and phenols because it combines with them.

Drying Agent Techniques

Begin by mechanically removing any water that is apparent as a second phase. Use an eye dropper or separatory funnel (Technique 6). Then add a small amount of powdered drying agent directly to the organic solution. If the powder clumps together, add more of the anhydrous salt. If a second liquid phase appears, **decant** (pour off) to separate the phases; then add more drying agent to the organic layer. Allow the mixture to stand for 5 to 15 min with occasional swirling. It is even better to arrange for continual stirring with a magnetic stirrer. Next, decant the liquid from the hydrated salt or filter it by gravity filtration. When a solution is dry, it should be clear, and the drying agent should swirl easily and not appear clumpy. In most cases, drying is as complete as it will get in 15 or 20 min. When the literature states "Dry over . . . ," it refers to the above process.

When a considerable amount of dissolved water is present, you will find it advantgeous to dry the solution in two steps: (1) Use the less expensive, high-capacity, low-intensity drying agent like sodium sulfate to remove most of the water. (2) Use a higher-intensity agent like magnesium or calcium sulfate to complete the process.

Keep anhydrous salts away from skin and eyes. Their desiccant action might cause severe irritation.

When drying agents are used to remove water, *all* of the drying agent must be removed by decanting or filtering before any distillation or other heating of the liquid is undertaken. The reason is that most salt hydrates used as drying agents give up their water of hydration again at higher temperatures.

If you want to produce exceptionally dry, nonhydroxylic organic liquids, you can use drying agents that chemically react with water. Sodium or a metal hydride is commonly used. Preliminary drying with a high-capacity anhydrous salt is an absolutely essential step. Otherwise the vigorous decomposition of water could be hazardous. Drying with sodium is a slow process and should be begun a day or two in advance of anticipated use of the solvent. The sodium must be cut into very tiny pieces or extruded into a fine wire with a sodium press, then immediately put into the solvent. Sometimes the solvent is distilled from the sodium and stored over fresh sodium pieces.

Solvents to be dried with sodium or a metal hydride must be first dried to remove most of the water.

Never use sodium to dry halogenated solvents. An explosion could result.

Work behind a safety shield when drying solvents with sodium or metal hydrides.

Drying by Azeotropic Distillation

In cases wherein water is only slightly soluble in an organic liquid and forms a minimum-boiling binary azeotrope (Technique 7) with it, you can dry the solvent by distillation (Technique 7). Because the azeotrope distills first, the dried solvent will be what remains in the flask. You can tell that an azeotrope is distilling because the two-phase distillate will be milky in appearance. When the distillate appears as one phase, the process is complete.

Sometimes a liquid that does not form a minimum-boiling binary azeotrope with water will form a ternary azeotrope when a third solvent is added. For example, 95% ethanol can be dried by distilling with benzene.

Solutions are not usually dried by azeotropic distillation because concentration of the solution results.

2.3 DRYING GASES

Gases can be dried by passing them through a container containing a desiccant, which can be a solid or liquid. Anhydrous calcium chloride or concentrated sulfuric acid is commonly used.

Figure 2.3 depicts the drying of a gas by a solid drying agent. The size of the tube and flow rate must be such that it takes several seconds for the advancing gas front to pass through the desiccant.

Figure 0.17 illustrates the apparatus used for drying a gas; the trap on the right side contains the sulfuric acid.

2.4 EXPERIMENTAL PART

Time Required: 1½ hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Swirling	(0.4)
Labeling	(0.13)

You will be given a test tube containing about 15 ml of ethyl acetate (IUPAC ethyl ethanoate) saturated with water. Your problem is to dry the organic liquid of water by using the techniques of Section 2.2.

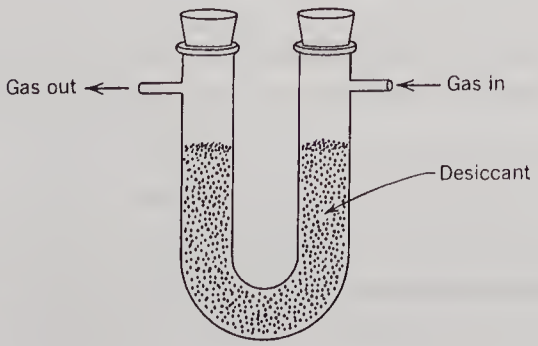


FIGURE 2.3 U-tube with solid desiccant for drying gases.

Drying ethyl acetate. Weigh to four significant figures a stoppered 50-ml Erlenmeyer flask and record this tare weight. Pour the wet ethyl acetate into the flask and weigh the flask again. Subtract the tare weight and record the mass of the aqueous solution.

Remove a drop of liquid with a stirring rod and immediately touch it to a piece of cobalt(II) chloride test paper. Allow the spot to dry. If you see nothing, repeat, adding a new drop to the same spot. Record your observations.

Tare a small beaker to the nearest 0.01 g. Into the beaker weigh about 2 g of anhydrous $MgSO_4$ to three significant figures (to the nearest 0.01 g). In small increments and with continual swirling, add the magnesium sulfate to the ethyl acetate solution. Observe the mixture carefully after each addition for clumping of the powder or formation of a second liquid phase. Do not forget to record your observations! If a second liquid phase forms when the first small amounts of desiccant are added, do not decant. (In *this* case you want to be able to easily recover all of the $MgSO_4$.) Add more $MgSO_4$ until it remains powdery when added and after a 2-min period of swirling. Weigh any leftover anhydrous $MgSO_4$ and put it in the assigned recovery container. When you think the liquid is dried of water, test the liquid again with cobalt (II) chloride test paper and record the results.

Tare the vial in which you plan to turn in your sample of dry ethyl acetate. Using an ordinary conical glass funnel and a medium porosity filter paper folded into a cone, filter the $MgSO_4$ from the ethyl acetate mixture, allowing the filtrate (the liquid that comes through the filter) to run into the tared vial. Weigh the vial again so you can determine the final weight of the dried liquid. Label the container and turn it in to your instructor.

Dry the filter cake (the hydrated $MgSO_4$) by an appropriate method described in Section 2.1 and weigh it. Dispose of the salt as required by your instructor by either putting it in an assigned recovery container or by dissolving it in water and pouring it down the drain.

Calculate the amount of water present in the original sample by subtracting the weight of anhydrous $MgSO_4$ used from the weight of the filter cake. Calculate the weight of ethyl acetate in the original solution by subtracting the weight of water present from the weight of the original wet solution.

Using the amounts of anhydrous magnesium sulfate used and the amount of water present in the solution, calculate the number of moles of each and then the formula of the hydrate $MgSO_4 \cdot xH_2O$.

Using the weight of ethyl acetate in the original sample and the weight recovered, calculate the percent yield.

Note: Although it worked this time, testing an organic liquid with cobalt chloride test paper is *not* a generally reliable method of determining if it is dry (sometimes organic solvents will ligate and extract the cobalt into the solvent).

Writing the discussion. In the discussion section of your notebook report you should draw conclusions about and discuss the following: Did the drying agent seem to be effective as indicated in Table 2.1? How do you know? If the drying agent did not seem to be as effective as indicated by Table 2.1, suggest a reason. Roughly, how much water was present in the water-wet ethyl acetate? Was this amount sufficient to cause clumping of the drying agent or to cause a formation of a second liquid phase? If you were to repeat this process, would you alter your method any? If so, how? Based on the formula $MgSO_4 \cdot 7H_2O$, did you add enough, too little, or too much desiccant? How much ethyl acetate seems to have been lost in the filter cake, filter paper, and by evaporation? Can these losses be reduced or are these losses to be expected in drying liquids?

2.5 EXERCISES

Prelaboratory

1. Without using heat or vacuum, how can you, in a simple way, air dry a solid faster than by setting a flask of it on the bench top?

2. What physical properties of a solid should you check before drying it in an oven?
3. If the indicator Drierite in your desiccator is pink, what course of action do you suggest?
4. Make a flow diagram of the procedure you will follow when instructions tell you to dry a liquid over anhydrous magnesium sulfate.
5. What precautions should be taken when using a vacuum desiccator?
6. Which desiccant would provide a greater extent of drying—calcium chloride, or calcium sulfate? Why?
7. Make a flow diagram for the experiment in Section 2.4, noting that you will not allow a second liquid phase to form during addition of desiccant.

Postlaboratory

1. Will heating increase the rate, extent, or both, of drying a solid? Explain.
2. Does application of vacuum increase the rate, extent, or both, of drying a solid? Explain.
3. Could calcium sulfate dihydrate be used as a drying agent? Explain.
4. Write the equation that shows the chemical reaction that takes place (a) when sodium is used as a drying agent; (b) when calcium hydride is used.
5. Outline a procedure for drying a water-wet cake of benzoic acid by azeotropic distillation with benzene.
6. A student placed 5 g of damp benzoic acid on a watch glass and put it in an oven below the melting point of the acid. The next morning she was surprised to find only 0.5 g of the dry acid left on the watch glass and long needle-like crystals around the oven opening. What do you think happened?
7. A student decided to dry a sample of ethyl acetate with lithium aluminum hydride. Explain whether this was a wise choice of drying agent. (Hint: How do esters typically behave in the presence of strong base?)

TECHNIQUE 3

THERMOMETERS, MELTING POINTS, AND BOILING POINTS

For the organic chemist two important and widely used physical properties are the melting points of solids and the boiling points of liquids. These properties are useful to indicate purity and identity.

In this section we shall examine melting and boiling point behavior of organic substances and techniques of determining melting and boiling points. Because a thermometer is the instrument used to measure melting and boiling points, we shall also investigate its characteristics and the correct ways to use it.

In this textbook we shall follow the custom of using symbols that differentiate between temperature and change in temperature. For example, 10 °C means a centigrade (Celsius)

temperature, whereas 10 C° refers to a change in temperature or an interval or distance on a thermometer.

3.1 THERMOMETERS

A **thermometer** is an instrument used for measuring temperature and is an important tool for the organic chemist. Figure 3.1 illustrates the construction of a common laboratory thermometer.

When you inspect the student thermometer, you will see that the separations between degree markings are quite close together. For this reason alone, you will have difficulty making precise measurements of temperature. However, you probably will be able to estimate to the nearest 0.3 or 0.5 degree, but in terms of significant figures, your measurements to the right of the decimal will be in doubt. Always report the uncertainty in your measurement along with the temperature. For example if your thermometer shows 102.0 °C but you can read only to the nearest 0.5 degree, report the temperature as 102 °C ± 0.5 °C. Ordinary laboratory thermometers are also often inaccurate because of irregularities in the bore through which the thread of mercury moves.

Thermometers commonly in use today have a ring around the stem somewhat below the scale graduations. You might also find an inscription like "76-mm immersion." This **immersion mark** tells you how deeply to immerse your thermometer in fluid (liquid or gas) to have the scale graduations be applicable. Commonly, a thermometer intended for distillation requires about a 75-mm immersion, whereas one designed for melting points takes about 25-mm immersion. If there is no immersion ring, the thermometer is of the total immersion type. That is, if you want an accurate temperature measurement, you must immerse the thermometer in fluid to the top of the mercury thread in the bore. In practice it is unlikely that laboratory workers will totally immerse the mercury thread, therefore unequal expansion of glass and mercury will result in error. The error is not of much consequence in ordinary lab work if the temperature is under 100 °C. However, a typical error for a total immersion thermometer because of partial immersion at 200 °C might make the temperature appear about 5 °C lower than actual. The immersion error is, of course, temperature-dependent.

When using a total immersion thermometer, the extent of the error, known as the **stem correction**, can be calculated from the following equation:

$$\text{stem correction} = KN(t_1 - t_2) \tag{3-1}$$

wherein K = the apparent coefficient of thermal expansion of mercury in glass at the observed temperature as shown in Figure 3.2; N = the length (measured in degrees) of that part of the mercury thread above the surface of the fluid; t_1 = the temperature of the mercury bulb (the observed temperature); and t_2 = the temperature at the center of the nonimmersed portion of mercury column, which can be determined by holding the bulb of a second thermometer against the first thermometer. Sometimes it is estimated, without using a second thermometer, as one-half of the difference between room temperature and the temperature on the thermometer. The stem correction is added to the observed temperature in order to obtain the corrected temperature.

One of the best ways to circumvent errors arising from stem corrections and other thermometer irregularities is to calibrate the thermometer. Once you calibrate it, you need not make stem corrections. To make a thermometer calibration, obtain the melting or boiling points of a number of substances; then compare the thermometer readings with the *literature values* (known accurate values) for the substances. Known melting points and boiling points can be found in the chemical literature (handbooks, lab books, etc.) After calibration make a *calibration curve* like the one shown in Figure 3.3. From then on, correct every determination on your thermometer by the amount indicated on the calibration curve.

Customarily, a thermometer to be used for melting points is calibrated by immersing it 25 mm into the bath liquid (see Section 3.2); one to be used for distillations is calibrated

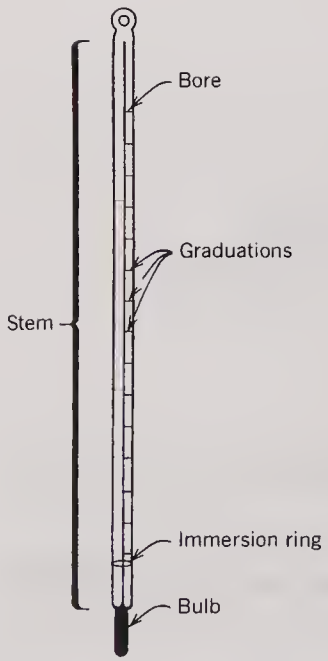


FIGURE 3.1 The parts of a thermometer.

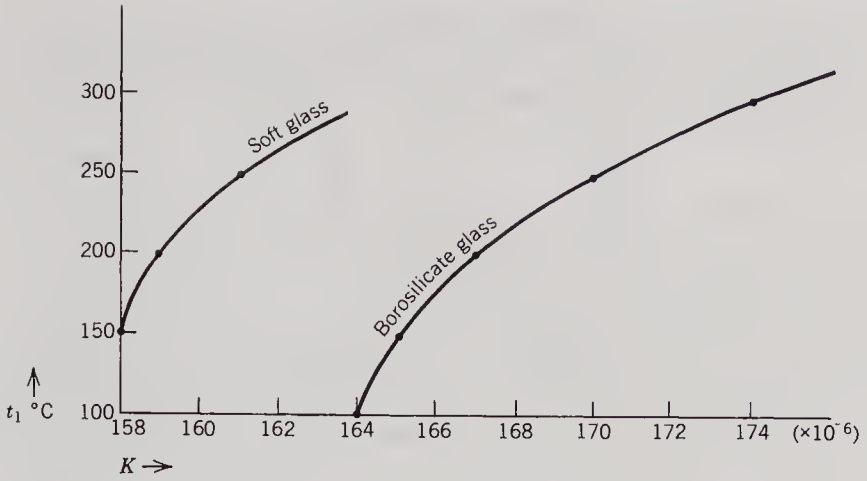


FIGURE 3.2 Relationship between observed temperature and *K*.

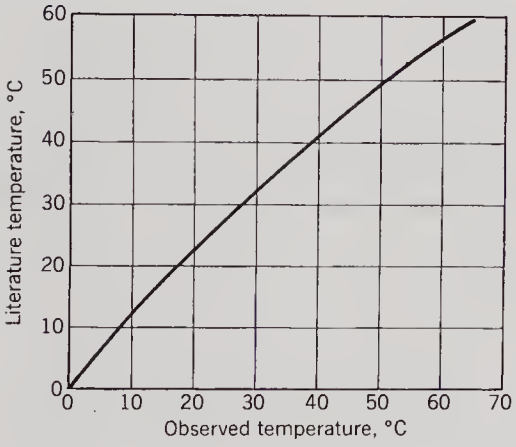


FIGURE 3.3 Calibration curve for thermometer.

for a 75-mm immersion (so the bulb of the thermometer is just below the side arm of the distilling flask.)

If either a stem correction is used or a thermometer correction is employed from a calibration curve, report the observed temperature as corrected temperature, for example 36.8 °C, cor.

3.2 MELTING POINTS DISCUSSION

The temperature at which the solid phase of a substance changes to liquid is the *melting point*. Stated another way, the melting point is the single temperature at which solid and liquid phases can exist in equilibrium with each other as heat is applied or removed. To clarify the relationship between these definitions we shall need to refer to Figures 3.4, 3.5, and 3.6.

Melting Points of Pure Substances

Figure 3.4, a plot of vapor pressure of a substance at various temperatures, illustrates phase equilibria among solid, liquid, and gas phases of a pure substance. Remember that vapor pressure is the pressure exerted by molecules in one phase against those of another phase, and can be thought of as the tendency of molecules to escape from the phase they are in. In Figure 3.4, conditions of equilibrium exist only along the lines between the phases. The arrows represent the reversible transfers of molecules as they escape from one phase into another. You can find the equilibrium vapor pressure of liquid at any temperature along the line *AB*. Likewise, along line *BC*, you can find the

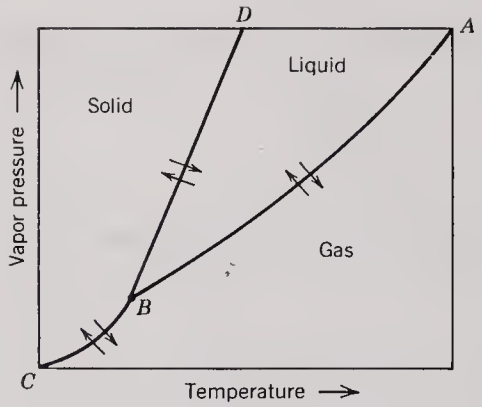


FIGURE 3.4 Phase equilibria.

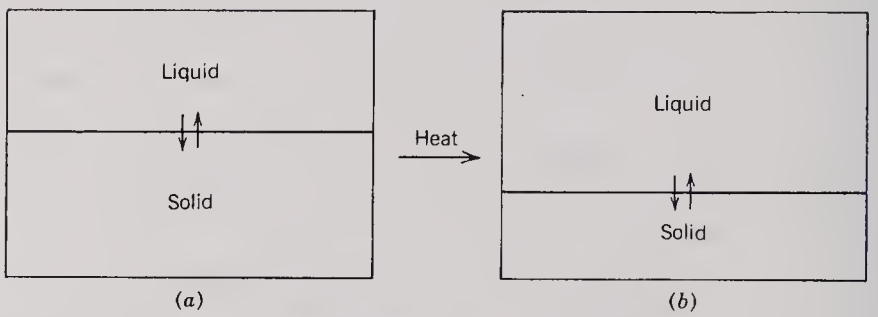


FIGURE 3.5 Vapor pressure equilibria between solid and liquid.

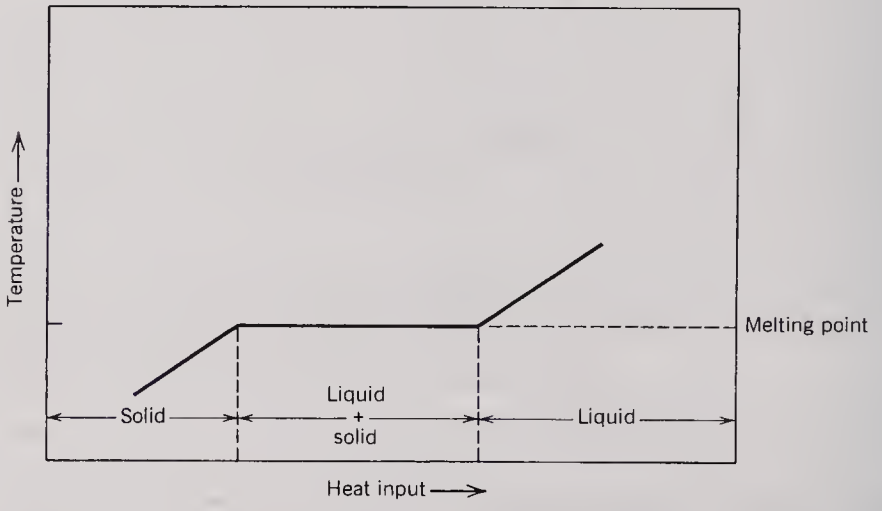


FIGURE 3.6 Phase changes with heat input and temperature.

equilibrium vapor pressure of solid at any temperature. Line *BD* represents the temperature and vapor pressure conditions at which solid is in equilibrium with liquid. You will recall that point *B*, at which all three phases are in equilibrium, is the **triple point**. Many organic solids do have appreciable vapor pressures and tend to **sublime** (pass directly from solid to vapor), especially at higher temperatures. However, for most solids, the vapor pressure at about 1 atm is small enough that we need not be too concerned with equilibria between solid and gas, as found along line *BC*. Let us concentrate our attention, then, on the more typical solid, and refer to the simplified diagram in Figure 3.5.

Figure 3.5*a* illustrates the vapor pressure equilibrium between solid and liquid phases of a typical organic substance near atmospheric pressure. Because of the low vapor pressure associated with solids, melting points are not noticeably influenced by normal atmospheric pressure changes. At the melting point, the vapor pressures of the solid and liquid phases are equal and molecules move in both directions at an equal rate. If heat is added to the system at the melting point, the equilibrium will shift in the direction of

liquid, then, when the heat is removed, reestablish itself. Molecular movement will again be equal in both directions. The temperature will not have changed, but more of the substance will be liquid, as shown in Figure 3.5*b*. As long as any solid remains, all heat input will go into separating molecules from the crystal and the temperature will remain the same.

Figure 3.6 shows the relationship among heat input, temperature, and phase change for a pure substance. Below the melting point, only solid is present. As heat is supplied, intermolecular vibrations in the crystal increase and the temperature rises. When the melting point is reached, additional heat input goes into separating molecules from the crystal but the temperature remains the same. When all solid has been changed to liquid, molecular motion within the liquid will result from added heat and the temperature of the liquid will rise. Notice that when you follow this diagram from right to left it shows that the freezing point and melting point of a substance are the same. Because the temperature does not change during melting, slow enough application of heat gives a single temperature at which the solid melts, and we observe a sharp melting point.

Melting Points of Impure Substances

Let us look again at Figure 3.5*a*, which illustrates the vapor pressure equilibrium between solid and liquid, which we shall now designate as A. If we dissolve a small amount of a second substance B in the liquid phase of A, more of the solid phase of A will melt even though no additional heat is supplied because the presence of B lowers the vapor pressure of liquid A. Because the escaping tendency of molecules in solid A is now greater than in liquid A, the equilibrium shifts toward the liquid phase. Without heat input, the temperature of the solid phase will then decrease because the separation of molecules from the crystal lattice required energy. In effect, then, the presence of an impurity in the liquid phase depresses the melting point of a solid.

Now let us consider the melting point of a solid A which contains foreign molecules B within its crystal structure. As soon as A begins to melt, B dissolves in liquid A and lowers the vapor pressure of the liquid. Therefore, the impure solid has a lower melting point. A second way that impurity B within the crystal lowers the melting point is by weakening the intermolecular forces between molecules of A. The decreased attraction between A molecules leads to a lower energy requirement for separating them. As you might suppose, the greater the amount of impurity, the lower the melting point. Figure 3.7 illustrates the lowering of the melting point.

Figure 3.7, a **phase diagram**, depicts the melting of the component mixture, A plus B. The upper region of the diagram represents a single phase consisting of a liquid solution of A and B; the lower region is a single phase made up of solid A and B. The

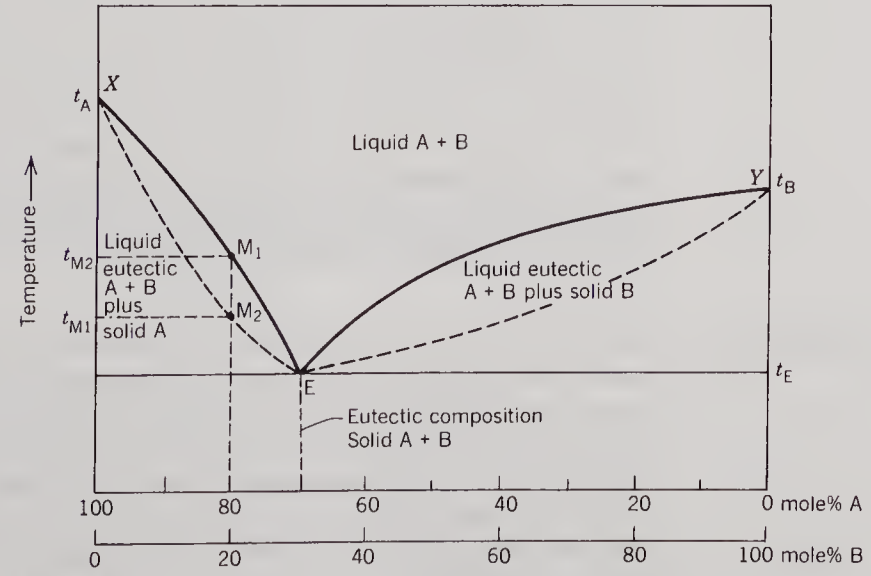


FIGURE 3.7 Phase diagram of a two-component mixture.

portions between the straight and curved lines represent two-phase systems composed of solid A or B in liquid A and B. The solid present depends on the proportion of A and B in the original mixture. The points t_A, t_B, t_E, and T_M, are the respective melting points of A, B, the eutectic, and a mixture consisting of 80 mole% A and 20 mole% B. A **eutectic** is a mixture so composed that it has a single sharp melting point just like that of a pure solid. You probably recall that mole% relates moles of a substance to the total number of moles present. For example, if 4 moles of A are mixed with 1 mole of B, the mole% A is given by

$$\frac{4(100)}{4 + 1}$$

The dotted curved lines from E to X and E to Y represent the observed beginning of melting. The corresponding solid curved lines represent the observed completion of melting. Notice on Figure 3.7 that theoretically there are three points with no melting point range: the melting point of pure A, of pure B, and of the eutectic. All combinations of A and B melt over a range of temperatures, the broadness of which depends on the mole% of each. Notice that the broadest melting point ranges are about halfway between the pure substance and the eutectic. The observed melting point range of A containing 20 mole% B is given by the temperature range t_{M1} to t_{M2}.

Now let us consider the melting of mixture M (80 mole% A and 20 mole% B). We apply heat to the mixture of solid A + B and the temperature rises; when it gets to t_E, A and B melt together at constant temperature in the proportion of the eutectic mixture, in this case 70 mole% A and 30 mole% B. Because B is present in M in smaller molar quantity (20 mole%) than A, excess A will be left when all of B is melted. At this point solid A will be in the presence of liquid eutectic at the eutectic point, t_E. Then as we apply more heat, more of A melts, changing the composition of the liquid. The presence of more A in the melt increases the vapor pressure of A in the liquid, hence the equilibrium shifts toward solid A. To melt more of A, we must increase the temperature with additional heat. As more and more A molecules enter the liquid, the equilibrium temperature of the two-phase system rises. Thus we see a rise in temperature along line EX until all of A has finally melted at temperature T_M. Notice that T_M is well below the melting point of T_A, the melting point of pure A. If B were present in greater molar quantity than A, we would observe the same effect but moving along the line EY rather than along EX. Experimentally, the observed melting range is less than the actual melting range since we can not see the initial melt until a considerable amount of it is present.

The above described melting point behavior is characteristic of most organic substances. The exceptions are few, but there are exceptions: (1) You have undoubtedly already noticed that a mixture of eutectic composition has a sharp melting point; therefore you could mistake a eutectic mixture for a pure compound. (2) If the eutectic composition has a very high mole% of A and the melting points of A and B are far apart, a small amount of B could actually *raise* the melting point (see postlab exercise 8). (3) The heat of melting might result in a chemical reaction to yield new compounds with different melting points. (4) Occasionally you might observe a rather sharp melting point that leaves a second unmelted substance. In a mixture of A and B, the higher the melting point of B and the weaker the intermolecular attractions between A and B, the less likely will be any change in melting point of A.

Mixture Melting Points

We have seen that the mixture of two substances ordinarily exhibits a lower, broader melting point range than does either pure substance. We can use this fact to help identify a compound. Suppose we suspect that unknown compound Q is substance B. We then intimately mix Q with an equal amount of known substance B and take the melting point of the mixture. If the mixture melting point is depressed or broadened in relationship to the melting point of B, we know Q and B are not the same. If, however, we find the mixture melting point to be that of B, we can assume that Q and B are almost certainly the same compound.

3.3 MELTING POINT TECHNIQUES

There are two general types of melting point apparatus: heating baths and electrical devices.

Using a Thiele Tube

The Thiele tube (Figure 3.8) is a readily available heating bath. Its shape creates convection currents of the oil which fairly well prevent formation of temperature gradients and thus obviate stirring. The sample is contained in a capillary tube held to the thermometer by a slice of rubber tubing.

High-boiling, stable liquids that are suitable for the bath include glycerine, paraffin oil, silicone oil, and cottonseed oil.

The sample should be dry and finely divided. You will probably have to pulverize it by grinding it with a small mortar and pestle (preferably made of agate which is nonporous) or with your flat-end stirring rod on a watch glass.

Do not allow chemicals to come in contact with your skin.

Clean up all spills promptly with a paper towel or brush and discard such wastes into a container assigned by your instructor.

Use thin-wall capillary tubes 1–2 mm in diameter and about 6–8 cm long. You can use prepared tubes, or you can make melting point capillaries by drawing out soft glass tubing and sealing one end. Keep the capillary tubes in a covered container so that they do not become contaminated.

Press the open end of the tube onto a small pile of the powdered sample. Turn the tube upright and cause the sample to fall and compact into the sealed end of the tube by (1) gently tapping the tube on the bench top, (2) gently rubbing the tube with a file, or (3) dropping the loaded capillary through about a 30–40 cm length of glass tubing. Repeat the introduction of sample until the capillary contains a column no more than 3 mm high.

Secure the loaded capillary to the thermometer with a small slice of rubber hose so that the sample is next to the thermometer bulb. Suspend the thermometer in the liquid bath with rubber sufficiently above the liquid level so that expansion of heated liquid will not reach it and so that the immersion ring of the thermometer is at the top of the liquid. Please see Figure 3.8.

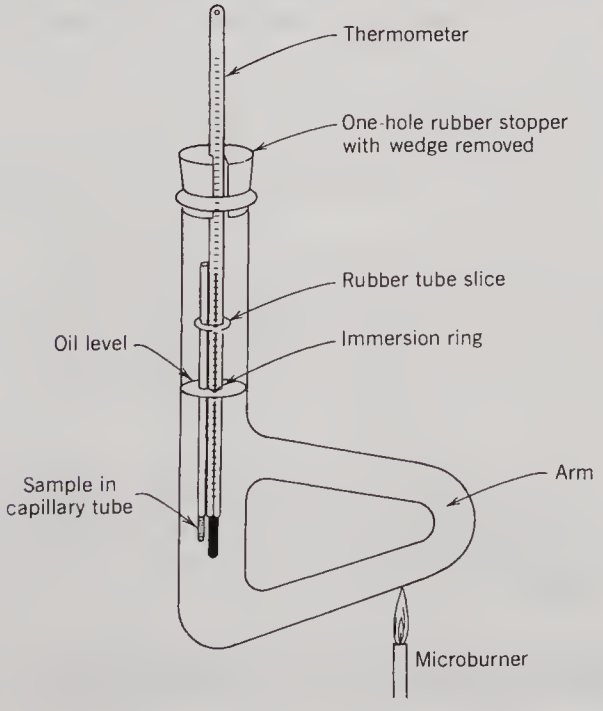


FIGURE 3.8 Thiele tube melting point determination.

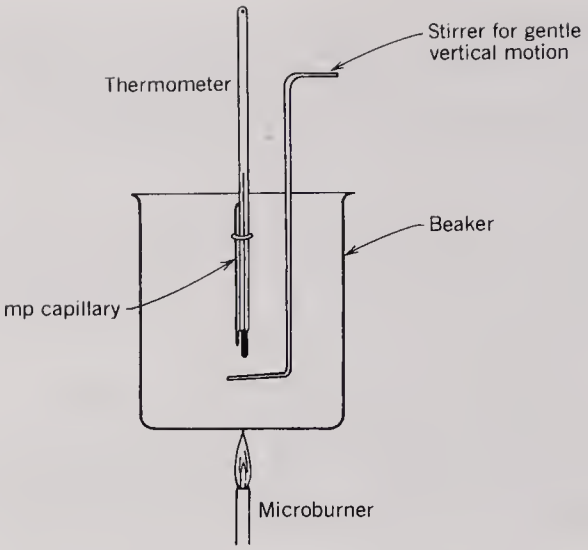


FIGURE 3.9 Simple beaker bath.

Heat the Thiele tube with a microburner. Using a gentle flame and holding the burner by its base, move the flame slowly back and forth along the bottom of the Thiele tube arm. Apply heat quite strongly at first, then more gently so that as the melting point is approached the rate of heating is about 1 C°/min.

If a Thiele tube is not available use a simple beaker bath as shown in Figure 3.9.

If you are going to use a Thiele tube or other oil bath system for melting or boiling point, examine the oil to be sure there is no water present.

Never use a flame for Thiele tube or distillation boiling points unless you have a flame permit.

Discontinue heating the Thiele tube if the oil starts to smoke.

Check the Thiele tube for stars or cracks before using.

Using an Electrical Apparatus

The many kinds of electrical melting point apparatus are all operated by electrical resistance heating. We observe the sample through a magnifier, an advantage of such equipment being that we can use smaller samples.

If your laboratory has an electrical apparatus, your instructor will show you how to use it. The heating rate at the melting point should be about 1 C°/min. Electrical melting

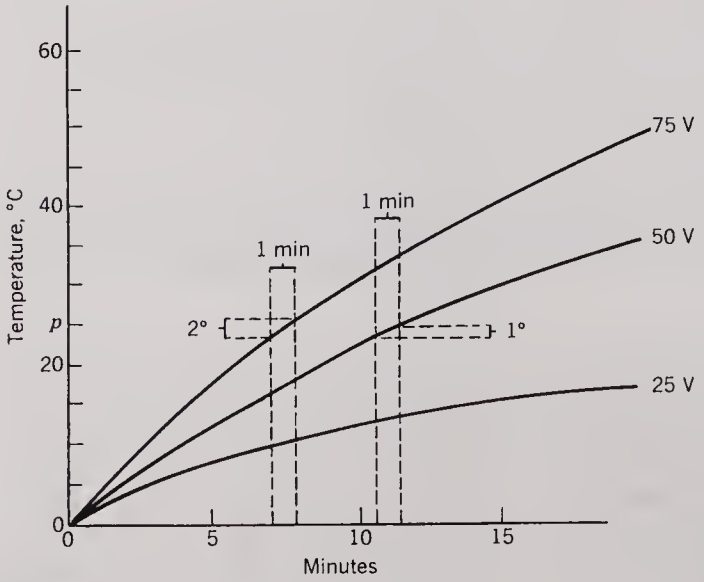


FIGURE 3.10 Heating curves for electrical mp device.

point apparatuses generally do not heat the sample linearly. At each successive higher setting of the potentiometric control knob, the rate of heating increases. However, at higher temperatures, heating decreases and finally levels off. The plots of temperature versus time in Figure 3.10 are curves for the hypothetical voltage settings at the right ends of the curves. From these curves you can see that the rate is greater at higher voltage settings; therefore in the interest of saving time you should use a high setting initially and then turn the potentiometer knob to a lower setting as the melting point is approached. For a compound of melting point *p* on the curve, use a setting of 50 V rather than 75 V because the slope of the curve gives a 1 C°/min rise rather than a 2 C°/min rise.

Avoid turning electrical melting point devices on or off in the vicinity of flammable vapors.

Observing and Recording the Melting Point

Sometimes it is difficult to tell when a substance is actually melting because it might undergo decomposition, discoloration, sublimation, softening, and/or shrinkage at or below the melting point.

Many organic compounds, such as amino acids, salts of amines, salts of carboxylic acids, and carbohydrates melt with decomposition over a relatively wide range. When a compound decomposes while melting, record the melting point or melting range followed by a lower case d, indicating decomposition. For example, L-methionine decomposes at 283 °C, so you would show its melting (decomposition) point as 283 °C,d.

Decomposition is most often accompanied by yellow or brown discoloration. Some thermally unstable compounds might exhibit some decomposition below their melting points as they undergo eliminations during such events as decarboxylation or anhydride formation. The decomposition products formed then act as impurities to lower and broaden the melting point of the substance.

When a solid compound has a very high vapor pressure, as has naphthalene (moth balls), for example, it might sublime below or at its melting point. Evidence of sublimation is sometimes a decrease of substance quantity and/or appearance of crystals at a cooler part of the sample container. Under such circumstances you must determine the melting point of the compound in a sealed capillary tube.

It is not unusual to observe a softening or shrinking just before melting, when solvent of crystallization is lost and crystal pattern changes. We take actual melting to begin when liquid is clearly visible.

It is important that we heat the sample slowly near its melting point to ensure that the mercury in the thermometer and the sample are at the same temperature. The rise in temperature should not be greater than about 1 C°/min, although the rate can be greater at somewhat below the melting point. When you do not know the melting point, you can save time by preparing two samples, using one to quickly obtain the approximate melting point at a high-temperature change rate, and the second to make the careful determination.

Record the melting point *range*—viz. mp 120–124 °C—along with indications of decomposition (d) and/or correction (cor). You will probably find that most substances with which you work will melt over a range rather than at a single point. Most *pure* organic compounds melt within a range of 0.5 C° or melt with decomposition over a range of about 1 C°.

Mixture Melting Points

The two components must be intimately mixed. Put approximately equal amounts of the two components in a small agate mortar or on a watch glass and grind them together thoroughly. Proceed with the melting point as described above.

Evacuated Tube Melting Points

Some organic compounds sublime appreciably at atmospheric pressure; others, because of combination with oxygen at elevated temperatures, decompose rather than melt. In

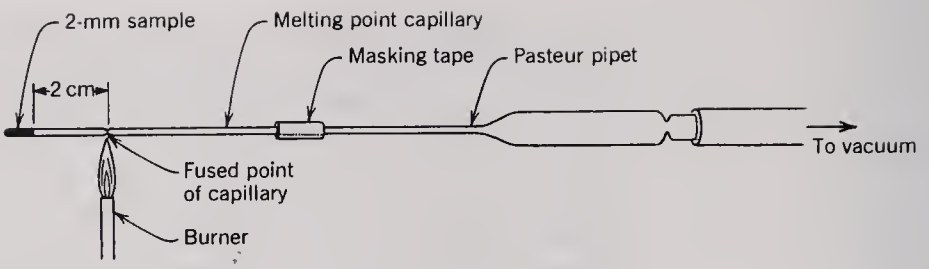


FIGURE 3.11 Making an evacuated melting point capillary.

either case, you can obtain a much more accurate melting point in a sealed, evacuated tube.

Load a 1–2 mm sample into the bottom of a melting point capillary in the usual manner. Next, attach the capillary to a Pasteur pipet or drawn out piece of glass tubing with a piece of masking tape wrapped tightly all the way around (Figure 3.11). Next, connect the large end of the pipet to a high-vacuum pump with a section of vacuum hose, turn on the pump, and evacuate the tube for about 30 s. If the sample sublimes easily under vacuum at room temperature, try cooling the sample-containing tip (*tip only*) in a cold bath during evacuation. Next, using a microburner, gently warm the melting point capillary about 2 cm above the sample to sublime away traces of crystals at that point. Then quickly increase the heating so that the capillary collapses and fuses at that point. Remove the masking tape and attach the capillary to the thermometer so that the sealed point on the tube is below the heating bath liquid. Finally, obtain the melting point in the usual way.

Before lighting a burner, check with your instructor for approved flame-permit areas and times.

3.4 BOILING POINTS DISCUSSION

Vapor Pressure and Boiling

A liquid is said to **boil** when vapor bubbles form within the interior of a liquid and break at the surface. For boiling to occur, the vapor pressure of the liquid must equal the external pressure acting on its surface. The vapor pressure is temperature-dependent, as shown by the vapor pressure-temperature curve for water in Figure 3.12. Notice that water has a low vapor pressure (4.6 torr) at its freezing point, but that it increases as temperature increases. The vapor pressure of water equals 760 torr, standard atmospheric pressure, when the temperature is 100 °C. Since boiling occurs under these conditions, 100 °C is called the **standard**, or **normal**, **boiling point** of water. Of course, if the atmospheric pressure (or other external pressure) is less than 760 torr, water will boil at a lower temperature than 100 °C. The temperature at which the vapor pressure of a liquid equals the external (usually atmospheric) pressure is defined as the **boiling point**. Liquids other than water have vapor pressure-temperature curves of a shape similar to that of water. Liquids with higher vapor pressures (lower boiling points) are said to be more *volatile*.

At any temperature within a closed vessel, molecules of liquid escape from the surface, and some molecules return from the vapor state back to the liquid. When the region above the liquid becomes saturated with vapor, the rate of return equals the rate of escape, and an equilibrium is established. The vapor pressure that defines the boiling point is measured at equilibrium. If we put a thermometer into a flask of boiling liquid we find that the boiling we usually observe occurs at a temperature slightly above the defined boiling point because observed boiling occurs under nonequilibrium conditions. A more accurate determination requires measurement under equilibrium conditions.

Several procedures exist for determining boiling points. We shall examine two common ways that represent compromises among accuracy, speed, and sample conservation.

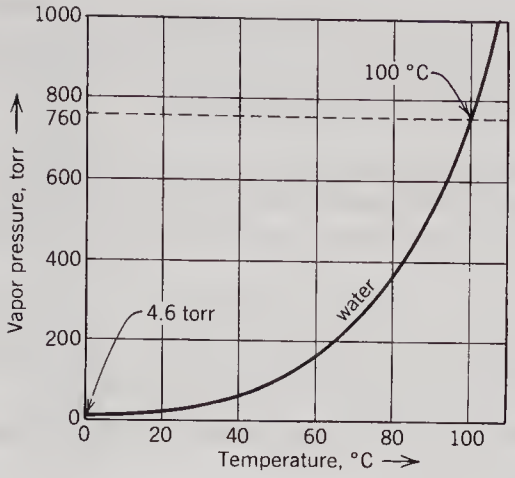


FIGURE 3.12 Vapor pressure—temperature curve.

Molecular Considerations

Empirically, we know that boiling points (1) increase as molecular mass increases within a series of compounds of the same class, (2) decrease with chain branching, and (3) increase with polarity.

In a homologous series, the increase in boiling point due to molecular mass is ascribed to the greater molecular surface area available for van der Waals interactions. Increase in branching gives a smaller molecular surface area and fewer intermolecular attractions to other molecules. Therefore branched molecules are less tightly held together. The increase in boiling point due to increasing polarity is because stronger intermolecular forces arise from more intense dipole charges.

It all adds up to the fact that molecules are more difficult to separate from each other when they are held more tightly together. Greater energy of separation requires a higher temperature, hence a higher boiling point.

3.5 BOILING POINT TECHNIQUES

The Distillation Method

We usually take the boiling point of a liquid that is being purified by distillation as the distillation proceeds. This method of purification is discussed in Technique 7. If you want to use the distillation method to obtain a boiling point, you can use a simple apparatus like that in Figure 7.1. With the distillation method you measure the temperature of the vapor, which is the same as that of the boiling liquid but which is less likely to be superheated or contaminated by the presence of other substances. The apparatus also permits you to distill over a few milliliters of contaminants, if necessary, before determining the boiling point.

During a distillation boiling point determination, the rate of boiling might vary, usually for one of two reasons: (1) Often the rate changes suddenly due to superheating of a portion of liquid that is not boiling smoothly. The sudden boiling might be violent enough to throw some of the superheated liquid up into the column of the flask and even out the side arm. Be sure to use boiling chips. (2) During distillation, lower boiling contaminants might first distill over, after which the boiling point rises.

Always insert the thermometer to the same point into the distilling flask or column and so that the mercury bulb is just below the side arm. Standard distillation flasks and columns of all sizes have the same distances from the top of the column to the side arm. Therefore, you can use the immersion ring on the thermometer to help set it in corks or rubber stoppers at a position so that the same mercury column length will always be exposed to vapors.

Examine your glassware for cracks and stars that might cause a vessel to break while being heated.

Be sure that the apparatus is open to the atmosphere at the receiver end. Pressure buildup in the apparatus can lead to an explosion if you heat a closed system.

Introduce water into the bottom of the condenser and remove it from the top. Cooling is most efficient this way because the entire space between the inner tube and jacket is filled with water. For liquids boiling at temperatures above 150 °C, do *not* put water in the condenser: it might break.

Use hose clamps to secure hoses to the condenser. A loose water hose could spray water into heating mantles or other electrical equipment or onto the hot oil of an oil bath. Spraying water might startle you or someone else and cause equipment to be upset.

Put about 10 ml of the liquid to be tested and a couple of boiling chips into a 25-ml distilling flask; then heat it to boiling. You might need to wrap the column with aluminum foil, leaving a small slit for observation.

Never add a boiling chip to an already heated liquid: sudden, violent boiling might occur.

Keep flames away from the vicinity of flammable vapors.

To save time, heat the liquid rapidly until boiling begins. Then heat it more slowly while the ring of condensing vapor rises up the column. (You might not be able to see the ring.) By carefully controlling the rate of heating, hold the condensate ring about 1 cm above the side arm. By this time the thermometer bulb will be bathed in vapor and you will observe hot liquid nearly in equilibrium with the vapor condensing on the bulb. Allow drops of liquid to condense and drip into the test tube receiver at the rate of about 1 drop/s. If the liquid being tested is pure, you will at first note a rapid rise in temperature as the condensate ring moves past the thermometer bulb; then you will observe a leveling to a constant temperature. Record this temperature as the boiling point. In the case of a known pure liquid like a boiling point standard, you can stop at this point. If, for a nonstandard liquid, the temperature levels off for a while and then rises more than about 1.5 C° and levels off again, more than one substance is present, and your liquid is not pure! However, as the flask empties, you might note a slight rise in temperature caused by superheating of the vapors. Ordinarily, you should distill the liquid until about only 2–3 ml remain. After each boiling point determination, put the liquid in the distilling flask and in the receiver into the recovery container provided for that liquid. Rinse the flask twice with wash acetone (IUPAC propanone), and put the rinses into the acetone recovery. Dry the flask of acetone by evaporation or blowing dry air from your laboratory air line into it (some lab air lines are quite dirty, however). Use fresh boiling chips for each new boiling point determination because when the wetted chip cools, liquid is drawn into the pores, and the boiling action depends on their being filled with air.

Whenever you determine a boiling point, record the atmospheric pressure.

The Siwoloboff Microtechnique

The Siwoloboff method has the advantages of being applicable to smaller amounts than the distillation method and of obviating errors caused by superheating of vapor and by lower boiling points sometimes observed for high-boiling liquids resulting from the time lag involved in transferring heat from the high-temperature vapor to the mercury. The Siwoloboff method is generally more accurate.

The Siwoloboff microtechnique utilizes a melting point capillary inverted in a length of 5-mm glass tubing which in turn is attached to a thermometer as shown in Figure 3.13.

Seal one end of a 10–12 cm piece of 5-mm-diameter glass tubing. Put in a few drops of the liquid to be tested; then attach the tubing to a thermometer with a thin slice of rubber hose so that the bottoms of the tube and thermometer bulb are at the same height. Put into the 5-mm tube a 6–7 cm melting point capillary tube with the sealed end up. Place the entire assembly in an oil or water bath (depending on the required temperature) with the rubber hose slice above the oil level so that it does not swell and allow the tube to fall off the thermometer. A Thiele tube works well for the oil bath.

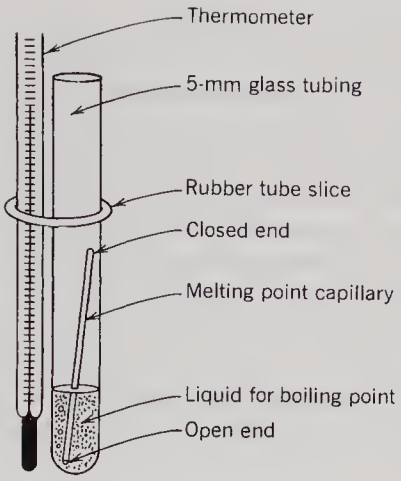


FIGURE 3.13 Siwoloboff boiling point system.

Heat the oil bath as you would for taking a melting point until bubbles rapidly and continuously emerge from the capillary and from its submerged tip. Immediately remove the heat source and record the temperature. The temperature will probably be slightly higher than the boiling point of the liquid. Next you must watch for the cessation of bubbles and the entry of liquid into the capillary. The boiling point is that temperature at which the liquid levels inside and outside the capillary are equal. (It is the boiling point because when the levels are equal, the vapor pressure inside the capillary must be equal to the atmospheric pressure.) Repeat the determination at least once. You might have to use a new capillary tube because the liquid that has entered the tube is not always easily expelled. However, if you begin reheating immediately after observing the boiling point you might not have to use a new capillary tube. Note that whenever you know the approximate boiling point you can save time by bringing the bath rapidly to just below the boiling point and then slowly raising the temperature slightly above and then lowering it again to get the boiling point. Calculate the mean temperature from your repeated determinations. Record the atmospheric pressure and make appropriate pressure and calibration corrections (Section 3.1).

Do not allow spilled liquids to come in contact with your skin or to evaporate into the laboratory atmosphere. Carefully absorb them into a paper towel and discard it into a container assigned by your instructor.

3.6 BOILING POINT CORRECTIONS

When you take boiling points at atmospheric pressures, the barometer rarely reads 760 torr. For normal atmospheric pressure deviations of up to 20 torr, you can obtain, for the usual lab thermometer, correction of a boiling point to 760 torr from the expressions

$$t_{cor} = t + 0.00012(760.0 - p)(t + 273) \qquad (3\text{-}2)$$

for nonassociated liquids, and

$$t_{cor} = t + 0.00010(760.0 - p)(t + 273) \qquad (3\text{-}3)$$

for associated hydrogen-bonded liquids such as water, alcohols, and carboxylic acids. In these equations, t = the observed temperature, and p = the observed atmospheric pressure in torr. As a rule you can expect that boiling points will change about 0.5 C° for a 10-torr change in atmospheric pressure at around 760 torr; at lower pressures, each halving of the pressure will result in about a 10 C° lowering of boiling point. If you do not make a pressure correction, you must record along with the boiling point the atmospheric pressure at the time of boiling point determination, for example, "bp 106 °C(746 torr)."

3.7 EXPERIMENTAL PART

Your anticipated use of your thermometer might help you decide whether to use boiling point or melting point standards, or your Instructor might have specific requirements in mind. If your laboratory has an electrical resistance melting point apparatus, you will probably calibrate your thermometer by using distillation method boiling points. Your thermometer then will be calibrated under conditions of the many distillations you will perform during the next several months.

Inspect your thermometer. Make certain that there are no breaks in the thread of mercury. Compare your thermometer to Figure 3.1, seeking in particular the immersion ring. Whether the thermometer is designed for 25-mm immersion, 75-mm immersion, or total immersion is immaterial if you are going to calibrate it. If you are going to use the thermometer for both melting and boiling point determinations, you will need to calibrate it both ways.

A. Melting Point Thermometer Calibration

Time Required: 3½ hr

Review Techniques and Principles: Lab notebook (1)

Calibration. Select from Table 3.1 reference substances that your instructor recommends, using solids melting 30–40 C° apart. Using the Thiele tube method of Section 3.3, obtain a melting point for each substance, being careful to insert the thermometer into the oil the same distance each time (to the melting point immersion ring or 25 mm). Make a table of melting points, like Table 3.2. Label your thermometer with your name and notebook page identification so that it will not be confused with someone else's.

TABLE 3.1 Some Reference Standards for Calibration of a Thermometer by the Melting Point Method

Substance	*Melting Point °C*
Ice–water	0.0
[a]1,4-Dichlorobenzene	53.1
Phenylacetic acid	77
1,2-Dihydroxybenzene (catechol)	105
Acetanilide	114.3
Benzoic acid	122.4
Urea	135
Propanedicarboxylic acid (malonic acid)	135.6
Monophenylurea	147
Citric acid	153
Salicyclic acid	159
Butanedicarboxylic acid (succinic acid)	188
3,5-Dinitrobenzoic acid	205
[a]Anthracene	216.2–216.4

[a]Sealed tube required because of sublimation.

TABLE 3.2 Collection of Temperature Data

Standard Substance	*Literature Temperature, °C*	*Observed Temperature, °C*
Water–ice	0.0	0.5
N-Phenylbenzenamine (diphenylamine)	53.5	54.4
8-Hydroxy quinoline	76	77.0
N-Ethanoylbenzenamine (acetanilide)	114.3	114.3
Monophenylurea	147	146

Plot the observed thermometer temperatures as abscissae and the literature values as ordinates. Using a good graph paper, connect the points to make a smooth curve. Paste or tape the plot into your notebook so that it becomes a permanent part thereof.

Computer analysis. If your chemistry department has an appropriate personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR*, and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations. You can use the computer disk to work on certain postlaboratory questions as well as experimental data.

To save on computer time, you should have the following information ready to use: for thermometer calibration—experimental melting point and the corresponding literature melting point; for melting point correction from calibration data—the observed temperature; for melting point correction by stem correction—the observed temperature, the coefficient of thermal expansion, the number of degrees on the thermometer above the bath fluid, and the temperature at the center of the nonimmersed portion of the stem.

Writing the discussion. Discuss the reasons for differences in literature and observed melting points.

B. Calibration for Boiling Point of a Thermometer

Time Required: 3½ hr

Review Techniques and Principles:

Lab notebook (1)
Glassware (0.2)

Calibration. Select from Table 3.3 reference substances that your instructor recommends, using liquids boiling 30–40 C° apart. Using the distillation method of Section 3.5, obtain a boiling point for each substance, being careful that the thermometer is inserted into the distillation head the same distance each time (so the top of the thermometer bulb is even with the bottom of the side arm).

Wrap the flask and column to above the side arm with aluminum foil for the substances boiling at temperatures greater than 90 °C. This will help to prevent cooling of the column and resulting condensation of vapors before they reach the thermometer

TABLE 3.3 Some Reference Standards for Calibration of Thermometer by the Boiling Point Method

Substance	*Boiling Point at 760 torr, °C*
Dichloromethane (methylene chloride)	40
Acetone	56.2
Chloroform	61.7
Methanol	64.96
Tetrachloromethane (carbon tetrachloride)	76.54
Water	100.0
Toluene	110.6
Chlorobenzene	132
Bromobenzene	156
Cyclohexanol	161.1
Aniline	184.13
Benzyl alcohol	205.35
Methyl salicylate	223.3
Quinoline	238.05

bulb. Do not let the aluminum foil come in contact with a heating mantle. When you are finished with a given liquid, pour it into its assigned recovery container.

Make a table of boiling points similar to that shown in Table 3.2. Include a fourth column for the observed boiling point corrected to 760 torr (use the boiling point correction method of Section 3.5). Be sure to label your thermometer with your name and notebook page identification so that at some future time it will not be confused with someone else's.

Using a good graph paper, plot the pressure-corrected boiling points as abscissae and the literature values as ordinates. Connect the points to make a smooth curve. Paste or tape the plot into your notebook so that it becomes a permanent part thereof.

Computer analysis. If your chemistry department has an appropriate personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR*, and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations. You can use the computer disk to work on certain postlaboratory questions as well as experimental data.

To save on computer time, you should have the following information ready to use: for thermometer calibration—experimental boiling point, the corresponding literature boiling point, the atmospheric pressure, and whether the liquid is associated or nonassociated; for boiling point correction from calibration data—the observed temperature, the atmospheric pressure, and whether the liquid is associated or nonassociated; for boiling point correction by pressure correction only—the observed boiling point, the atmospheric pressure, and whether the liquid is associated or nonassociated; for boiling point correction with stem correction—the observed boiling point, the coefficient of thermal expansion, the number of degrees on the thermometer above the fluid (above the immersion ring or the inside of the still head), the temperature at the center of the portion of the stem above the immersion ring or the inside of the still head bathed in vapors, the atmospheric pressure, and whether the liquid is associated or nonassociated.

Writing the discussion. Discuss gradual or sudden changes in observed boiling points and propose reasons for the same; your calculated pressure corrections of observed boiling points relative to significant figures allowed by reading your thermometer; and reasons for observed differences in literature and experimental boiling points.

C. Identification of an Unknown Solid

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook (1)

You will be given a sample of one of the following compounds: urea (mp 135 °C), malonic acid (IUPAC: propanedicarboxylic acid, mp 135.6 °C), L-arabinose (mp 159–160 °C), or salicylic acid (IUPAC: 2-hydroxybenzoic acid, mp 159 °C).

Procedure. Obtain a melting point by one of the ways described in Section 3.3 to determine with which compound you are working. Then make mixture melting point determinations as described in Section 3.3 to identify your unknown.

Writing the discussion. State the identity of your unknown. Then, based on your experimentation, defend your conclusion. Discuss the purity of your unknown by comparing the experimental melting point with the literature melting point and explaining wide, high, or low melting point ranges.

3.8 EXERCISES

Prelaboratory

1. At what part of your thermometer will you expect to find an immersion ring?
2. List the basic steps used to calibrate a thermometer.
3. What are two ways that the impurity of a substance will be indicated by its melting point?
4. To what rate of temperature change should a sample be subjected as the melting point is approached? Why is the rate important?
5. When you do not know the melting point of a sample, how can you save time during the melting point determination?
6. What does "cor" mean? What justifies its use when reporting a melting point?
7. How much sample should be put into a melting point capillary?
8. List steps, including sample preparation, necessary in taking a melting point in a Thiele tube.
9. Why must the rubber hose slice be kept above the level of an oil bath?
10. List two methods for determining boiling points along with their advantages.
11. List the steps necessary in taking a distillation boiling point.
12. Where should the condensate ring be held during distillation determination of a boiling point?
13. How fast should drops of liquid be allowed to drip into a receiver during boiling point determination by the distillation method?
14. List the steps necessary in taking a Siwoloboff boiling point.
15. Define boiling point. How does this definition relate to the Siwoloboff method of determining boiling points?
16. Why are boiling chips changed after each determination of distillation boiling point?
17. A student was obtaining a distillation boiling point on a liquid with a fairly high boiling point. The distillation temperature was observed to fluctuate. Suggest a reason for such temperature behavior and a remedy for it.

Postlaboratory

1. What is the corrected temperature of a liquid that has an apparent temperature of 250.00 °C when measured on a 300.00 °C maximum borosilicate glass total-immersion thermometer immersed to 30.00 °C and when the temperature at the center of the nonimmersed portion of the mercury thread is 110.00 °C?
2. What is the corrected temperature of a liquid that has an apparent temperature of 50.0 °C when measured on the thermometer with the calibration curve of Figure 3.3?
3. What is the corrected boiling point of a nonassociated liquid whose observed boiling point is 58.20 °C at 740.0 torr as measured on the thermometer with the calibration curve of Figure 3.3?
4. The melting point of NaCl is 801 °C, that of benzocaine ($C_9H_{11}NO_2$) is 91–92 °C. Describe the melting point behavior you would expect for benzocaine mixed with about 10% sodium chloride and explain.
5. The melting point of a pure unknown was found to be 80.1 °C. The unknown was thought to be one of three known compounds all with a melting point of 80.1 °C. Describe the procedure for identifying the unknown as one of the three knowns.
6. $CH_3CH_2CH_2CH_2$—OH and CH_3CH_2—O—CH_2CH_3 are position isomers. Why does the former have a higher boiling point?

7. A student had one vial containing pentane and another containing its position isomer, 2,2-dimethylpropane (neopentane). The vials were unlabeled and he decided to identify them by boiling point. Without looking in a handbook, he knew which would have the lower boiling point. Explain.
8. Draw a melting point composition phase diagram like that of Figure 3.6 using the following data: t_A = 40 °C, t_B = 160 °C, t_E = 30 °C, eutectic composition = 97 mole% A and 3 mole% B. Draw a curve that will show how presence of 6 mole% B could *raise* the apparent melting point of A.
9. Using the theory for the effect of impurities on the melting point of a solid, explain how impurities affect the freezing point of a liquid.

TECHNIQUE 4

FILTRATION

Filtration is the process of causing a liquid-solid mixture to encounter a porous barrier so that the liquid passes through and the solid is left behind. The liquid that passes through is called the **filtrate,** and the remaining solid is the residue, or **filter cake.** In general, there are two purposes for filtrations: (1) to remove solid *impurities* from a liquid, and (2) to separate solid *product* from a liquid. The procedure is primarily the same in either case. There are basically two types of filtration: gravity and vacuum.

4.1 FILTER PAPER

Filter paper, available in many kinds, sizes, and grades, forms the primary barrier in most filtrations. Common terms that relate to the properties of filter papers are (1) **flow rate,** a relative measure of how fast a liquid will pass through the paper, (2) **retention,** the ability of the paper to prevent passage of solid particles, and (3) **porosity,** the number and sizes of pores in the paper. A moment's reflection will show you that the three terms are inter-related, as you can further ascertain by looking at Table 4.1, which lists some common types of general-purpose filter paper.

TABLE 4.1 Properties of Filter Papers

Type and Designation					*Particle Size Retained, mm*		
Whatman	*Fisher*	*VWR*	*Flow Rate*	*Porosity*	*Whatman*	*Fisher*	*VWR*
4	—	617	Very rapid	Coarse	20–25	—	Coarse Gelatinous
1	P8[1]	615	Rapid	Medium coarse	20–25	10	Coarse
2	P5[2]	613	Medium	Medium	8	6	Medium
3	P4	610	Slow	Fine	6	2	Fine
5	P2	—	Very slow	Very fine	2.5	<2	

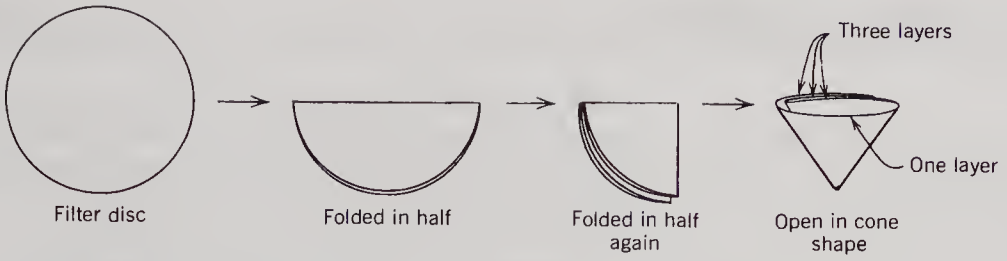


FIGURE 4.1 Folding a filter cone.

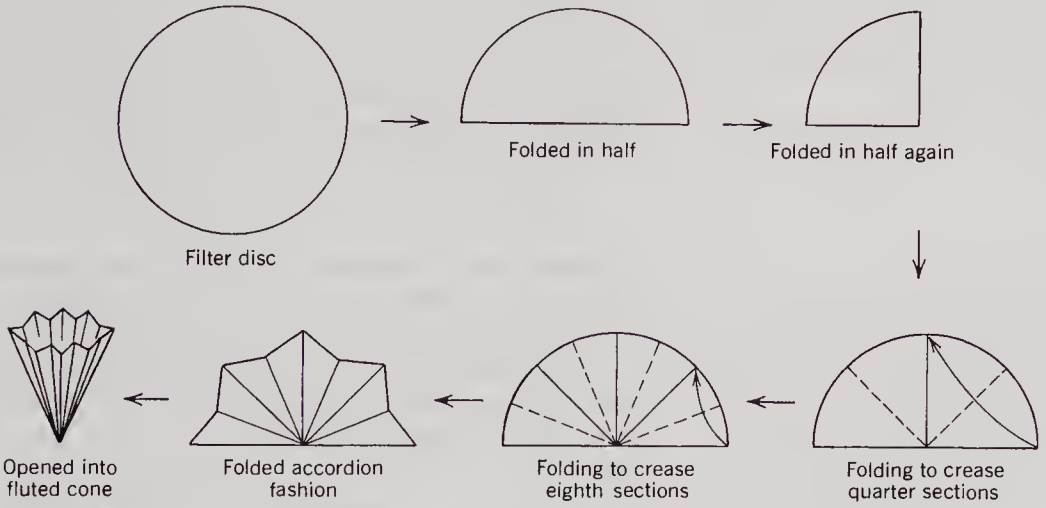


FIGURE 4.2 Fluting filter paper.

For most filtrations, you will use disc-shaped paper. You will use the paper as a flat disc for vacuum filtration. For gravity filtration with a conical funnel you will use one of two common forms: (1) cone-shaped (Figure 4.1), and (2) fluted (Figure 4.2).

To choose appropriate filter paper for a particular application, you must know something about the size of particles you are to remove and the kind of filtration you are to perform. For example, you would not choose a porous paper to trap fine particles, especially when using vacuum filtration.

In gravity filtration, choose a cone shape when the solid to be collected is the product you want to keep and when you must be able to easily remove the product from the filter. For example, if your product consists of very fine crystals or a pasty material, you can scrape it from a conical filter more readily than from the folds of a fluted filter.

Choose a fluted shape when rapid filtration is important, as it is in filtering a hot solution from which crystals readily precipitate. A fluted filter hastens filtration first by providing a large surface for the mixture to run through, and second by permitting air to leave the flask along the folds. A fluted filter is satisfactory for collecting product crystals when they are large and easy to remove from the filter paper.

To make a cone-shaped filter, please refer to Figure 4.1. Fold the filter disk in half, then in half again. Then open it into a cone shape so that half of the cone has three layers and the other half has one layer.

To make a fluted filter, please refer to Figure 4.2. Fold the filter disc in half, then in half again. Open it to a semicircle; then fold each quarter toward the center so that a crease is made down the center of each quarter section. Next, crease each eighth section down the center. Now there are creases wherever you are to make the fold. Starting at one end of the open semicircle, make the pie-shaped eighth folds again, but this time in fan or accordion fashion, making each fold in the direction opposite to the previous one. Separate the two semicircular sides and crease the folds once more lightly in order to strengthen the fluting. Open into a fluted cone.

4.2 GRAVITY FILTRATION

To get ready for gravity filtration, first select a filter paper with the properties you need and of such size that the top of the folded paper will be 5 or 10 mm below the rim of the funnel. For the ordinary conical funnel, the radius of the paper will be a little less than the diameter of the funnel (funnel size). For example, you use a 60-mm radius (120-mm-diameter) paper for a 65-mm funnel.

After you have selected the filter paper, prepare the conical or fluted filter, place it in the cone of the glass funnel, and put the funnel in the neck of an Erlenmeyer flask (see Figure 4.3). If the setup will be at all top heavy, clamp the flask to a ringstand so it will not tip, or support the funnel in a ringstand ring above the flask. Next, to make the filter paper stay where it belongs and to rinse down any loose fibers from the filter paper, wet the filter with a few milliliters of solvent involved in the procedure to follow. Discard the rinsings and pour in the mixture to be filtered, portionwise if necessary. For more about techniques of filtering hot and cold mixtures, please refer to Section 5.3.

Sometimes a funnel sits so tightly in the neck of an Erlenmeyer flask that air cannot easily escape from the flask. This slows down or stops filtration. You can easily circumvent such a problem by putting a hose clamp, paper clip, of wad of paper between the funnel and flask neck, as shown in Figure 4.3.

When you are working with small amounts of liquid, you can make a filter by putting a small, loose plug of glass wool just above the narrow part of an eye dropper. Using a second eye dropper, drop the solution into the wide part of the eyedropper filter. The technique is illustrated in Figure 4.4.

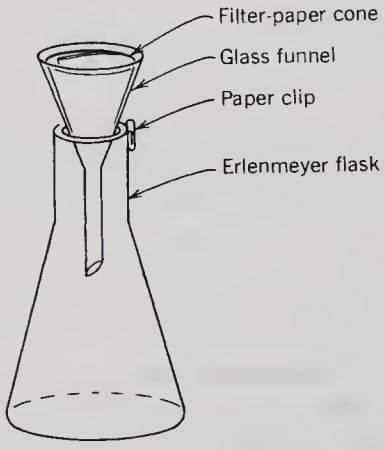


FIGURE 4.3 Gravity filtrations.

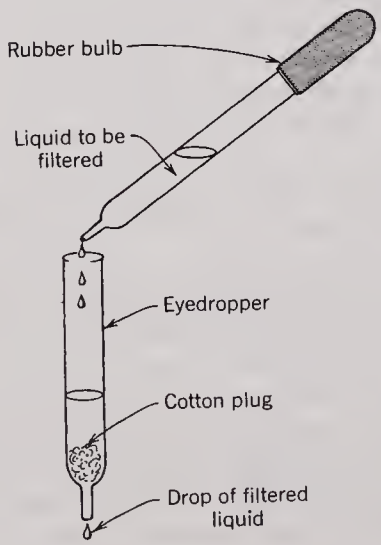


FIGURE 4.4 Eyedropper filter.

4.3 VACUUM FILTRATION

The Water Aspirator

The most common source of vacuum in the laboratory is the **water aspirator,** or water pump, illustrated in Figure 4.5. The aspirator operates on the Bernoulli principle: when a fluid moves above a certain speed in a pipe it creates a turbulence. The turbulent behavior of the fluid creates friction along the walls of the pipe. When the turbulent fluid passes by a small opening in the pipe, frictional forces drag air into the pipe. On the water aspirator, the small opening is in the form of a nipple. Attachment of a flask or other closed vessel to the nipple by a thick-wall hose allows air to be drawn by the Bernoulli principle out of the flask, thereby creating a vacuum. The maximum vacuum attainable by a water aspirator is no greater than the vapor pressure of water, ordinarily about 25 torr. Still, that is an appreciable vacuum.

To generate the Bernoulli effect, the velocity of water passing through the aspirator must be high; so turn on the water full blast when using a water aspirator.

Filtration

Vacuum filtration (suction filtration) is faster than gravity filtration. A vacuum filtration apparatus is shown in Figure 4.6. A Büchner funnel is used for large filter cakes and a Hirsch funnel for small ones. Place a Büchner or Hirsch funnel in a neoprene adapter on a filter flask (suction flask). If a neoprene adapter is not available you can use a rubber stopper with a hole the size of the funnel stem's midpoint. Connect the filter flask nipple to the water trap with heavy wall tubing (thin-wall tubing will collapse when the system is evacuated). Connect the nipple of the trap to the water aspirator. Clamp the flasks to a ringstand because the assembly is quite top heavy and will fall easily. Choose a filter paper with the desired porosity characteristics and of such a size that the diameter of the filter is *slightly* smaller than the diameter of the funnel. The paper should be small enough to remain flat but large enough to cover the holes in the filter plate. Put the paper on the plate and wet it with a small amount of the liquid to be used in the filtration so the paper will adhere to the plate and prevent materials from passing under the paper during filtration.

Next, turn on the water full blast and then pour the mixture to be filtered onto the filter paper. The partial vacuum created by the water aspirator will draw the filtrate into the suction flask, leaving the solids behind. When most of the liquid has been drawn through the filter cake but before the residue has begun to air dry, it is customary to rinse the cake with a small amount of liquid to help remove impurities that were dissolved

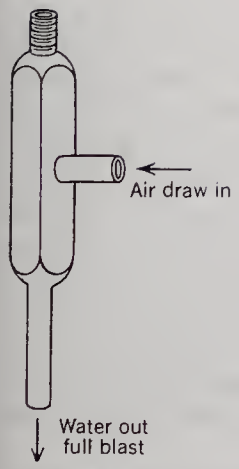


FIGURE 4.5 Water aspirator.

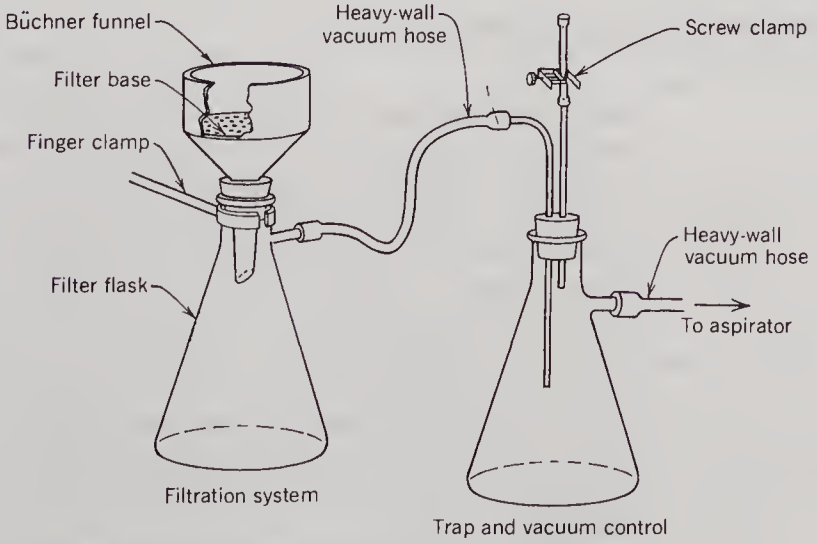


FIGURE 4.6 Vacuum filtration apparatus.

in the filtrate. Allow filtration to continue until dripping into the filter flask is reduced to about 1 drop/5 sec. A detailed description of suction-filtering crystals from a solution is given in Section 5.3.

If you can, work with a shield between yourself and systems under vacuum.

To avoid implosions, carefully inspect for flaws in all glassware to be used in suction filtration.

Sometimes water pressure at the aspirator falls off considerably, particularly when many people are using water at the same time. If the water pressure gets too low, the vacuum already produced in the filter flask can draw water through the side arm of the aspirator into the suction flask were it not for the trap. Also to prevent water from entering the flask, you should *never turn off the water before the screw clamp on the trap is opened.* If water starts to flow into the apparatus, you can stop it by opening the screw clamp.

When many people are using water aspirators, you should watch to see that sinks at the ends of the lab bench do not overflow.

To prevent slipping and falling, always promptly clean up water spilled on the floor.

4.4 REMOVAL OF RESIDUES FROM FILTERS

You can remove reasonably large or loose crystals from a conical or fluted filter by turning the filter on its side or upside down and tapping it with a spatula. Or you can gently rake them out with your spatula or flat-end stirring rod.

To remove loose crystals from a Büchner or Hirsch funnel, tilt the funnel on its side and gently rake the crystals out.

Removing a finely divided or pasty residue requires careful manipulation so as to avoid removing filter paper fibers along with the residue. If you can, gently scrape the residue from the filter with the flat side of the spatula rather than the end. To do this, you might find it advantageous to remove the filter paper from a Büchner plate or to open a conical filter. Then lay it on a flat glass plate or a clean sheet of paper on the bench top. Sometimes you can bend the filter paper backward and the residue will fall off. You must remove some pasty residues from the filter while they are still damp because they become tightly pasted to the filter paper as they dry.

4.5 DIATOMACEOUS EARTH FILTERS

Some precipitates are so fine and/or so gelatinous that during filtration they either pass through or clog the pores of the filter paper, rendering the filtration very tedious or practically impossible. For such precipitate, you can make your work easier if you aid the filtration capability of paper by covering it with a layer of **diatomaceous earth,** a chemically inert, finely ground preparation of diatom shells found as mineral deposits in ancient seabeds. Celite®, Hyflo Supercil®, and Filter Aid® are commercially available brands of diatomaceous earth. You can more easily remove tiny and/or gelatinous particles from a filtrate when you use diatomaceous earth because the surface area of the trapping filter medium is now much increased and the tiny precipitated particles cannot pack as closely together. Filtrations using diatomaceous earth are, of course, used only when the *filtrate* contains the desired product. Also, you would not use a diatomaceous earth filter when crystals of product might separate from the filtrate and deposit in the filter.

Using a convenient size beaker, make a slurry of a diatomaceous earth by stirring it into a liquid. (A thin suspension of a finely divided solid in a liquid is referred to as a

slurry.) Choose the liquid on the basis of its ability to satisfactorily suspend the solid and its compatibility with solvents to be used in the filtration that will follow. Suitable liquids for diatomaceous earth are water, methanol, ethanol, or chloroform (IUPAC trichloromethane). For an 8-cm-diameter funnel, use two or three tablespoons of the filter aid. Assemble a suction filtration apparatus like that shown in Figure 4.6 and turn on the water aspirator. In a single addition, pour the well-mixed slurry onto wet, medium porosity filter paper resting on the Büchner funnel filter plate. Form a level layer from 1 to several mm thick, depending on the type and amount of material to be filtered. The funnel must be level as you pour the slurry. If some diatomaceous earth comes through into the filter flask, suck a small wash of solvent through the system and put the solvent in its appropriate recovery vessel. Draw the liquid down to the top of the filter so that it is still moist on top. *Do not allow the filter to dry out* or it will crack.

Use this filter in the same way you would use a simple filter. When you pour the solution onto the filter you must do it *gently* so as to not disturb the surface of the filter. An alternative is to put a patch of filter paper over a small part of the surface of the diatomaceous earth and pour onto the patch.

4.6 EXPERIMENTAL PART
Precipitation and Filtration of Benzoic Acid

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Testing pH	(0.11)
Cooling	(0.5)
Drying solids	(2.1)
Melting points	(3.2)
Storing	(0.12)
Labeling	(0.13)

You will be given 10 ml of a 10% by weight aqueous solution of sodium benzoate (IUPAC sodium benzenecarboxylate) to which a small amount of floor sweepings has been added. Your problem is to remove the floor sweepings and obtain benzoic acid (IUPAC benzenecarboxylic acid) by precipitating it according to the reaction.

Recovery of benzoic acid. Tare a graduated cylinder or other container. After the mixture has been added to it, weigh the container again to determine the mass of the mixture.

Using a medium to coarse porosity filter paper, separate the floor sweepings from the mixture by gravity filtration. Collect the filtrate in a tared 50-ml or 125-ml Erlenmeyer flask. Weigh the flask again to determine the mass of the solution. Then dropwise with swirling, add concentrated hydrochloric acid to the clear filtrate until the pH of the liquid is about 2 as indicated on pH paper. Cool the mixture to room temperature or somewhat lower. The precipitate that forms will produce a thick aqueous slurry. Pour and scrape the mixture into a Hirsch funnel set up for vacuum filtration according to the instructions in Section 4.4. Be sure the water aspirator is on full blast when you begin to pour. Rinse all residue from the Erlenmeyer flask by adding small amounts of cold water and pour the rinsings onto the filter cake in the funnel. Let suction continue until drops of filtrate come through at a rate of about 1 drop per 3 s. Discard the filtrate down a drain only after you are certain that an adequate yield has been obtained.

Remove the filter paper with the filter cake from the funnel and set it on a watch glass to dry. Do not use an oven for drying because benzoic acid sublimes appreciably

at elevated temperatures. When the benzoic acid is dry it will easily peel off the filter paper.

Obtain a melting point and weigh the product. Put the product in a labeled vial and submit it to your instructor. Remembering that sodium benzoate was present to the extent of 10% of the original solution, calculate the approximate number of moles of sodium benzoate in the gravity-filtered solution, and the number of moles of dry benzoic acid recovered. Noting that the benzoic acid is produced from sodium benzoate in a 1-to-1 mole relationship, calculate that percent recovery of product based on the original mixture and on the gravity-filtered solution.

Writing the discussion. Discuss the two percent yields, considering the following: How do you account for loss in mass after gravity filtration? How does this loss in mass compare to loss in mass of final product? How does loss in moles compare? Is some product unavoidably lost during filtration? If so, what factors lead to the loss? Discuss the purity of the product as evidenced by its melting point compared with a literature melting point. Critically evaluate your technique and suggest how you could improve it in future filtrations.

4.7 EXERCISES

Prelaboratory

1. Describe the size filter paper that should be used in a Büchner or Hirsch funnel.
2. Why should a Büchner funnel apparatus be clamped in place?
3. With what solvent is a filter paper wetted before filtration begins?
4. How fast should water run through a water aspirator during suction filtration?
5. How thick should a diatomaceous earth filter be?
6. About what diameter filter paper should be used in a 120-mm conical funnel?
7. A student used a filter paper that was too large for the Büchner funnel and had to fold it up around the edges. Criticize this technique.

Postlaboratory

1. In terms of the Bernoulli effect, why is the water aspirator turned on full blast? Why then does a water pressure drop cause water to run out of the aspirator side spout?
2. Why will water be drawn into a suction filtration apparatus if the water aspirator is turned off before the screw clamp of Figure 4.6 is opened?
3. If you were preparing a diatomaceous earth filter and the solution to be filtered immediately afterwards contained a nonproduct precipitate suspended in 1-pentanol, what solvent would you use for the slurry? In preparing your answer, check in a handbook of chemistry and physics or similar source the solubility relationships of the various liquids.
4. Why might it be possible in some climates to get higher vacuum from a water aspirator in the winter than in the summer?
5. A student suction filtered a near boiling solution from which she wanted to save the filtrate. After attaching the hose from flask to aspirator, she turned the water on full blast and then poured the hot solution rapidly into the Büchner funnel. Criticize this technique.
6. A student prepared a conical filter, put it in a glass funnel, and rinsed it with water. Next he poured in a dilute hexane solution of a fatty acid which was contaminated with floor sweepings. Criticize this technique.

TECHNIQUE 5

RECRYSTALLIZATION

One of the major processes encountered in the organic laboratory is the purification of solids, for which recrystallization is the most useful method. (Another method, sublimation, is discussed in Appendix A.) *Recrystallize* literally means to crystallize (form crystals) again. The process essentially consists of dissolving impure crystals in an appropriate hot solvent and then cooling the solution. The cooling causes deposition of product crystals, often in shapes and arrangements of much interest and beauty. The impurities remain dissolved in the cold solvent.

5.1 DISCUSSION OF CRYSTALLIZATION

Crystallization Theory

Recrystallization from a solvent depends first on the fact that most solids are more soluble in hot solvents than cold solvents, and second that different materials are soluble to different extents in various solvents. In order for recrystallization to be successful, there must be a *large* difference in solubility of the solid material in hot solvent as compared to cold solvent. When you put a solid into a solvent and heat it, a solution results:

$$\text{solid} + \text{solvent} \underset{-\text{ heat}}{\overset{+\text{ heat}}{\rightleftharpoons}} \text{solution} \qquad (5\text{-}1)$$

When you cool the solution, solid separates again because it is less soluble at the lower temperature. Sometimes the process is called **crystallization** when the crystal grows slowly and incorporates only product molecules; and it is called **precipitation** when the crystal grows rapidly and incorporates impurities as well as product.

Crystallization is usually more desirable than precipitation because it results in a purer product. When the hot, saturated solution is allowed to cool slowly, a small crystal initially forms and grows slowly as the solubility of the dissolved material is decreased by cooling. If at any time during this process the temperature is held constant, an equilibrium is established, that is, the molecules leaving the crystal and molecules attaching to the crystal are equal in number. Equilibrium encourages the growth of crystals made up of just one kind of molecule because orientation of molecules in a crystal lattice is an exacting and selective process.

It is unusual for different materials to crystallize in the same lattice. However, if the equilibrium of equation 5-1 is shifted rapidly by sudden cooling, some impurity molecules will also deposit on the crystal because they can not get out of the way quickly enough as the crystal is being formed. Furthermore, rapid cooling causes formation of smaller crystals with a large combined surface area, making it difficult to wash them clean. Therefore the shift in equilibrium should be relatively slow. But if the shift in equilibrium is too slow, it is possible for a crystal to grow around molecules of solvent and impurities, forming a sealed-in pocket. Therefore, as a general rule of thumb, most successful recrystallizations take from 10 min to 24 hr, depending on the material to be recrystallized, the impurities present, and the solvent system used. For these reasons you should record the length of time you allowed the crystallization to proceed. Subsequent melting point

or other determinations of purity will then suggest whether you should have proceeded with a different rate of crystallization (rate of cooling).

Most recrystallizations involve purifying crude product crystals that have impurities in the crystal lattice and adhering to the surface. Because impurities generally have solubility characteristics that are similar to those of the desired product, you can successfully separate the product from such impurities only when there is either a considerable difference in their solubilities or when the impurity is present in relatively small quantity.

Consider the case shown in Figure 5.1. The solubility curve for product A shows that at 80 °C, 10.0 g are soluble in 100 ml of solvent. Impurity B has a similar solubility curve. If you initially dissolve 10.0 g of A and 11.0 g of B in 100 ml of solvent at 80 °C, cooling the solution to 30 °C precipitates 5.0 g of A along with 7.5 g of B (11.0 − 3.5), a very unsuccessful operation. However, if the original solution at 80 °C contains 3.5 g of B or less, the solution can be cooled to 30 °C without precipitating any B, and you can recover 5.0 g of pure A. 5.0 g of A and all of impurity B will remain in the leftover solution known as the **mother liquor.**

Sometimes you must repeat crystallization to obtain pure product crystals. If 10.0 g of A and 5.0 g of B are present in the initial solution at 80 °C, cooling the solution to 30 °C will precipitate 5.0 g of A mixed with 1.5 g of B. This leaves 5.0 g of A and 3.4 g of B in solution. The ratio A/B has improved from 10/5 to 10/3, but A is still not pure. If you now dissolve the precipitated mixture in 50 ml of fresh solvent and heat it to 80 °C, all 5.0 g of A and 1.5 g of B will dissolve (this is equivalent to putting 10.0 g of A and 3.0 g of B in 100 ml at 80 °C). Cooling again to 30 °C will deposit 2.5 g of pure A and no B!

In our first example, you noticed that 7.5 g of A was not purified. Such loss is a universal aspect of recrystallization, and you can do nothing to prevent it. Of course, you would lose less A if A were less soluble at the lower temperature, if B were more soluble, or if B were present in smaller amount. You can see therefore that you should take care during prior syntheses and separations to see that your methods minimize presence of impurities.

Sometimes even though enough solute will dissolve to produce a saturated solution at the higher temperature the solute will not precipitate again as the solution is cooled. Such a situation results in a cold, *supersaturated* solution, which contains more solute than is required for saturation. Supersaturation occurs when the first crystals do not form readily.

Solvent System

The most crucial feature of recrystallizing is the selection of solvent because the product should exhibit reasonably high solubility in hot solvent and low solubility in cold solvent.

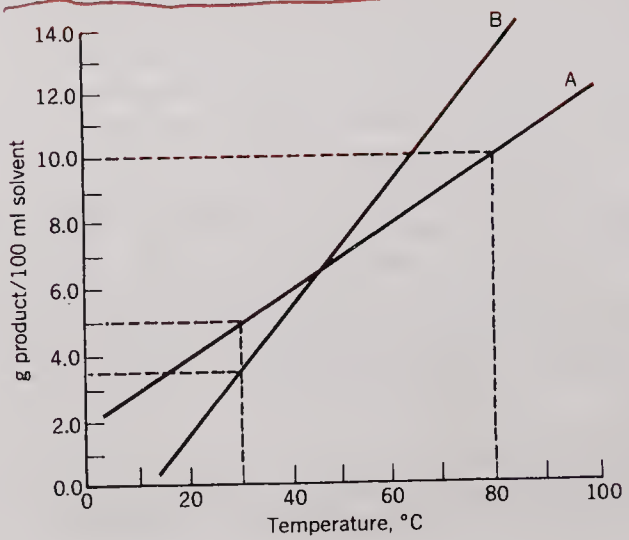
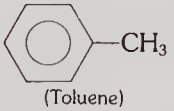


FIGURE 5.1 Solubility curves.

TABLE 5.1 Solvents. In General, Polarity Increases from Bottom to Top

Class of Solvent	*Generalized Structure R = alkyl or aryl*	*Example*
Water	HOH	HOH (Water)
Carboxylic acids	RCOH ‖ O	$CH_3C(=O)OH$ (Acetic acid)
Carboxylic acid amides	RC(=O)NR_2	$HC(=O)N(CH_3)_2$ (*N*, *N*-Dimethylformamide)
Alcohols	ROH	CH_3CH_2OH (Ethanol)
Amines	RNH_2, R_2NH, R_3N	$(CH_3CH_2)_3N$ (Triethylamine)
Ketones	R—C(=O)—R	$CH_3C(=O)CH(CH_3)CH_2CH_3$ (3-Methyl-2-pentanone)
Esters	R—C(=O)—OR	$CH_3C(=O)OCH_3$ (Methyl acetate)
Alkyl halides	R—Cl	$CHCl_3$ (Chloroform)
Ethers	R—O—R	$CH_3CH_2OCH_2CH_3$ (Ether)
Aromatic Hydrocarbons	Ar—R	 (Toluene)
Alkanes	RH	$CH_3CH_2CH_2CH_2CH_3$ (Pentane)

The slope of the solubility curve should obviously be steep. Because, in practice, solubility curves like those in Figure 5.1 are usually not available, you will select solvents either by consulting the chemical literature or by trial and error, using your knowledge of solvent and product structures.

The solubility of an organic substance depends on the polarities and sizes of the solute and solvent molecules. For a first approximation, one can use the rule of thumb, "like dissolves like." That is, if solute is polar, it will require a polar solvent to dissolve it. For example, CH_3OH dissolves in HOH but not in $CH_3CH_2CH_2CH_2CH_3$. In order to choose a good recrystallization solvent, the solubility of the solute in the solvent should be marginal at room temperature. You will find that it takes some practice to choose a solvent for a particular application, but you can start by trying to choose one from Table 5.1.

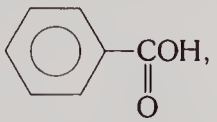
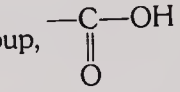
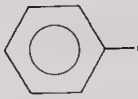
Let us choose a solvent for recrystallizing benzoic acid,  ,

TABLE 5.2 Commonly Used Solvent Pairs

Ethanol-water
Acetic acid-water
Acetone-water
Dioxane-water
Chloroform-methanol
Petroleum ether-diethyl ether
Petroleum ether-toluene
Ligroin-toluene

has a polar functional group,  , which is attractive to the polar functional groups that we find in water, alcohols, amines, aldehydes, ketones, amides, and other acids. However, the phenyl ring of benzoic acid is nonpolar and is attracted to less polar solvents like ethers, benzene, and alkanes. We should guess that benzoic acid will be too soluble in benzyl alcohol,  , because of structural similarities. We should expect it to be marginally soluble in water, partly soluble because of the polarity likeness of the two hydroxyls, and partly insoluble because of the differences in polar hydroxyl and nonpolar phenyl.

When you can not find a single common solvent that is satisfactory for recrystallization, you can use a solvent pair. You can make a solvent in which crystals are too soluble less solubilizing by adding a second miscible solvent in which the crystals are much less soluble. Table 5.2 lists a number of common solvent pairs. The ligroin and petroleum ether listed in Table 5.2 are actually hydrocarbon mixtures. Pentanes and hexanes predominate in petroleum ether, whereas higher boiling hydrocarbons predominate in ligroin.

The usual techniques for selecting a solvent are discussed in Section 5.3.

Oiling Out

Oil is a term often used to refer to water-insoluble organic liquids. Sometimes when a hot solution is cooled, the product separates as an oil rather than as crystals. This process is known as **oiling out.**

Oiling out is most likely when you are recrystallizing low-melting solids or when you are using organic-aqueous solvent pairs. Oiling out so often involves low-melting solids because a low melting point is often associated with an appreciable solubility in nonpolar solvents. The consequence is that you often must work with very small solution volumes or with aqueous solvent pairs. If the boiling point of the solvent is higher than the melting point of the solid being recrystallized, the solid might melt in addition to, or instead of, dissolving. As an oil the crude product acts as a solvent for impurities, which distribute themselves between the two immiscible phases (discussed in Technique 6), the oil and the solvent. As the recrystallization mixture cools, the oil might become an amorphous, impure solid.

Fractional Crystallization

In fractional crystallization two solute products with different solubilities are crystallized to separate one from the other as in resolving + and − isomers of 1-amino-1-phenylethane (Experiment 28). The process is essentially the same as any recrystallization, except that one of the "impurities" present is also a product that one wants to recover. Fractional crystallization is a more exacting process of adjusting concentrations or of filtering off the less soluble product before the other begins to crystallize.

5.2 DISCUSSION OF DECOLORIZING

Many crude crystals or solutions of crystals are colored by a small amount of colored impurity with a high molar absorptivity (extinction coefficient) (see Technique 14).

Decolorizing carbon, also called activated carbon or charcoal, is often, but not always, effective for removing colored materials and other finely dispersed or colloidal matter that is too small to be trapped by filter papers. It is particularly good for the elimination of the colored polymeric or resinous materials that so often form in trace amounts during many organic reactions.

Decolorizing carbon is a finely divided charcoal with a surface area of up to 2000 m^2/g. The charcoal contains many multiple bonds and a generous number of hetero atoms. Oxygen in particular is present in the form of hydroxyl groups, which attract impurities by hydrogen bonding. The most adsorptive charcoal is made from wood. Animal charcoal (boneblack) contains considerable amounts of calcium and phosphorus and is less effective. Some commercially available wood charcoal preparations are Darco, Norit, and Nuchar.

Decolorizing carbon removes materials by **adsorption**, the attachment of materials to the surface of a solid by intermolecular attractions.

The charcoal owes its adsorption capabilities to its large surface area and its ability to enter into a multitude of nonbonded interactions.

5.3 THE TECHNIQUES

Recrystallization contains several identifiable steps: selection of a solvent, dissolution of the impure (crude) product, decolorizing, hot gravity filtration, cooling of the solution, cold filtration, washing, and drying. We shall examine each in turn, and then discuss the recrystallization of small samples.

Selection of Solvent

When you are going to recrystallize a known compound, you can often find in the chemical literature (such as a journal, handbook, or laboratory manual) suggestions about what solvent or solvent combination to use. However, if the suggested solvent system does not work well because the impurities in your sample are different from those in the literature, or if your compound is not listed in the literature, you will have to use a trial and error process to select the solvent.

Based on the composition and structure of the compound to be dissolved, you should choose a few likely solvents of a similar composition and structure. At this point you will need to keep several preliminary criteria in mind: The solvent (1) should have a boiling point less that 130 °C so that the crystals can be quite easily dried; (2) should have a boiling point below the melting point of the crystals; (3) should have a low flammability if possible; and (4) should not react with the crystals.

Before you begin your recrystallization, test your choice of solvent by placing a matchhead size of crude solid in a small test tube, and adding a few drops of the likely solvent. If on agitation, the solid does not dissolve, you should heat the mixture to near boiling. If the solid dissolves, put the test tube in a beaker of cold water to see if the solid deposits. If it does, you are all set! If the solid does not dissolve at near boiling temperature, add more solvent and heat it again. If a very small amount of cold solvent dissolves the crude crystals, the solvent is not satisfactory because (1) too much product would remain in the solvent and/or (2) there would be so little solvent that it could not be removed from the crystals by filtration. If an extremely large amount of hot solvent is required to dissolve the crude product, it also might not be satisfactory because of (1) the size of equipment needed for recrystallization, and (2) the cost of solvent.

Errors in judgment regarding suitability of a solvent can arise (1) when supersaturation occurs, making crystallization very slow unless you employ seeding or scratching (see crystallization section); (2) when you must use large amounts of solvent, making it

difficult for molecules to find each other and form crystals (patience is indicated!); (3) when dissolution is very slow but possible, making it easy to add too much hot solvent; (4) when a large amount of impurity is present or when the impurity is less soluble than the desired product, resulting in recrystallization of the impurity rather than of the product. Never discard a solution until you are certain that you have the right product.

Check out the chemical hazards of solvents to be used in recrystallizations.

Choose solvents of low flammability if possible.

If burners are used for heating solutions, check with your instructor about flame-permit areas or permissible times.

Dissolving the Impure Product

Start with a measured amount of solvent. Select an Erlenmeyer flask of sufficient size so that it will be less than half-filled with solution when the solid is dissolved. Put the solid in the flask with a boiling chip, and add about 50% of the amount of solvent you expect will be necessary. If you do not know how much will be required, use a small amount to start with. Fit the flask with a condenser as shown in Figure 5.2. (The condenser is very often omitted for higher boiling solvents, especially water.) If using solvents that boil below 95 °C, use a steam or water bath for heat; if using higher boiling solvents use a hot plate, oil bath, or burner, making your choice as a matter of convenience and safety (check with your instructor).

Bring the mixture to a boil. The condenser will keep the solvent from boiling away. If you are not using a condenser, heat the mixture only to near boiling. If the solid does not all dissolve, add another small amount of solvent through the condenser and again bring the solution to boiling. Continue the solvent addition and heating until all solid has dissolved. However, make an eyeball estimate of how much solid is present before each small addition and if the amount of solid does not appear to change as solvent is added, it indicates that you might have an insoluble impurity. Addition of more solvent will only make your product solution more dilute and result in recovery of fewer pure crystals. Filter off the insoluble impurity.

If a mixed solvent system is chosen, heat both solvents to near the boiling point of the lower boiling solvent. Dissolve the product in a *minimum* amount of the solvent in which the product is soluble. Then add the second hot solvent dropwise to the near boiling solution until you observe a slight turbidity (cloudiness). The cloudiness is evidence of a second phase and indicates that you have exceeded the solubility of the product.

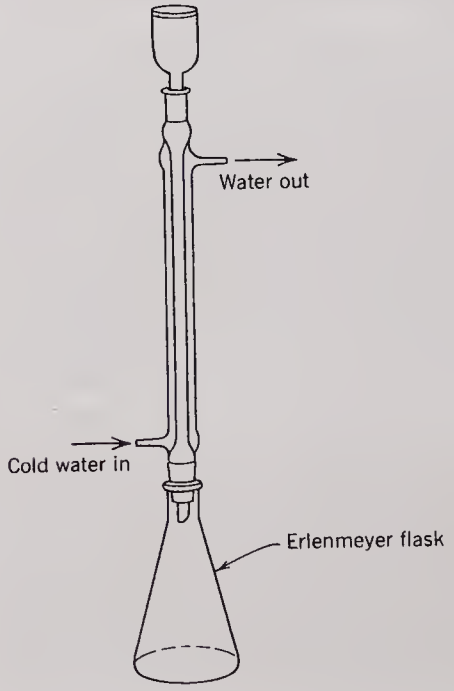


FIGURE 5.2 Dissolution apparatus.

Next, add dropwise just enough of the first hot solvent to make the turbidity disappear. Set the solution aside to cool in the same manner as when a single solvent is used. If you add too much of the second hot solvent or allow the solution to cool too rapidly, the product might oil out. If it does, reheat the solution and add more of the first solvent.

Decolorizing

If the product or the solution is not off color, you can skip this step.

After the crude crystals are dissolved, allow the solution to cool a few degrees below its boiling point unless the solution is already boiling. Then add to the hot solution decolorizing carbon in an amount of about 1% by weight of the crude crystals. You can eyeball the amount by volume if you want to, but excesses should be avoided in order to prevent adsorption of the product as well as the colored impurity. Now stir the mixture for a couple of minutes and gravity filter it hot through a fluted filter, as described in Technique 3 and in the following section.

Be sure to cool the solution before adding charcoal. Otherwise violent boiling might ensue.

If the crystals easily deposit from solution as it is cooled, it might be advisable to add about a 10% excess of hot solvent before decolorizing.

Because adsorption on charcoal is not as efficient at higher temperature, you must sometimes decolorize in a solvent in which the crude product is very soluble at room temperature. Furthermore, decolorizing seems to work best in hydroxylic solvents (water, alcohols, and acids). So, if necessary decolorize the crystals in the *decolorizing solvent,* then distill it off (Technique 7) before the *recrystallization solvent* is added.

Hot Filtration

After dissolving your product you should filter the solution if it contains insoluble particles such as solid reaction impurities, dust, granules of cork, decolorizing carbon, and filter-paper fibers. Use gravity filtration rather than suction filtration because the reduced pressure of the latter will evaporate the hot solvent of the filtrate. First put fluted filter paper in a funnel and pour in 4–5 ml of solvent. The entire filter cone surface should be raised while it is in the funnel to wash the paper free of fibers. Save the solvent, if it is not water, and put it in a recovery container.

Now place the funnel containing the filter paper in an Erlenmeyer flask. If the dissolved solid is likely to crystallize easily, use a stemless funnel.

Filter the solution to remove solid impurities while it is hot. The biggest problem likely to arise during hot filtration is the premature crystallization of product in the filter or stem of the funnel due to cooling of the solution while the filtation is in progress. You can help avoid this problem (1) by using a 10–20% excess of solvent, (2) by preheating the funnel in an oven or by pouring hot solvent through the filter into a beaker resting on a steam bath or hot plate as in Figure 5.3, (3) by keeping the filter and funnel hot during filtration, using an Erlenmeyer flask in place of the beaker in Figure 5.3, and (4) by using a stemless funnel. The apparatus in Figure 5.3 allows hot solvent vapors to bathe the underside of the funnel. If you preheat the funnel by this method, discard the solvent before beginning to filter. If crystals begin to form in the filter paper or on the funnel,

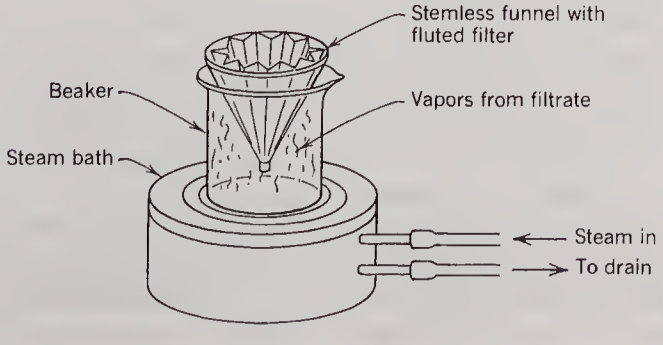


FIGURE 5.3 Hot filtration.

add enough boiling solvent to redissolve them and allow the solution to pass through the filter into the flask.

If the solvent is low boiling, its volume will be reduced by evaporation during filtration, and you will have to add enough solvent to make up for the loss. If excess solvent has been added you will have to remove some by distillation or evaporation until crystals begin to appear. At this point, heat the mixture to boiling and dilute it with just enough solvent so that when hot all crystals are dissolved. No crystals should ever be apparent just before cooling begins since those that form by contact with cold container walls are likely to be impure.

Crystallization

For the reasons mentioned in Section 5.1, the rate of cooling should be such that neither very tiny nor very large crystals form. Needle-type crystals of about 2–10 mm in length and prism-like crystals of about 1–3 mm dimensions should be grown. To obtain such crystals, allow the solution to cool slowly, perhaps by placing it on a pad of paper towels or a cork ring and wrapping it in a few towels for insulation. You can also obtain slow crystallization by taking advantage of the high specific heat of water: Suspend the Erlenmeyer flask in a large container of water at the initial temperature of the hot solution and allow both to cool together. Sometimes it is possible to allow faster crystallization to occur without obtaining tiny crystals. It depends on the materials with which you are working. It is even possible at times to accelerate the process by cooling the hot solution under a cold water tap or by putting the flask into an ice bath early in the process.

If the crystallization is to take place overnight or longer, or if the solvent is relatively volatile, you must stopper the Erlenmeyer flask to prevent evaporation. If solvent evaporates, the crystals become coated with impurities deposited from the mother liquor.

Solutions are often cooled below room temperature in order to obtain the highest possible yields. This is particularly appropriate when the amount of impurity is small. It is not appropriate when the amount of impurity is large or when an impure oil forms at lower temperatures. To cool the solution below room temperature, simply set the Erlenmeyer flask in an ice bath or refrigerator.

A variation of the above is to allow the solution to cool down to room temperature, filter off the crystals, and then cool the solution further. This method decreases likelihood of precipitating impurities along with the first-formed crystals.

Another means of obtaining a higher yield is to grow a second crop of crystals. After the initial filtration to remove purified product, distill the solution or simply heat it to boil away solvent and increase the concentration. The amount of solvent to remove depends on the kinds and amounts of impurities present and has to be judged empirically as you proceed. The hot solution is then set aside to cool and yield the second crop of crystals, which often is not as pure as the first crop and should not be mixed with it unless analysis indicates similar purity.

Sometimes a solution will not yield crystals readily. Several techniques can be tried: (1) You can scratch the inside of the flask vigorously with a sharp-end stirring rod, moving the rod vertically in and out of the cooled solution. The scratching should be energetic enough to be heard. (2) You can add a tiny amount of pure or impure crystal to the cold, supersaturated solution. The small crystals provide sites for larger crystals to grow on. This method is known as **seeding.** (3) Sometimes you can aid crystallization by cooling the mixture in an ice-salt bath to about -10 °C or in a dry ice-acetone bath to about -70 °C. Of course, the solution should not be cooled until it freezes. It is generally a good idea to cool the mixture for a few minutes to initiate crystallization, then allow it to warm slowly to room temperature to crystallize at the faster rate associated with higher temperatures. (4) Sometimes you can initiate crystallization by adding a few small chunks of dry ice to the solution to produce cold spots.

Now let us consider what to do about oiling out. During cooling of the hot recrystallization solution, the cloudy appearance of a second phase might indicate formation of an oil. Confirmation is the observation that the cloudiness is being replaced by tiny droplets or by the gathering of an insoluble liquid at the top or bottom of the solution.

Oiling out is difficult to handle, but you can approach it in several ways:

1. *Try to avoid conditions that cause it.* (a) Choose a solvent if possible that has a boiling point below the melting point of the solid, or avoid heating the solvent above the melting point. (b) Use a larger amount of solvent than usual so the solution remains unsaturated down to a lower temperature. The lower the temperature at time of separation, the more likely it is that crystals rather than oil will separate. In the case of solvent pairs, try less of the poorer solvent or more of the better solvent. (c) You can try precrystallization purification of a low-melting solid by extraction (Technique 6), precipitation, or distillation (Technique 7) of the solid.
2. *Try to stop the oiling out once it has started.* (a) Scratching, as described above, sometimes helps at the time that you first observe formation of the oil. (b) Vigorous agitation or swirling of the flask contents can be helpful when you first observe formation of the oil. (c) Seed the mixture that is oiling out with a product crystal at a temperature below the melting point of the crystal and below the temperature at which the crystal will dissolve.
3. *Try to work with the separated oil.* Sometimes you can recrystallize the oil or amorphous product more satisfactorily than the original crude product.
4. *Try combinations of all of the above techniques!*

Cold Filtration

After crystals have formed, separate them from the mother liquor by suction filtration, using a Büchner funnel for large amounts and a Hirsch funnel for small amounts. Use that size funnel which will not become more than half-filled with product.

Check for stars or cracks in glassware to be used for suction filtration.

If crystals are removed from the flask prematurely, the filtrate will still contain product. You must determine experimentally if the crystallization process is complete by setting the filtrate aside in a stoppered Erlenmeyer flask at the temperature of prior crystallization and observing whether more crystals form.

Sometimes it is necessary to stir the crystals just before filtering to break up a crystallized mass that has resulted from the growth of individual crystals into one another. If possible, it is a good practice after vacuum is applied to the system to pour a large amount of the cold mother liquor into the filter before the crystals because filter paper might become occluded (clogged) and slow the process if crystals are poured in first. Also, if you filter too slowly, the mother liquor will become warm and begin dissolving the crystals again. After most of the mother liquor is filtered through, you should dump the remainder containing the bulk of the crystals into the funnel at once. Such a procedure is not possible, however, when large amounts of crystals are present in relatively little solvent. In such cases, you must mix the crystals uniformly with the solvent by swirling and then rapidly pour them into the funnel until the funnel is nearly full. Allow the level of solvent to fall to just above the crystal level; then pour in another batch of swirled mixture. During filtration you should keep the level of the liquid in the funnel above crystal level so that the crystals remain wet until after washing. If the crystals are sucked dry before washing, impurities from the mother liquor will be left on them while they dry.

It might sometimes be necessary to decrease suction by allowing air to enter the filter flask through the clamped-off hose (see Figure 4.5).

Remove product crystals that remain in the flask in one of two ways: by scraping them out with a rod or spatula, or by putting some ice-cold solvent or preferably ice-cold mother liquor filtrate into the flask to rinse them out. (They are less likely to dissolve if the filtrate is cold.)

Washing Crystals

When the liquid has at last fallen to the top of the crystals, or at least before they have had air sucked through to dry them, you must wash them. When the solvent is more volatile than water, you must take special care not to let too much solvent evaporate.

To wash the crystals, pour fresh cold solvent over them. Use a minimum amount

of solvent if the crystals exhibit much solubility. In such a case it might be wise to remove the filtrate from the flask before rinsing so that if an appreciable amount of crystals should dissolve during rinsing they can be more readily recovered. Two washings are customary, but if the crystals are somewhat soluble in ice-cold solvent, one washing might be all that is practical. Finally, allow the crystals to be sucked dry of solvent until dripping into the filter flask ceases.

Sometimes a filter cake is so dense in the funnel that you cannot satisfactorily wash it by simply adding solvent to the funnel. This situation is more likely to occur if your crystals are quite small. It is then necessary to add the wash solvent to the funnel and very judiciously stir the crystals into the solvent. You must take care not to make holes in the filter paper, lift it off its base, or rub filter-paper fibers into the mixture! If you maintain a slight vacuum by adjusting the screw clamp on the trap, it will help to keep the filter paper on its base. Try not to let much solvent be drawn through the filter while you are stirring. An alternative to washing in the funnel is to dump the contents from the filter paper into a beaker containing the appropriate amount of cold solvent, stir thoroughly, and then filter again. If the literature states, "wash thoroughly," this is probably the method expected. Allow the crystals to be sucked dry enough so that dripping almost stops. Sometimes to squeeze solvent out, you must press them to the bottom of the funnel with the bottom of a beaker, with the wide end of a clean, dry cork, or with your flat-end stirring rod. An excellent way to compress crystals in a funnel is to tie a flexible rubber sheet over the top of the funnel and let the vacuum draw it down onto the crystals.

Use a pad to protect your palm from glass breakage if you use a beaker to press crystals into a Büchner funnel.

Place a shield between you and the evacuated filtration equipment so that if an implosion occurs you will not be struck by flying glass.

Drying Crystals

Dry the crystals by one of the methods described in Technique 2. The most common way of drying crystals is to allow them to air dry.

If a vacuum desiccator is used for drying, be sure that it is inside a protective container. Implosion of a vacuum desiccator is extremely dangerous.

Recrystallizing Small Samples

You can readily appreciate that when very small amounts of solid or solution are involved, the usual methods of recrystallization will result in large losses. Therefore, when the amount of crude solid is less than about 0.1 g or if the volume of solution is under 5 ml some modified techniques are in order.

Use a test tube rather than a flask for crystallization. For hot filtration, use a very small funnel with a small, loose plug of cotton or glass wool located in the stem, or use the eyedropper filter of Figure 4.4. Alternatively, put a small plug of cotton or glass wool at one end of a glass tube and a rubber bulb at the opposite end. Draw the hot solution through the plug into the tube as if you were using a pipet. Remove the plug with tweezers and discharge the hot contents into a clean test tube. If the solid crystallizes readily or if very small amounts or liquid are involved, you can use an eyedropper instead of a glass tube section. It is a good idea when using cotton plugs to first test the device with pure solvent to be certain it will function properly.

You can perform the cold filtration for recovery of final crystals with the cotton plug located in the stem of a funnel at the apex of the cone. You can sometimes get a very good separation by centrifuging, then removing the mother liquor with an eyedropper from the centrifuge tube. You might need to draw out the tip of the eyedropper.

Wash the crystals in the test tube by adding a small amount of cold solvent, mixing the solid and solvent, and centrifuging again.

Dry crystals in the test tube. It is a good idea to lay the tube on its side so that liquid left in the tube will be spread out over a larger area and evaporate more readily.

5.4 EXPERIMENTAL PART
Purification of Benzoic Acid or Salicylic Acid

Time Required: 3 hr

Techniques to Review:

Lab notebook	(1)
Stirring	(0.4)
Heating and cooling	(0.5)
Drying solids	(2.1)
Melting points	(3.3)
Filtration	(4)
Storing	(0.12)
Labeling	(0.23)

You will be given a 1.0-g sample of benzoic acid (IUPAC benzenecarboxylic acid) or salicylic acid (IUPAC 2-hydroxybenzenecarboxylic acid) mixed with 0.5 g of dark brown sugar and a small amount of floor sweepings. The solubility of benzoic acid in water is 2.2 g/100 ml at 75 °C and 0.27 g/100 ml at 18 °C; the solubility of salicylic acid in water is 1.76 g/100 ml at 75 °C and 0.18 g/100 ml at 20 °C; the solubility of sucrose (the sugar) in water is 179 g/100 ml at 0 °C. Both acids crystallize *very* easily. Instead of dark brown sugar, your mixture might contain 0.5 g of white sugar along with 0.08 g of martius yellow dye.

Your problem is to purify the substance by the recrystallization techniques of this chapter, then to identify it by its melting point. You must remove the floor sweepings, decolorize the solution, and obtain the substance in good crystalline form.

Procedure. Put the entire mixture into a 125-ml Erlenmeyer flask. Use water near the boiling point to dissolve the mixture. Watch to see that all white lumps of acid have dissolved. Because the acids crystallize so easily, you will need to use about a 20% excess of water beyond the point of complete dissolution.

Add a small amount of decolorizing carbon and decolorize the mixture according to the instructions in Section 5.3. The filtrate should be no more colored than pale yellow after decolorizing. Do not overheat the mixture by letting it boil while sitting on the hot plate. Sometimes overheating appears to produce a brown substance that cannot be removed with charcoal. If your solution turns dark, continue the recrystallization anyway.

Using a fine filter paper, separate the carbon and floor sweepings from the mixture by gravity filtration into a second 125-ml Erlenmeyer flask. Rinse the first flask with about 5 ml of water and add the rinse to the second flask. Attach an eyedropper or Pasteur pipet to a length of rubber hose and insert it into the flask so that its tip is just above the liquid level. Through this assembly introduce a slow stream of air into the flask to help entrain water vapor as it escapes from the surface. Wrap the flask above the liquid level with aluminum foil to help prevent refluxing as the solution boils. Boil away excess water until crystals begin to appear on the surface of the liquid or around the edge of the flask and will not dissolve again when pushed down into the hot water. Do not boil the solution down to less than about 10 ml. Next, add just enough hot water to dissolve the crystals. Set the flask aside and allow the crystals to form in accord with the techniques in Section 5.3.

Using vacuum filtration and a Hirsch funnel, filter off the crystals. Rinse the flask with filtrate to wash remaining crystals into the Hirsch funnel. Rinse the crystals in the Hirsch funnel with about 1 ml of ice-cold water, and dry them. Make a decision about whether you will obtain a second crop. Do not discard the mother liquor until you are sure you are finished with it, then flush it down the drain with several like volumes of water. Identify the substance as one of the two acids by melting point. Put the dry product in a labeled vial and submit it to your instructor. Calculate the percent yield. Look up the melting point in a handbook of chemistry and physics.

Writing the Discussion. Discuss your technique relative to percent yield and product purity as evidenced by comparing the experimental melting point with that of the literature. Criticize your technique and suggest means of improvement. Include a statement about how the sugar and impurity were separated from the acid. Defend your identification of the acid.

5.5 EXERCISES

Prelaboratory

1. Why is the cold mother liquor poured into a Büchner funnel before the crystals?
2. Why is only a small quantity of hot recrystallization solution poured through the filter at a time? Why is a short stem funnel used? Why is the filtration performed on a steam bath?
3. Why should you record the length of time crystallization was allowed to proceed?
4. List at least three ways product losses could be reduced during the overall recrystallization procedure.
5. Why are crystallization solutions usually not cooled quickly?
6. Why is the level of mother liquor not allowed to fall below the level of crystals during the cold filtration?
7. Prepare a flowchart outlining your procedure for the experimental part.
8. A student tried to crystallize a solid from a hot 70% ethanol-water solution. After cooling, an oil was obtained. She separated the oil, cooled it in an ice-salt bath to solidify it, then tried to crystallize it again. Explain whether she is likely or unlikely to be more successful the second time.

Postlaboratory

1. If 1.75 g of salicylic acid is dissolved in 100 ml of water at 75 °C, how many grams of crystals can crystallize at 20 °C?
2. Please refer to Figure 5.1. If 11.0 g of A along with 9.0 g of B are dissolved at 90 °C, what is the maximum amount of pure A that can be recovered?
3. Do you think that two substances of practically equal solubility behavior which are present in the same amount in a mixture could be separated by crystallization? Explain.
4. Why is ice-cold filtrate preferred to ice-cold solvent for rinsing crystals from a flask into a Hirsch or Büchner funnel?
5. An elemental analysis of a recrystallized compound thought to be $C_8H_8O_2$ was found to be high in carbon even though it had a very sharp melting point. How might a step in the recrystallization procedure have contributed to the faulty analysis?
6. Would you use vacuum filtration and Büchner funnel for filtering a hot, saturated solution of crystals? Why?
7. Would you choose propanoic acid, or water, for recrystallizing *endo*-5-norbornene-2,3-dicarboxylic acid. Why?
8. A student prepared a solid ester from a solid acid by reacting the acid with an alcohol. The ester was contaminated with unreacted acid. Suggest a method for removing the acid before recrystallizing the ester. (Hint: See solubilities section of Organic Qualitative Analysis.)
9. It is stated in Section 5.3 that the efficiency of charcoal in removing (adsorbing) impurities decreases with an increase in temperature. Does this suggest that adsorption on charcoal is exothermic, or endothermic? Explain.

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TECHNIQUE 6

EXTRACTION

Extraction is transferring a solute from one phase to another. Remember, a phase is a homogeneous substance or homogeneous mixture that is obviously distinct from other homogeneous substances or mixtures present. The solute is removed from one phase by adding to it an immiscible solvent in which the solute is more soluble. If a compound is extracted from a solid into a liquid, it is referred to as a **solid-liquid extraction**. An example is the preparation of tea by extracting into water materials from the solid tea leaves. The transfer of a substance from one liquid into another is called **liquid-liquid extraction**.

Extractions are widely used and are relatively simple processes. A great many organic reactions are followed by workups employing some kind of extraction as part of the purification procedure. The isolation of natural products commonly employs extraction.

6.1 DISCUSSION OF EXTRACTION

Extractions from Solids

Organic molecules can be adsorbed on the surface of a solid or can be held within it. For molecules held on the surface, the binding is the result of intermolecular forces; for molecules within the solid, there may be mechanical trapping as well as intermolecular binding. To free an adsorbed or trapped molecule from a solid, the intermolecular attractions that bind the molecule must be overcome by stronger or more numerous attractions. Freeing molecules from the interior of a solid may require permeating the solid with a solvent along with or preceded by mechanical grinding to make the interior more accessible. Coffee beans, for example, are gound in order to make the various components of coffee easier to extract. Heat is commonly applied to decrease the intermolecular interactions that bind the desired component.

Extractions from Liquids

Liquid-liquid extraction involves the distribution, or partitioning, of a solute between two immiscible liquid phases. Usually water and an organic solvent immiscible with water are the two phases.

Imagine a mixture of substances dissolved in a solvent and then allowed to intimately come in contact with a second, immiscible liquid. If one particular substance of the mixture is more soluble in the second liquid than the other substances are, and that particular substance is more soluble in the second liquid than in the original mixture, that substance will transfer into the second solvent, largely leaving the others behind. The transfer takes place at the interface between the two liquid phases.

To cause a substance to transfer from one liquid into the other at a practical rate, you must shake the immiscible liquids together, causing each liquid to separate into tiny droplets which mingle intimately with each other. The effect is to vastly increase the surface area of the interface between the two liquids, effecting a more rapid transfer of solute. The most complete transfer you can hope for is one in which equilibrium is established, that is, one in which enough solute has been extracted so that as many molecules of solute are moving back into the first phase as are moving into the second phase.

The Distribution Coefficient

At equilibrium, no further net transfer can occur, and the ratio of concentrations of the solute in each layer is constant. This constant, K_D, is known as the **distribution coefficient**, or **partition coefficient**, defined mathematically by

$$K_D = \frac{C_2}{C_1} \tag{6-1}$$

C_1 and C_2 are concentrations in grams per liter or grams per milliliter of substance in solvent 1 and solvent 2. The coefficient is constant for a given solute and a given solvent pair. It is necessary to define which solvent is considered to be solvent 1 and which is 2 because the constant defined one way is the inverse of that defined the other way. For example, we must know which phase is the organic ("oil") phase, and which is water. K_D is usually called either a water/oil coefficient or an oil/water coefficient. The usual assumption is that the concentration in organic phase is in the numerator; therefore K_D is an oil/water distribution coefficient. In this book, the oil/water relationship will always be implied when discussing K_D.

Any organic compound with a K_D greater than 1 can be efficiently separated from aqueous solution, and if K_D is around 100, only one extraction will suffice. In most cases, multiple, successive extractions with a small amount of solvent are required. Such multiple extractions are more efficient than one extraction with a larger amount of solvent.

Let us consider an example of extraction from water into ether for a solute with a K_D of 10.0. If the aqueous solution has a concentration of 5.00 g in 300 ml of water and is extracted with 100 ml of ether, the amounts in either phase at equilibrium can be found. Let x be the amount left in water at equilibrium. Then, solving for x, as in equation 6-2, gives the following results:

$$\begin{aligned} K_D &= \frac{C_{\text{ether}}}{C_{\text{water}}} \\ 10.0 &= \frac{(5.00 - x)/100}{x/300} \\ \frac{10.0x}{300} &= \frac{5.00 - x}{100} \\ 1000x &= 1500 - 300x \\ x &= 1.15 \text{ g in the aqueous layer} \\ 5.00 - 1.15 &= 3.85 \text{ g in the ether layer} \end{aligned} \tag{6-2}$$

Notice that x is the amount of solute left in the water after one extraction. If K_D were 20.0, it would be similarly shown that only 0.652 g would remain in the aqueous layer. Try it! Two successive extractions each employing half the volume of extracting solvent are more efficient than a single extraction (see postlab exercise 3).

Salting Out

Extraction can be more efficient if you saturate the water layer with a salt. The purpose is to make the organic materials less soluble in the aqueous phase, and is particularly important when the organic compound is partly soluble in water. The presence of the

TABLE 6.1 p*K* Related to pH of Extracting Medium

Base	*Approximate* pK_a *of Protonated Base* RNH_3^+	*Minimum pH of Acid Solution Required in Extraction*
RNH_2, R_2NH, R_3N (aliphatic amines)	11	7
$ArNH_2$ (aromatic amines)	5	1

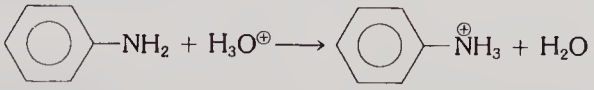
TABLE 6.2 p*H* of 5% Solutions

Compound	*Approximate pH of 5% Aqueous Solution by Weight*
NaOH	14
Na_2CO_3	11
$NaHCO_3$	8
Acetic acid	3
HCl, H_2SO_4	1

salt increases the value of K_D by making the ionic strength of the aqueous layer greater. In essence, the water molecules are more attracted to the ions of the salt than they are to the organic compound; hence the organic compound is *salted out*. We can use any water-soluble salt for this purpose, but generally use sodium chloride or sodium sulfate hydrate because they are relatively inexpensive.

Extractions of Bases

You can make organic bases more water soluble by causing them to react with dilute inorganic acids, commonly 5 or 10% hydrochloric acid. Consider an organic base dissolved in a solvent immiscible with water. If you shake this solution with that of an aqueous acid, the base will come in contact with hydronium ions, capture a proton, and become a water soluble cation:

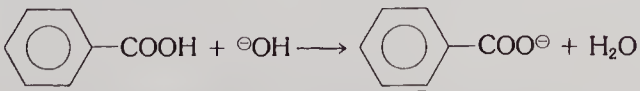


Aniline Anilinium (6-3)

In equation 6-3, aniline reacts with hydronium to become an anilinium ion, which is water soluble, and is extracted almost completely into the aqueous phase. The effectiveness of the extraction depends on the base strength and the concentration of protons available. To get a reasonably complete extraction, the aqueous layer should have a pH 4 to 5 units below the pK_a of the protonated base, as indicated in Table 6.1. From this table we see that an aliphatic amine like ethylamine would require a pH of extracting medium to be no higher than 6–7, and it would be better if it were 4–5. We see from Table 6.2 that a 5% acetic acid solution would be satisfactory as an extracting medium for an aliphatic amine, and we can correctly surmise that less than a 5% hydrochloric acid solution would suffice.

Extractions of Acids

Except for the lower molecular weight acids of fewer than about four carbons, organic acids are not very soluble in water. You can make organic acids more water soluble by converting them into anionic salts, as the example in equation 6-4 shows:



Benzoic acid Benzoate (6-4)

TABLE 6.3 p*K* Related to pH of Extracting Medium

Acid	Approximate pK_a	*Minimum pH of Base Solution Required in Extraction*
ArOH (phenols)	10	14
RCOOH (aliphatic carboxylic acids)	5	9
ArCOOH (aromatic carboxylic acids)	4	8
Mineral acids	<0	4 or less

When you shake an aqueous base with a solution of the organic acid, the hydroxide ions abstract a proton from the acid and generate a water-soluble anion.

The efficiency of extracting an organic acid is dependent on the pH of the basic extraction medium; roughly, to get reasonably complete extraction, the pH of the base solution should be about 4 or 5 pH units higher than the pK_a of the acid. Table 6.3 lists common types of organic acids along with rule of thumb pK_as. From it we see that an aromatic carboxylic acid like benzoic acid requires that the pH of the basic aqueous solution be no less than 8. Looking at Table 6.2, it is apparent that we might use a 5% solution of sodium bicarbonate for the extraction.

After extraction, an acid can be recovered by acidifying the salt solutions with *mineral acid* (an inorganic acid like HCl or H_2SO_4), thereby precipitating the organic acid. If the organic acid is a solid, it can be filtered from the aqueous solution; if it is a liquid, it can be extracted from the water into an organic solvent. The solvent can then be evaporated or distilled off. Figure 6.1 is a flow diagram for the extraction and recovery of the solid, benzoic acid.

Washes

During the workup following a chemical reaction, solutions often contain impurities and leftover reagents that can be removed by extraction. Such extractions, primarily intended

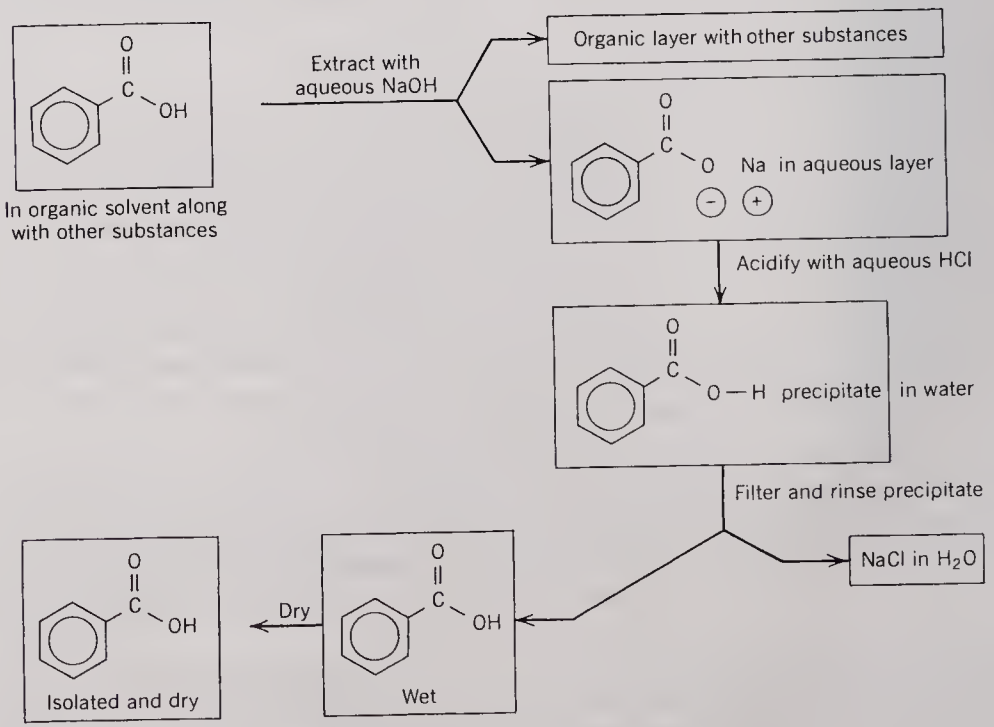


FIGURE 6.1 Flow diagram for isolation of solid organic acid.

to remove unwanted chemicals, are referred to as **washes,** and when the literature directs you to "wash the solution with . . ." it simply means to perform an extraction to remove impurities.

Several types of washes are commonly used: (1) *water* for removing salts and organics with reasonably good water solubility; (2) *saturated aqueous salt* (like NaCl, Na_2SO_4) for removing salts and organics when a salting out effect is desirable or to help prevent emulsions; (3) *aqueous acid* (like HCl, $HC_2H_3O_2$) for removing basic materials; (4) *aqueous base* (like NaOH, Na_2CO_3, $NaHCO_3$) for removing acid materials; (5) *aqueous bisulfite* for removing aldehydes and ketones (see Experiment 34). Before washing with acid, base, or bisulfite, you should use a preliminary water wash to remove most of the impurities and avoid potentially dangerous exotherms.

6.2 EXTRACTION TECHNIQUES

Solid-Liquid Extractions

You can sometimes obtain the intimate contact necessary for extraction by simply grinding the solid in a mortar and pestle in the presence of an appropriate solvent. This procedure is used in the isolation of pigments from spinach in Experiment 5.

You can perform many extractions satisfactorily by boiling a ground or chopped solid in a solvent. This method is utilized in the extraction of limonene from orange peel in Experiment 6.

If you want to extract a solid quantitatively, or if the equilibrium is not favorable for extraction into the liquid phase, you can use a Soxhlet extractor. A Soxhlet extraction apparatus is shown in Figure 6.2. Put the solid in a thimble made of a porous material like a filter paper and place it in the extraction chamber where refluxing solvent drips down on it. The solvent collects in the chamber until the depth gets to the top of the siphon arm, at which time the liquid drains into the boiling flask. In this way the solid is continually bathed in solvent free of the extract; hence the equilibrium is always shifted in the direction of extraction. The solution in the flask becomes increasingly concentrated in the desired component until no more can be extracted from the solid in the thimble.

Liquid-Liquid Extractions

The Solvent

To be a good extraction solvent, it should possess three essential features: (1) it must be practically immiscible with the solution to be extracted; (2) it should have a relatively low boiling point so it can be easily removed by distillation or evaporation from solute

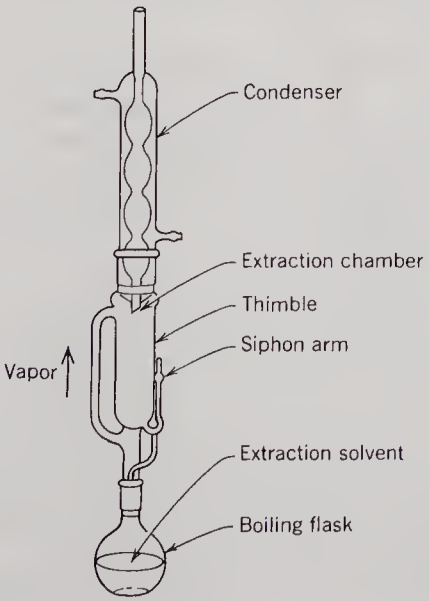


FIGURE 6.2 Soxhlet extractor.

after extraction; (3) it should dissolve the solute better than does the solvent from which it is being extracted.

Some solvents that are commonly used to extract aqueous solutions are ether (bp 35 °C, d 0.71), pentane (bp 36 °C, d 0.63), methylene chloride (bp 40 °C, d 1.34), chloroform (bp 62 °C, d 1.48), and hexane (bp 69 °C, d 0.66). There are advantages and disadvantages to each of these: Ether, pentane, and hexane have low boiling points, but are very flammable; moreover, ether tends to form explosive peroxides when standing in contact with oxygen in air. Pentane and hexane are easily dried, whereas ether dissolves some water. Methylene chloride and chloroform are nonflammable but are more toxic and more easily lead to formation of emulsions during extractions. **Emulsions** are suspensions of small droplets of one immiscible liquid in another.

Keep flames away from areas where flammable extraction solvents are being used. Do not operate switches of unmodified electrical devices in areas where their vapors can collect.

Perform extractions in a fume hood if possible.

In experimental procedures, the volume of extraction solvent will often be specified for you, but as you gain more experience you will make this decision yourself. As a rule, the *total* volume of extraction solvent is approximately equal to the volume of liquid being extracted, but the total volume is most likely to be divided into two or three successive extractions to gain greater efficiency.

Separatory Funnel Operations

Liquid-liquid extractions are performed with a separatory funnel with properly fitting stopper and stopcock. Grease glass stopcocks *lightly* with stopcock grease, keeping grease away from the hole. Do not grease Teflon stopcocks.

Support the separatory funnel in a ring on a ringstand, as shown in Figure 6.3. Old timers recommend that you cut and split three 3 cm pieces of rubber tubing and slip them over the inside of the ring to cushion the funnel and prevent breakage. Put a glass funnel in the neck of the funnel and *close the stopcock*. Add the solution to be extracted to the funnel; then add the extraction solvent. Do not let the total volume in the separatory

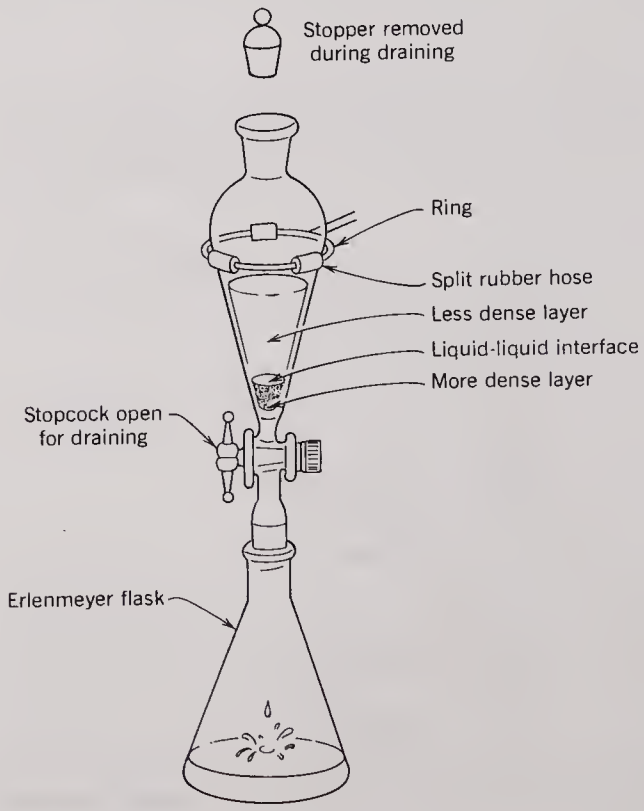


FIGURE 6.3 Separatory funnel.

FIGURE 6.4 Using the separatory funnel.

funnel be greater than two-thirds to three-quarters of the funnel volume or there will be no room for mixing. If a low-boiling solvent (like ether) is to be used it is a good idea to cool both solution and solvent to below room temperature to reduce volatilization during the extraction. Wet the stopper with water (to keep it from sticking tightly and so organic solvents are less likely to leak out) and insert it into the neck of the separatory funnel.

It is essential that the solution to be extracted is cool so that low-boiling solvents will not volatilize, create pressure within the funnel, and blow out the stopper along with hot or dangerous contents.

Hold the funnel in both hands, one hand on the stopcock and stem, and one hand on the stopper and neck, as shown in Figure 6.4. Rock the funnel gently back and forth lengthwise once, point the stem up, and slowly open the stopcock to release excess vapor pressure. Repeat this procedure until only a small spit of vapor is observed. You can now mix the phases more vigorously, but also with occasional opening of the stopcock to test for pressure. With vigorous shaking, 10–30 sec is often sufficient to transfer solute from one phase into another to the point that equilibrium is established. When emulsions are likely to form, a slow, rocking motion must be used and 5 or 10 min might be required, depending on the size of the funnel and sample.

Vent the separatory funnel frequently during extractions in order to avoid building up vapor pressure and blowing out the stopcock and perhaps dangerous contents. This is especially important with bicarbonate or carbonate washes of acidic solutions.

Point the tip of the separatory funnel away from yourself and others when releasing pressure.

After mixing, hold the funnel upright, swirl it once to set up a gentle rotary motion of liquid inside the funnel, and set it in the ring of the ringstand. The swirl is to help prevent formation of droplets of one immiscible phase within another along the funnel walls.

After allowing the two immiscible liquids to clearly separate, *remove the stopper* to admit air and allow the lower liquid to smoothly drain into an appropriate container. Drain the lower liquid to the point that the upper liquid barely reaches the stopcock hole. Swirl the funnel a little again if necessary to make droplets coalesce (come together and form one phase). After swirling, a small lower layer might be observed again. Draw it off also. If the upper phase is to be removed from the funnel, remove it by pouring it *out the top* of the funnel to prevent remixing the upper phase with the small amount of second phase left in the funnel stem.

You must often repeat extractions with fresh solvent. During repeated extractions, it is unnecessary to remove the upper phase in the funnel when the upper phase originally

contained the substance of interest. It is obviously important to know in which phase the substance is originally found. Use the densities of the liquids to make this decision. Or, if you have any doubts, remove a few drops of the lower layer and put them into a test tube containing a few drops of water. If, after agitating the tube, two phases are apparent, the lower layer is not the aqueous phase; if you see only one phase, the lower layer is aqueous. If you think you need confirmation, repeat the procedure using the upper layer.

It is generally a good practice not to discard any materials until all are surely identified!

To clean up after liquid-liquid extractions, remove the stopper and stopcock of the separatory funnel, clean off grease with chloroform, then wash all components thoroughly. Unless they are made of Teflon, do not replace the stopper and stopcock until you are ready to use them again.

Dealing With Emulsions

Emulsions are troublesome, and prevent a clear separation of the two phases in the separating funnel. What you might observe is a mixture of droplets between two clear phases. An untrained observer might interpret the mixture as a third phase. Emulsions sometimes break up and the components separate if allowed to stand 5 or 10 min. If, after 5 or 10 min, no improvement is noted, it is a good idea to use other means to break up the emulsion:

1. Insert a stirring rod into the funnel and rub it against the glass wall, around and around in the region of the phase interfaces.
2. If the density difference between the two solutions is very small, add extra solvent to one of the layers to create a greater density difference and permit more ready coalescence of droplets. *Pentane* is useful for *decreasing* the density of an organic layer. *Tetrachloromethane* (carbon tetrachloride) is efficient at *increasing* the density of the organic phase. You can decrease the density of an aqueous phase by adding water or increase the density by adding an aqueous saturated salt solution.
3. Add a few drops of acetic acid (IUPAC ethanoic acid) to reduce emulsions that arise during extractions of basic solutions.
4. When emulsions form exceptionally easily, you can carry out the extraction in a round-bottom flask. Put a magnetic stirring bar in the flask and stir the contents gently for perhaps an hour. Then gently pour the two phases into a separatory funnel to make the separation.
5. If an emulsion layer is relatively small you can, in the interest of saving time, draw it off with the extract, trusting that later washes will make the separation more complete.

6.1 EXPERIMENTAL PART
Separation of Benzoic Acid and Naphthalene

Time Required: 3–3½ hr

Techniques to Review:

Lab notebook	(1)
Care of glassware	(0.3)
Gravity filtration	(4.2)
Testing pH	(0.11)
Suction filtration	(4.3)
Cooling	(0.5)
Drying solids	(2.1)
Melting points	(3.3)
Labeling	(0.13)
Evaporating and concentrating liquids	(0.6)
Storing products	(0.12)

You will be given a mixture containing 0.50 g of benzoic acid (IUPAC benzenecarboxylic acid) and 0.50 g of naphthalene, both dissolved in 15 ml of methylene chloride (IUPAC dichloromethane).

Making the separation. Put the solution into a small separatory funnel of appropriate size. Extract it thoroughly with 10 ml of 10% aqueous sodium hydroxide. Draw off the lower layer into a container labeled B. What is left in the separatory funnel is solution A.

Remember to be cautious about pressure release on the separatory funnel during washes.

Do not breathe solvent vapors. Work in a hood.

Wash solution A with 5 ml of methylene chloride. Drain off the lower layer and put it into its assigned recovery container. Pour the upper layer into a small beaker and cool it to about 15 °C. Add to it, with stirring, enough ice-cold 10% aqueous HCl until a pH of 1 is obtained. Vacuum filter the solid into a Hirsch funnel, using filtrate to rinse precipitate from the beaker into the funnel. Then discard the filtrate down a drain located in a hood. Dry the product and put it into a tared, labeled vial. △△

Rinse the separatory funnel thoroughly with water and put solution B back into it. Wash B with 10 ml of water and discard the wash down a drain in a hood. Drain off the lower layer into a small Erlenmeyer flask and dry it over anhydrous sodium sulfate for 10 min. Remove the drying agent by gravity filtration into an evaporating dish, and evaporate the methylene chloride on a steam bath in a hood. Remove the evaporating dish from the steam bath and allow it to cool to about 50 °C (hold the thermometer against the dish). If the liquid solidifies, the methylene chloride has evaporated. Prolonged heating will sublime the product and result in a lower yield. Weigh the solid as soon as it is dry of methylene chloride and put it into a labeled vial. △△ Put the used drying agent into a recovery container located in a hood. Calculate the percent yield.

Turn in your properly identified and labeled products to your instructor.

Writing the discussion. Several suggestions follow which might or might not be appropriate for writing your discussion. Decide which suggestions should be used.

1. Discussion of how to avoid emulsions.
2. The structure of 1-hydroxynaphthalene relative to the separation procedure used.
3. The densities of water and dichloromethane at various temperatures.
4. The densities of water and dichloromethane relative to the order of removing solutions from the separatory funnel.
5. The reason for the order of operations performed in the separation.
6. Your percent yields relative to that of your classmates and the reasons therefor.
7. The reason for venting the separatory funnel while using it.
8. How the separation from a solution of a basic substance like an amine differs from separation of an acid like benzenecarboxylic acid.
9. The physical properties of the separated substances related to their identities.
10. A critique of your technique.
11. The percent yield of naphthalene relative to its tendency to sublime.

6.4 EXERCISES

Prelaboratory

1. Assume that you are going to extract a compound from water into ether, using two successive extractions. Make a detailed stepwise summary of all operations in the procedure, paying attention to location of the solute at each step and the disposition

of each layer in the sep funnel. Start with step 1 as, "Put the sep funnel in the ring on the ringstand."

2. Repeat exercise 1 but with chloroform as the extraction solvent.
3. Make a flow diagram like that of Figure 6.1 for the entire procedure of the extraction experiment in Section 6.3.
4. Using the example of equation 6-2, show that if K_D is 20.0 that 0.652 g of solute would remain in the aqueous layer.
5. Make a flow diagram for the extraction and recovery of propanoic acid (propionic acid) from an ether solution containing other nonacidic chemicals. Use a handbook of chemistry and physics to obtain the appropriate properties of propanoic acid.

Postlaboratory

1. The partition coefficient for caffeine distributed between water and trichloromethane (chloroform) is 22. If 150 ml of coffee solution contains 0.80 g of caffeine and you extract once with 60 ml of trichloromethane, how much caffeine will remain in the aqueous layer?
2. If two successive extractions of 30 ml each are used, how much caffeine will remain in the aqueous layer of exercise 2? Which gives a more complete extraction, that in exercise 2 or 3?
3. Make flow diagrams showing how to separate by extraction techniques mixtures of (a) benzenamine and methylbenzene (aniline and toluene); (b) benzenamine and benzenecarboxylic acid (aniline and benzoic acid); (c) benzenamine, benzenecarboxylic acid, and benzenol (aniline, benzoic acid, and phenol).

TECHNIQUE 7

DISTILLATION

Distillation is the process of vaporizing a liquid in a boiling pot and then condensing it again where it will collect in another vessel. A **still** is the apparatus used for distillation. Stills have been used for many hundreds of years, notably for distilling wine and mashes, concentrating their alcohol along with water and smaller amounts of ketones, esters, and other flavor reagents to make various kinds of liquors like brandy, whiskey, vodka, and moonshine. Moonshine is really an illegal form of whiskey, and got its name from having been illicitly made at night by the light of the moon. I am sure your have seen pictures of a moonshiner's still with its large boiling pot and long coils of metal tubing used for condensing the vapors. A forerunner of the modern laboratory still that you will use is the retort (Figure 7.1), a closed vessel with a long outlet tube which acts as a crude condenser. (Don't you think every witty chemist should have a good *retort?*)

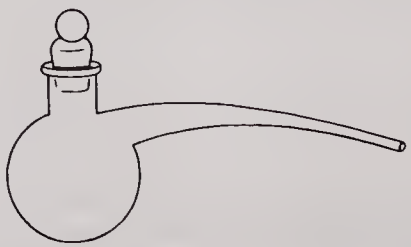


FIGURE 7.1 Retort.

Distillation is the most important and widely used process for purifying liquids. The four fundamental distillation processes that we shall examine in the techniques that follow are simple distillation, fractional distillation, vacuum distillation, and steam distillation.

7A Simple Distillation

Simple distillation is a process that permits you to separate a liquid from nonvolatile substances (usually solids), to separate liquids that have boiling points more than about 100 °C apart, or to separate two liquids with a smaller boiling point difference if one liquid makes up less than about 10% of the mixture. You can also use simple distillation to effect a rapid, crude separation prior to a more careful one. Always use simple distillation whenever possible because of the ease in setting up equipment and the rapidity with which you can perform the operations.

7.1 DISCUSSION OF SIMPLE DISTILLATION

Figure 7.2 illustrates a simple distillation apparatus. The liquid to be distilled is put into the flask, or **still pot.** The liquid is made to boil, and vapors rise up into the **still head** and out the **sidearm,** after which they condense to the liquid state in the **condenser.** The condensed liquid, or **distillate,** is collected in the **receiver.** The liquid and/or solid that remains in the pot at the end of distillation is the **pot residue.**

Simple distillation depends on boiling a liquid; boiling in turn is a function of vapor pressure. (You might want to review Section 3.4 on boiling points.) You can think of the vapor pressure of a liquid as representing the tendency for molecules of the liquid to escape from its surface. The molecules of a liquid are in constant motion, and the hotter they are the faster they move, perhaps fast enough to overcome their intermolecular attractions and escape from the liquid into the gas phase.

Distillation depends on a continual shifting of equilibrium. Remember LeChatelier's principle: If a stress is applied to a system in equilibrium, the equilibrium will shift so as to relieve the stress. In this case, the stress is the disturbing of the equilibrium vapor pressure in the pot. The stress is caused by making some of the molecules in the pot so

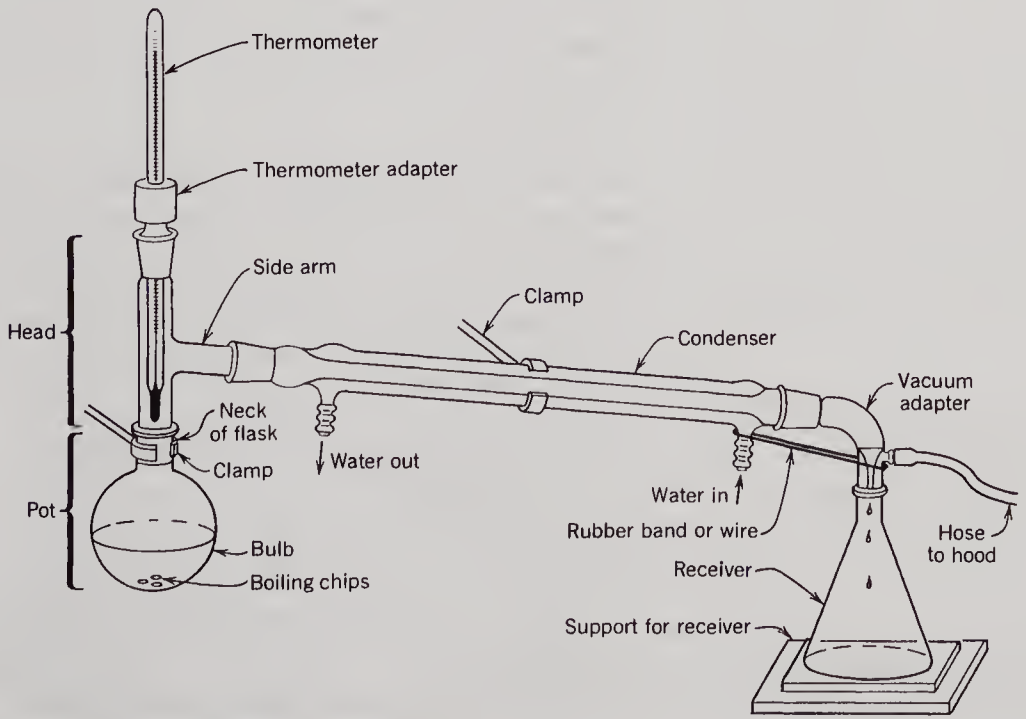


FIGURE 7.2 Simple distillation apparatus.

hot that the vapor pressure of the liquid exceeds the atmospheric pressure. The distillation process depends on this continual pressure to drive molecules of vapor into the condenser.

When distillation involves only one liquid substance in the presence of a nonvolatile solid, the composition of the vapor and distillate will be the same but different from the composition of the pot liquid. This is because the vapor pressure of the liquid is far greater than that of the solid; hence its molecules escape easily whereas those of the solid escape with difficulty.

As distillation of the solution proceeds, the temperature of the pot liquid increases because the solution is becoming more concentrated. But the temperature at the thermometer in the head will remain constant throughout distillation because the vapor composition does not change.

Let the pot be no more than two-thirds full because more liquid than this makes the surface area too small for rapid evaporation. A large flask permits more efficient vaporization, but it should not be too large because the volume of the flask then requires too much vapor to fill it, the consequence being that after the last of the pot liquid is vaporized, whatever vapor molecules are left in the flask and head cannot be condensed because there are no molecules exerting pressure to push them into the condenser. The amount of vapor in the flask and head along with the liquid required to wet their inner walls is referred to as the **holdup.** The holdup, along with liquid required to wet the inside of the condenser and adapter of a simple distillation apparatus can represent a loss of as much as one or more milliliters of liquid.

7.2 SIMPLE DISTILLATION TECHNIQUES

Select a round-bottom flask of such a size that it will be no more than two-thirds full. Using dry joints or very *lightly* greased ground glass joints, assemble an apparatus like that in Figure 7.2. Clamp the pot and condenser to a ringstand, and secure the condenser and vacuum adapter to each other by hooking a rubber band around their nipples. If the liquid to be distilled has a boiling point over about 100 °C or if your laboratory location is drafty, you might find it necessary to loosely wrap the column with aluminum foil in order to conserve heat and help prevent sporadic cooling by drafts.

Correct positioning of the thermometer is very important. Insert the thermometer into the still head through a rubber thermometer adapter or rubber stopper. Center the thermometer in the head with the top of the thermometer bulb lined up with the bottom of the sidearm so that the bulb will be bathed in distillate vapors just before they enter the condenser.

For a receiver, use a test tube, round-bottom flask, or Erlenmeyer flask. Then set the receiver on a support which can be easily removed if you should want to change receivers. If the boiling point of the distillate is less than 100 °C, put the receiver in a cooling bath like one of those in Table 7.1. The cooling bath decreases vapor pressure of the distillate and therefore reduces its evaporation. In general you should use a cooling bath temperature about 50 °C below the boiling point of the distillate. (Refer to Section 0.5 for controlling bath temperatures.)

If the distillation is conducted outside of a hood and you want to reduce release of

TABLE 7.1 Distillation Temperatures and Cooling Baths for 1-atm Pressure

Distillation Temperature, °C	*Bath Temperature, °C*	*Bath*
100	Room temperature	Not required
75–100	25–50	Tap water
50–75	0–25	Ice and water
50	0	Ice-salt

vapors into the laboratory beyond that possible with a cooling bath, attach a hose to the nipple on the vacuum adapter and run it into a hood. Another way to reduce evaporation is to cover the opening to the receiver with aluminum foil.

Ordinarily, we use tap water to cool a condenser, introducing water from a hose into the lower condenser nipple, and letting it flow out the upper nipple into a hose extending to a drain. If the boiling point of the distillate is over 150 °C, cool the condenser by simple density convection of room air or by blowing air through it from your compressed air source. The reason for using an air condenser is that the large difference in the temperatures of the cold water and hot distillate might crack the condenser. At the opposite end of the spectrum is the necessity of passing steam through a condenser jacket to keep a low-melting solid from solidifying in the condenser.

Choose as a heat source one of the methods discussed in Section 0.5. Usually a heating mantle or an oil bath is used, but if the distillate boils below about 90 °C, a steam or water bath would be satisfactory.

Examine your glassware for cracks and stars, which might cause a vessel to break while it is being heated.

Be sure that the distillation apparatus is open at the receiver end so that pressure cannot build up as the liquids vaporize. Such pressure buildup can lead to an explosion.

Check to be sure that water hoses to the condenser are on securely. Use hose clamps. A loose water hose could result in spraying water into heating mantles or other electrical equipment or onto the hot oil of an oil bath. Or it might just startle you or someone else so that a resultant sudden movement upsets equipment.

If it is necessary for you to insert glass tubing through stoppers, be sure to observe the usual percautions: glycerine, pad in palm, holding tube near base, gentle twisting, and gentle pressure to insert.

Check to ensure that there is no accumulation of flammable vapors in the area when you plug in or unplug heating mantles and other electrical equipment. Every electrical connection or disconnection involves sparking.

Make the distilling flask no more than two-thirds full. Add one or two boiling chips before heating commences. Regulate the heat input to the pot so the pot liquid boils smoothly and the **takeoff,** the rate at which distillate enters the receiver, is about 1–3 drops/s. Permit no **bumping,** that is, violent eruptions of large bubbles of liquid into the head. The temperature at the still head will remain only slightly above room temperature until the vapors reach the thermometer bulb, at which time the temperature will rapidly rise, and drops of condensate will fall from the thermometer bulb back into the pot. It is not uncommon for laboratory reagents to contain impurities and you might observe that the initial temperature at which distillate is collected is below that expected. Watch the thermometer, and when the temperature rises to the boiling point of the expected distillate, replace the receiver with another. We refer to the lower boiling distillate as a **forerun.** Do not let yourself be fooled by seemingly incorrect temperatures that are the result of using an uncalibrated thermometer or by not taking thermometer corrections into account!

Sometimes there are impurities present that distill with the product and you will have to collect the distillate over a range of temperatures. If low-boiling impurities cause the temperature deviation, you will collect distillate from about 4 C° below to 1 C° above the boiling point; if the impurities are high boiling, you will collect distillate from about 1 C° below to 4 C° above the boiling point. Many times the literature will tell you over what temperature range to collect. Collect the forerun, if any, up to the lower end of the boiling range.

Discontinue distilling any liquid that smokes or produces dense vapors. Remove the heating source immediately and move away from the apparatus until it cools.

Avoid adding boiling chips to a heated liquid. The sudden ebullience might eject the liquid from its container.

Keep vapors of volatile liquids in the laboratory at a minimum.

Keep flames away from the vicinity of flammable vapors.

Organic liquids should never be distilled to dryness, since peroxides, which are explosive at higher temperature, might be present. Many organics, notably ethers, form peroxides in the presence of oxygen in the air. Furthermore, a dry flask overheats rapidly and could crack a flask or ruin a heating mantle.

7.3 EXPERIMENTAL PART
Simple Distillation of an Unknown Liquid

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook	(1)
Boiling points	(3.5)
Melting points	(3.4)
Glassware	(0.3)
Storing products	(0.12)
Labeling	(0.13)

You will be given a solution consisting of 15 ml of an unknown liquid and 0.5 g of benzoic acid (IUPAC benzenecarboxylic acid). The liquid will be one of the following: methanol, 95% ethanol, or 1-propanol.

Procedure. Using the techniques in Section 7.2, distill the liquid. Wrap the neck of the flask and distillation head with aluminum foil or other insulation. Make a table in your notebook like that of Table 7.2. Using a 10-ml graduated cylinder as a receiver, collect 1-ml fractions, recording the temperature at the beginning of distillation when the first drop of liquid falls into the receiver and everytime a new 1-ml volume is collected. The cumulative volume is the sum of milliliters at each time that you record a temperature. When the dripping of distillate nearly stops and there is only about 0.5 ml of liquid left in the pot, remove the heat source. Before the pot cools, pour out the pot residue onto a watch glass. Rinse the cooled pot with about 1 ml of methylene chloride and pour the rinse onto the watch glass. After the substance cools and dries by evaporation, obtain a melting point. Turn in the purified liquid and pot residue to your instructor in labeled vials.

Identify the unknown liquid by comparing its boiling point with the literature boiling points for the unknowns. Calculate the percent yield. Using graph paper, make a plot of temperature as ordinate and cumulative volume as abscissa.

Writing the discussion. Discuss the identity of the liquid pot residue and why it did not distill. Note the shape of the plot on the graph paper and explain why it has that shape. Try to account for losses as indicated by your percent recovery. Identify and discuss how you came to that conclusion. Criticize your personal technique and suggest means of improvement where required.

TABLE 7.2 Distillation Data

Cut No.	*Time*	*Lapsed Time, min*	*Milliliters*	*Cumulative, ml*	*Temperature, °C*
0	8:15	0	0	0	44
1	8:20	5	2	2	45
2	8:25	10	2	4	45
3	8:30	15	2	6	45

7.4 EXERCISES

Prelaboratory

1. What is the maximum level to which a distillation flask should be filled?
2. Why should organic liquids in general not be distilled to dryness?
3. List three ways of reducing the presence of volatile vapors in the laboratory.
4. Make and label a diagram of a simple distillation apparatus.
5. *Eve Apprate* had 2.0 ml of a liquid solution consisting of a solid solute dissolved in a liquid solvent. She put it into a 250-ml distilling flask along with a boiling chip and assembled a simple distillation apparatus. Distillation yielded only a few drops of distillate. Suggest two reasons why the yield was so small.

Postlaboratory

1. *Ben Zoate* assembled a simple distillation apparatus and charged it with 50 ml of solution containing solid solute in liquid solvent. He inserted a thermometer into the pot as well as in the head. As distillation progressed he noted that the head temperature remained constant but the pot temperature increased for a while and then became constant. Explain. What should the student have observed in the pot after the pot temperature became constant?
2. A student had a liquid solution consisting of 0.4 g of a solid solute plus 2.00 ml of ethanol (ethyl alcohol). He put it into a 250-ml distilling flask attached to a head assembly with a 20-ml volume. One ml of liquid was necessary to wet the apparatus inside. The atmospheric pressure was 760 torr and the temperature inside the apparatus was at the boiling point of ethanol. Using the relationship $PV = nRT$, calculate the maximum amount of ethanol he could collect in a receiver at room temperature. Suggest how he could improve his technique.

7B Fractional Distillation

When more than one liquid is present in a mixture, simple distillation often will not suffice to separate the liquids from each other. A more sophisticated apparatus and a more careful and time-consuming approach are required.

Let us consider separating a mixture of methanol (methyl alcohol) and water, which mix with each other in all proportions and are therefore said to be infinitely miscible. Because the boiling points of the two compounds differ appreciably (bp water 100 °C; bp methanol 65 °C) they can be separated by distillation. However, if a mixture of equal volumes of methanol and water were distilled in a simple distillation apparatus, the initial temperature of the vapors at the thermometer bulb would be above that of methanol and would continue to rise throughout the distillation. At no point would the observed temperature be that of pure methanol. If, during the distillation, samples of distillate were taken regularly and analyzed they would be found to consist of solutions of methanol and water, the first such samples, called **fractions,** being richer in methanol, and the later fractions being richer in water. Although simple distillation would not be satisfactory for a good separation of the two components, a more efficient distillation column and technique could result in a sharp separation of the two liquids. The process of separating the components of a mixture by distillation into relatively pure fractions is called **fractionation,** or **fractional distillation.**

7.5 DISCUSSION OF FRACTIONAL DISTILLATION

Distillation depends on rapidly evaporating a liquid, the rate of evaporation being a function of temperature and atmospheric pressure. Evaporation results from the ability

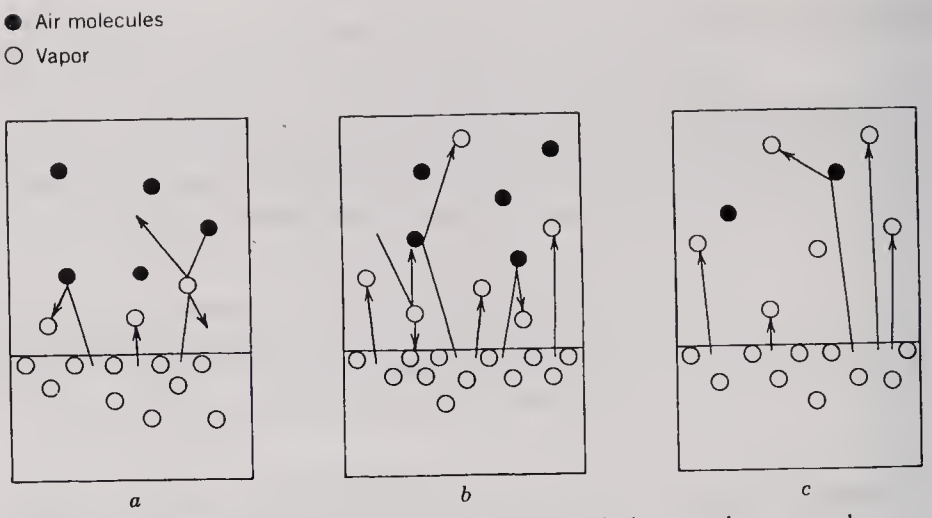


FIGURE 7.3 Evaporation of molecules from the liquid phase to the vapor phase. (*a*) Room temperature. (*b*) Increased temperature. (c) Decreased pressure.

of molecules to escape from the surface of the liquid and to push atmospheric molecules out of the way, as depicted in Figure 7.3. The rate of escape determines the vapor pressure of the liquid. There are two ways of increasing the number of vapor molecules above the liquid. First, we can increase the temperature of the liquid, thereby generating a greater number of extra-hot molecules that have sufficient energy to overcome intermolecular attractions and escape from the surface (see Figure 7.3*b*). Notice that in order to escape, the vapor molecules must not be driven back to the surface by collision with each other or with atmospheric molecules. Second, we can decrease the atmospheric pressure so there will be fewer atmospheric molecules to collide with emerging vapor molecules and drive them back to the surface (see Figure 7.3c).

Raoult's Law

When two infinitely miscible liquids are put together, the vapor pressure of each is reduced by the presence of the other because neither can occupy as much surface area as it can when it is alone.

Each component in a solution contributes to the total vapor pressure at the surface. If the contribution is in direct proportion to the mole fraction of the component, the component is said to be **ideal.** The concept of an ideal component is similar to that of an ideal gas. Although no mixture is completely ideal, many mixtures such as those of benzene-toluene and pentane-hexane approximate ideal behavior. Ideal solutions will be approximated when the components of the mixture are of similar size, have similar intermolecular attractions, and have vapor pressures (therefore boiling points) that differ considerably.

Raoult's law states that the pressure of an ideal liquid in solution is directly proportional to its mole fraction. This law can be stated mathematically as

$$P_A = X_A P_A^0 \tag{7-1}$$

wherein P_A is the vapor pressure of liquid component in solution, P_A^0 is the vapor pressure of the pure liquid, and X_A is its mole fraction in solution. Remember that **mole fraction** is the ratio of moles of a given component in solution to the total number of moles in solution:

$$X = \frac{\text{moles of component}}{\text{total moles}} = \frac{n_A}{n_A + n_B + \cdots} \tag{7-2}$$

Raoult's law shows us that the greater the mole fraction of a given component in solution, the greater is its vapor pressure and hence the number of molecules in the vapor above the liquid. For example, the vapor pressure of pure benzene is 400 torr at 60 °C. If its mole fraction (X_b) in solution is 0.50, its vapor pressure is given by

$$P_b = X_b P_b^0 \qquad (7\text{-}3)$$
$$= (0.50)(400 \text{ torr})$$
$$= 200 \text{ torr}$$

Pure toluene has a vapor pressure of 138 torr at 60 °C. If its mole fraction (X_t) is 0.50, its vapor pressure above the liquid is

$$P_t = X_t P_t^0 \qquad (7\text{-}4)$$
$$= (0.50)(138 \text{ torr})$$
$$= 69 \text{ torr}$$

So, if at 60 °C benzene and toluene are mixed together in equal molar quantities ($X_b = 0.50$ and $X_t = 0.50$), the benzene vapor pressure is 200 torr and the toluene vapor pressure is 69 torr. Since the number of molecules is directly related to the vapor pressure, there are 200 molecules of benzene for every 69 molecules of methylbenzene in the vapor. Therefore, inasmuch as the original solution contained an equal number of molecules of each (ratio of 200 to 200), the vapor above the solution is enriched in benzene.

Now you can see how Raoult's law applies to distillation. The vapor above the liquid is always enriched in the component with the higher vapor pressure, which is equivalent to saying that the vapor is enriched in the component with the lower boiling point.

Figure 7.4, a Raoult's law vapor pressure-composition diagram for the benzene-toluene mixture at 60 °C, provides us with the same information as solving Raoult's law equations. For example, point *a* shows us that when X_t is 1.0 (pure toluene), the vapor pressure of toluene is 138 torr; point *b* shows us that when X_t is 0.5, P_t is 69 torr. Points *c* and *d* similarly relate to benzene. The line from *a* to *c* repesents Dalton's law, which states that the total vapor pressure equals the sum of the individual vapor pressures. In this particular case for $X_t = 0.50$ and $X_b = 0.50$,

$$P_{total} = P_t^0 X_t + P_b^0 X_b \qquad (7\text{-}5)$$
$$= (138 \text{ torr})(0.5) + (400 \text{ torr})(0.5)$$
$$= 69 \text{ torr} + 200 \text{ torr}$$
$$= 269 \text{ torr}$$

The sum is diagrammatically found at point *e*. Note that the solution will not boil at 60 °C because the total pressure is less than atmospheric pressure.

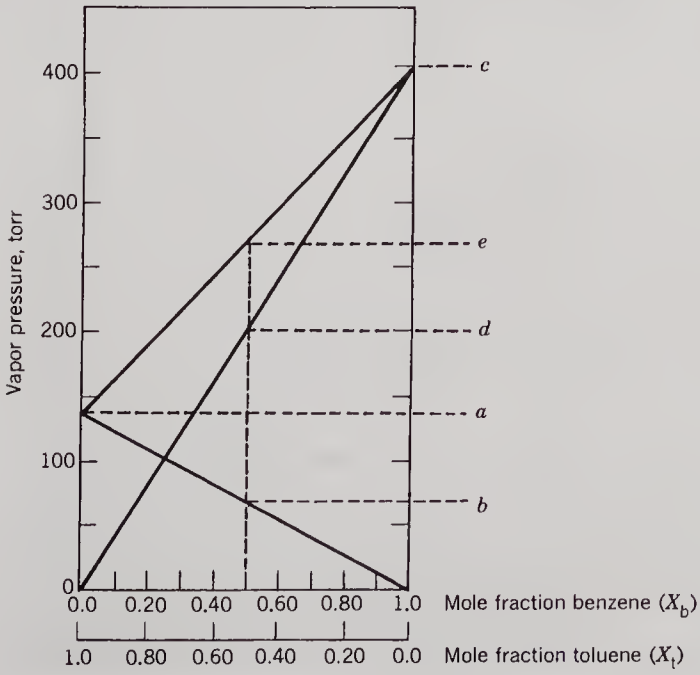


FIGURE 7.4 Raoult's law vapor pressure-composition diagram for benzene-toluene at 60°C.

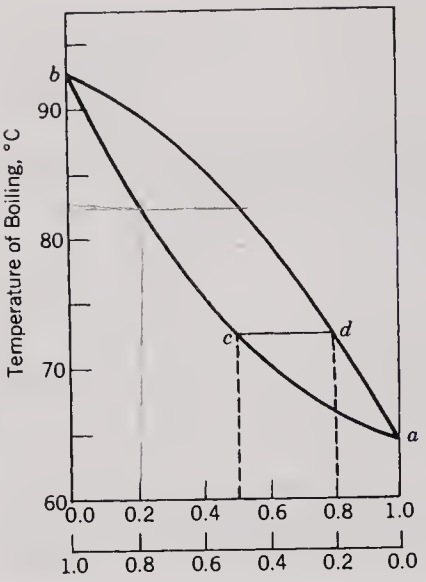


FIGURE 7.5 Vapor-liquid composition diagram.

Vapor-Liquid Composition Diagrams

Another useful diagram is the **phase diagram** of Figure 7.5, which gives us the mole fraction compositions of liquid and vapor phases at various temperatures. The upper line gives the mole fraction composition of the vapor, and the lower line gives the mole fraction composition of the liquid.

The particular system in Figure 7.5 represents a solution of low-boiling A and high-boiling B. Notice that when X_A is 1.0 (pure A) the composition of liquid and vapor are the same and the boiling point at *a* is 65 °C. When X_A is 0.5, X_B is 0.5, and the boiling point of the solution is 72.5 °C, as shown at c. You can find the mole fraction composition of the vapor at equilibrium by following the tie line from c to *d* and drawing a perpendicular line to the base. We find X_A to be 0.8 and X_B to be 0.2. What this illustration has taught us is that when the equimolar solution of A and B is boiled, the composition of the vapor is different from that of the liquid, being enriched in component A, the liquid with the lower boiling point.

The Process of Fractionation

Now let us look at Figure 7.6, which is fundamentally the same as Figure 7.5. If the solution L_1 consists of $0.1X_A$ and $0.9X_B$, it will boil at about 87 °C, yielding an equilibrium compostion of vapor V_1 of about $0.32X_A$. If vapor V_1 is condensed to liquid L_2, a simple distillation step has been performed, and the condensate is enriched in component A

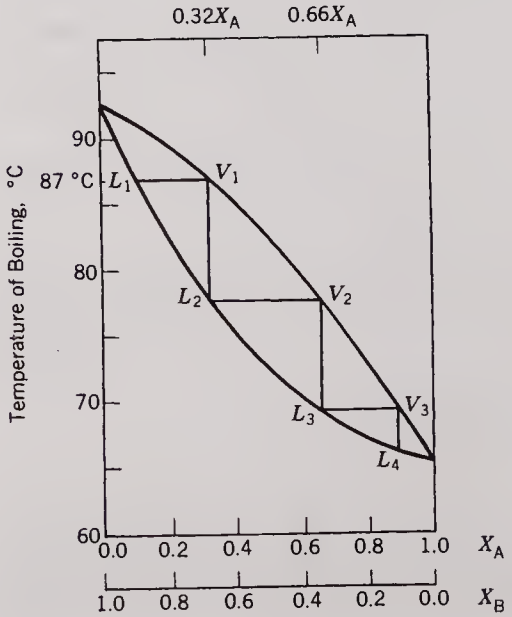


FIGURE 7.6 Fractionation diagram.

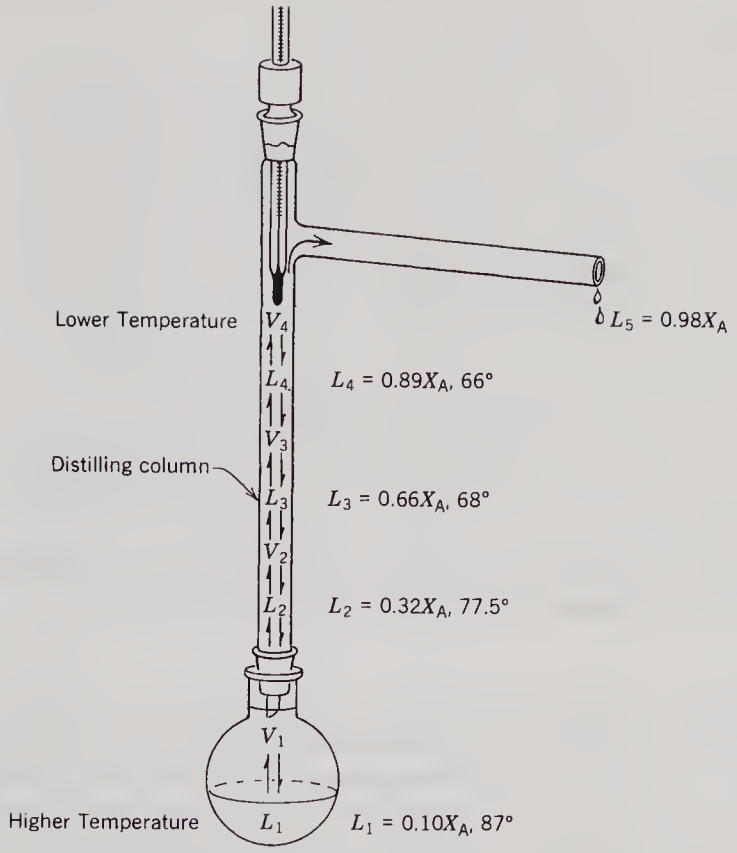


FIGURE 7.7 Schematic drawing of fractionation in a distillation apparatus.

(from $0.1X_A$ to $0.32X_A$). Now, if you take the distillate L_2 and distill it again, the boiling temperature is 77.5 °C and the vapor composition V_2 and distillate composition L_3 are about $0.66X_A$. The second distillation step is represented by the tie lines from L_2 horizontally to V_2 and then vertically to L_3. You could repeat the distillation again, along the tie lines L_3 to V_3 and V_3 to L_4.

The procedure of successive distillations just described would be experimentally tedious. But fractional distillation performs all of the simple distillation steps in one operation. Many fractionations are made to occur within a distilling column (Figure 7.7) which provides a large surface area on which many evaporation-condensation cycles can take place. The process requires that a temperature gradient be established in the column so that as the height up the column increases, the temperature decreases to the right degree for vaporizing condensate as it becomes continually enriched in the lower boiling component.

Figure 7.7 depicts the fractional distillation of the A–B mixture we have been discussing. There are several points about this drawing that you should note: First, it illustrates each distillation step as an equilibrium process, which in actual practice is not quite the case. Second, the figure shows that four simple and distinct distillation steps have occurred; so this distillation apparatus has four theoretical plates (see below). Actually, in most columns the process is continuous and allows vapors to be in constant contact with liquid progressively enriched in the lower boiling component. Third, you should note that the first distillation step takes place in the pot rather than the column. Finally, notice how the temperature decreases up the column as the mole fraction of the lower boiler, A, increases.

If the distillation process is carried out slowly enough to ensure that a multitude of vaporization-condensation cycles occur, the temperature at the thermometer bulb will remain constant at the boiling point of the lower-boiling constituent. If heat input is sufficient when the lower-boiling substance is nearly gone, the temperature will rise very rapidly up to that of the higher boiler and then level off again. Such behavior gives rise to the typical distillation curve shown in Figure 7.8.

If the distillation is performed too rapidly, the temperature will rise gradually and

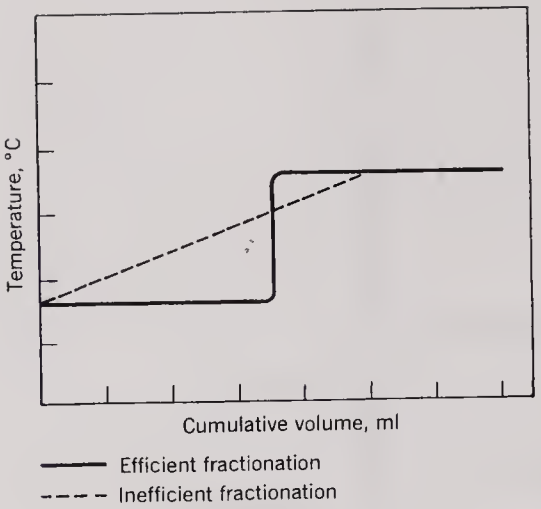


FIGURE 7.8 Distillation curve.

lead to a curve like that of the dotted line in Figure 7.8, which represents an inefficient distillation.

Efficiency

Distilling column efficiency is often given in theoretical plates, a term that comes from a type of industrial still composed of a column of dishlike plates arranged regularly in order of diminishing temperature. The plates collect condensed liquid and act like still pots, each pot capable of one condensation-vaporization cycle. A **theoretical plate** is a real or imaginary device that produces a difference in composition between liquid and vapor which is equal to that produced by a simple distillation under equilibrium conditions. One simple distillation step represents one theoretical plate, as does each evaporation-condensation cycle in Figures 7.6 and 7.7, including the cycle originating in the still pot of Figure 7.7. In Figure 7.7 the distillation apparatus has an efficiency of four theoretical plates, three of which are due to the column.

The higher the number of theoretical plates in a column, the more efficient it is, and the better it can separate liquids with boiling points close together. So, the number of theoretical plates necessary for a given separation depends on the difference in boiling points of the components of the mixture. The number of theoretical plates necessary to effect practically complete separation can be roughly calculated from

$$n = \frac{T_A + T_B}{3(T_B - T_A)} \tag{7-6}$$

wherein n is the number of theoretical plates, and T_B and T_A are the Kelvin boiling points of the less volatile and more volatile components, respectively. For example, in a pentane-hexane system, wherein boiling points are 36 and 69 °C respectively.

$$n = \frac{(273 + 69) + (273 + 36)}{3[(273 + 69) - (273 + 36)]} = 6.67$$

About seven theoretical plates would be required. (The result is not really good to three significant figures because of the way the equation was derived.)

The taller a column is, the more efficient it is. Therefore, it is also common to express efficiency in terms of **HETP,** the *H*eight of the column which is *E*quivalent to one *T*heoretical *P*late. HETP is very easily found by

$$\text{HETP} = \frac{h}{n} \tag{7-7}$$

wherein h is the height of the column in centimeters and n is the number of theoretical plates. For example, if a column is 22 cm high and is rated at 6.0 theoretical plates, the HETP of the column would be found to be

$$\text{HETP} = \frac{22 \text{ cm}}{6.0 \text{ plates}} = 3.7 \text{ cm/plate}$$

The lower the HETP, the more efficient the column is.

From this discussion so far, we might be led to believe that we should always choose a column of very high efficiency. However, we must remember that high efficiency requires many theoretical plates, which in turn require a large surface area upon which many vaporization-condensation cycles can occur. The large surface leads to a considerable column holdup, which is particularly undesirable when the volume of the mixture is small. A student or research fractionating column commonly has a holdup of 3 to 5 ml. Therefore, we must often make a compromise between purity and yield.

Reflux ratio is the ratio of the amount of condensate that falls back into the still pot to the amount of distillate that is collected in the receiver. For reasonable efficiency the reflux ratio should at least equal the number of theoretical plates.

Throughput is the maximum amount of distillate that can be obtained per unit time and still maintain near-equilibrium conditions. Throughput should be as high as possible in order to minimize the time for distillation, but should not be so high as to disturb the critically important temperature gradient. A related term **takeoff** refers to the amount of distillate obtained per unit time, whether or not near-equilibrium conditions prevail.

7.6 AZEOTROPES

No matter how carefully you distill a mixture of ethanol (ethyl alcohol) and water, ethanol, unlike methanol, cannot be separated completely from water. This is because ethanol and water form a binary azeotrope.

An **azeotrope,** also called a **constant-boiling mixture,** is a mixture of liquids which has a fixed composition and characteristic boiling point. Azeotrope is a term that was introduced by Wade and Merriman in 1911 to designate all binary and ternary mixtures that cannot be separated from each other by distillation. Azeotropy is a very common and complex phenomenon. Of 13,290 binary liquid mixtures listed in 1949, 6287 were azeotropes. Whether an azeotrope will be formed within a binary mixture depends on the relationships of molecular size, shape, and polarity.

If we consider molecules Q and R and the van der Waals and polar forces acting on them, we can conceive of interactions between Q molecules alone (F_{QQ}), between R molecules alone (F_{RR}), and between Q and R molecules together (F_{QR}). There are two possible relationships among the forces which lead to formation of azeotropes:

$$F_{QQ} < F_{QR} > F_{RR} \tag{7-8}$$

and

$$F_{QQ} > F_{QR} < F_{RR} \tag{7-9}$$

The first relationship results in a maximum-boiling azeotrope, and the second in a minimum-boiling azeotrope.

Maximum-Boiling Azeotropes

The first observations of maximum-boiling azeotropes were made in 1802 by John Dalton, who noticed that near the end of distillations involving aqueous HCl or HNO_3 the boiling point rose to a temperature higher than that of water and then remained constant.

Equation 7-8 teaches that when two components of a mixture have large polar attractions for each other, the attractive forces between unlike molecules can be greater than those between like molecules. The Q–R attractions can be so great that the ability of molecules at the liquid surface to vaporize is much reduced. Therefore, the total vapor pressure is less than would be expected from Raoult's law and we observe a negative deviation in the vapor pressure composition diagram of Figure 7.9. It is possible that at

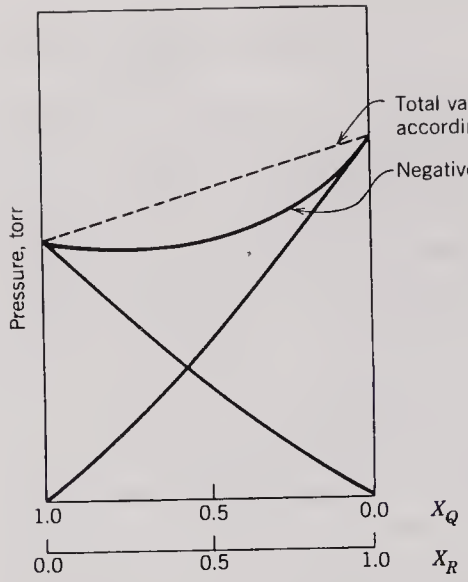


FIGURE 7.9 Vapor pressure composition diagram for Q–R at constant temperature.

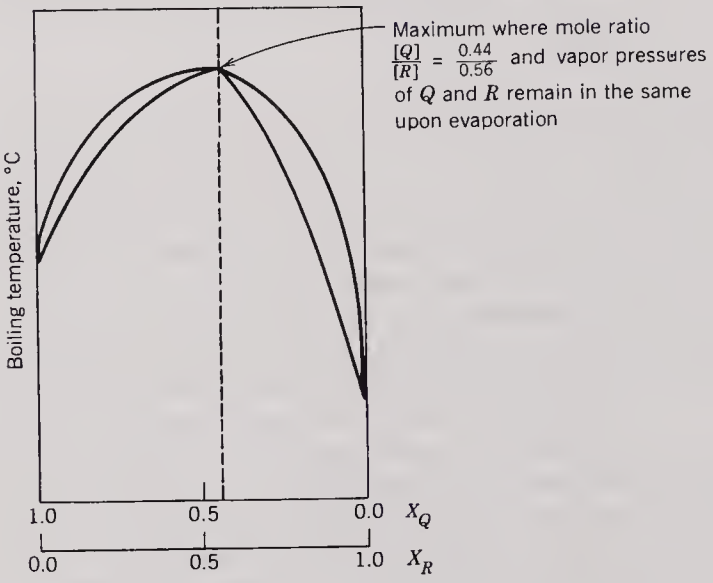


FIGURE 7.10 Boiling point composition diagram for maximum-boiling azeotrope.

a certain mole ratio of Q and R the attractive forces can be so great that upon evaporation the vapor pressures of Q and R remain the same. The consequence is that no fractionation of Q and R is possible and we observe in the boiling point composition diagram a maximum like that in Figure 7.10. It is this maximum that leads to classifying this type of azeotrope as maximum-boiling.

A maximum in the boiling point composition diagram is not *necessarily* a consequence of a negative deviation from Raoult's law. For example, mixtures of acetone (IUPAC propanone) and ether (IUPAC ethoxyethane) show a negative deviation but the vapor pressure of ether is so much greater than that of acetone that a constant-boiling mixture does not result.

Minimum-Boiling Azeotropes

Minimum-boiling azeotropes are far more common among organic mixtures than are maximum-boiling azeotropes.

We see from equation 7-9 that forces of attraction between like molecules can be greater than between unlike molecules. The greater the difference in structure, size, and polarity of the molecules, the more likely is a tendency toward immiscibility and a positive deviation from Raoult's law like that shown in Figure 7.11. If the positive deviation is great enough, there will be a mole ratio at which the vapor pressures of S and T remain the same during evaporation. The consequence is that no fractionation can occur and

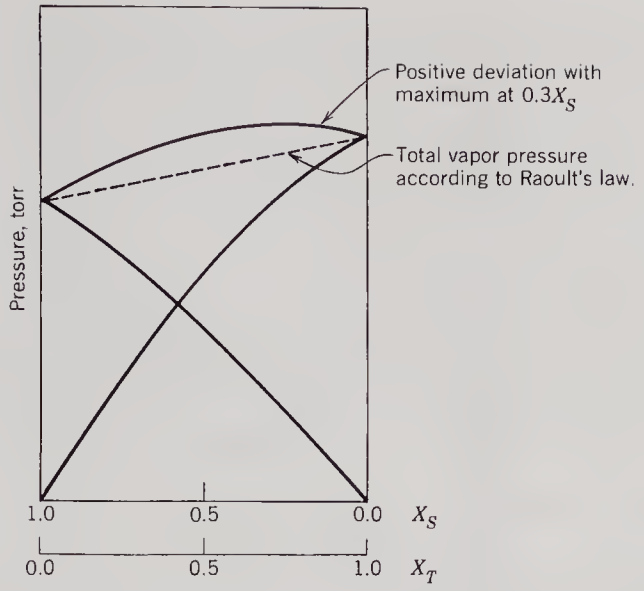


FIGURE 7.11 Vapor pressure composition diagram for S–T at constant temperature.

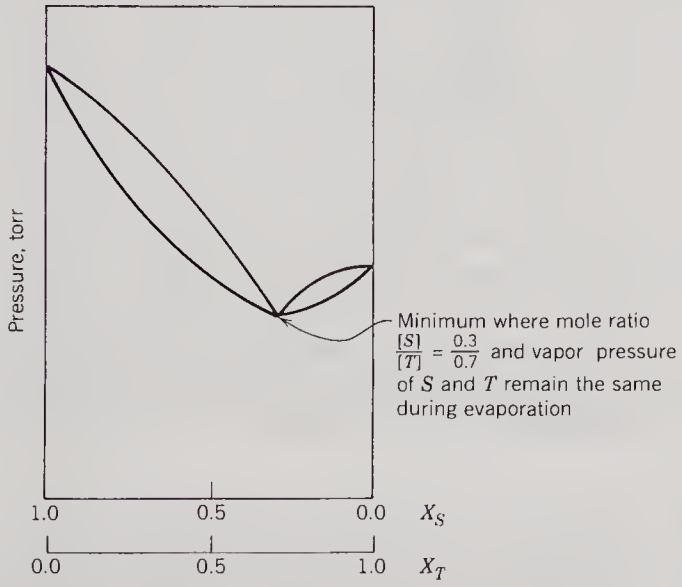


FIGURE 7.12 Boiling point composition diagram for minimum-boiling azeotrope.

we observe in the boiling point composition diagram a minimum like that in Figure 7.12. It is this minimum that leads to classifying this type of azeotrope as minimum-boiling.

Now, as an example, let us consider the solutions of two different alcohols with water. First, we note that methanol, CH_3OH (bp 65 °C), has a structure similar to that of water and a boiling point 35 °C below that of water. A mixture of methanol and water exhibit a positive deviation from Raoult's law but do not form an azeotrope. On the other hand, ethanol, CH_3CH_2OH (bp 78.5 °C), is structurally more different from water than is methanol because of its greater hydrocarbon character. It is less polar and larger than methanol, and its boiling point is only 22 °C below that of water. The consequence is that a mixture of ethanol and water exhibit a greater positive deviation from Raoult's law than the methanol-water mixture, and form a minimum-boiling azeotrope with a 95.6 ethanol–4.4 water mass percent composition and a normal boiling point of 78.2 °C.

7.7 FRACTIONAL DISTILLATION TECHNIQUES

Apparatus Set up an apparatus like that in Figure 7.13. Notice that the main difference between the fractional distillation apparatus and a simple distillation apparatus (Figure 7.2) is the

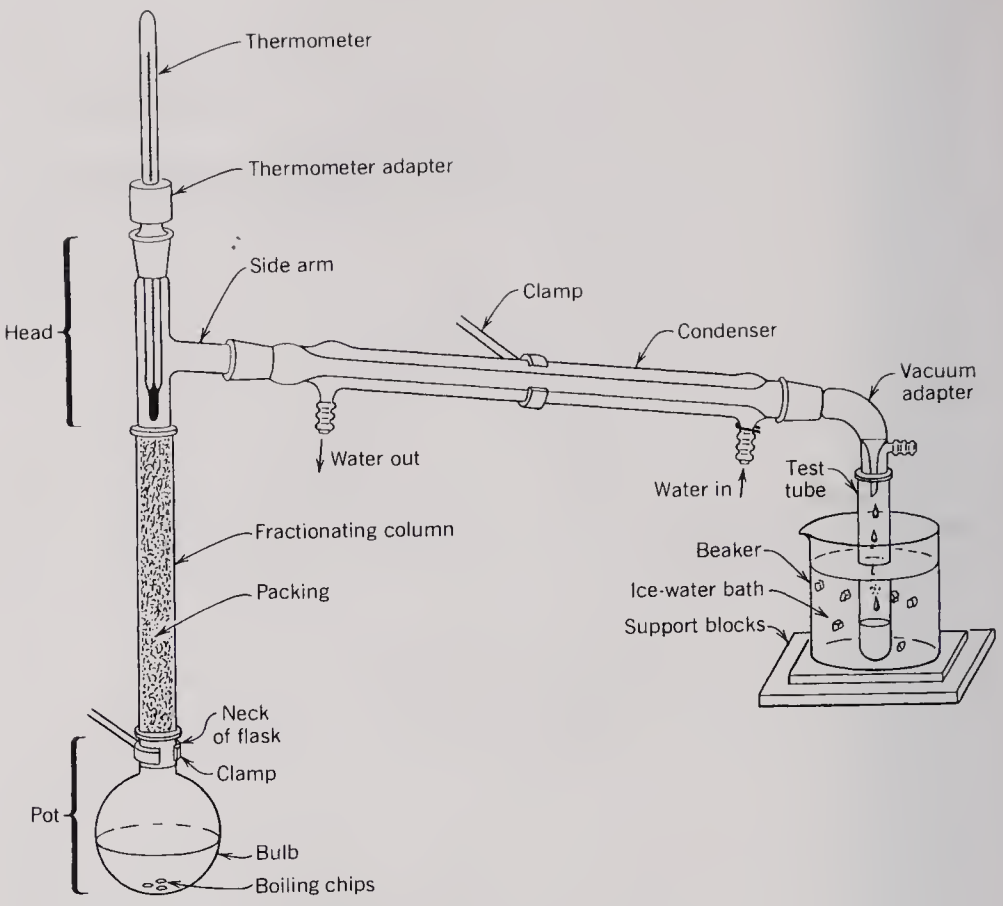


FIGURE 7.13 Fractional distillation apparatus.

inclusion of the fractionating column. Because of the ice-water bath, the reciever end of the apparatus in Figure 7.13 illustrates a system satisfactory for the collection of samples boiling between 50 and 75 °C.

The Column

Several types of columns are suitable for fractional distillation in the laboratory. One common and moderately efficient column is the Vigreux column, shown in Figure 7.14*a*. The Vigreux column has projections which are inclined at about 45° downward into the column, and are often found in pairs at opposite sides. A Vigreux column can be made

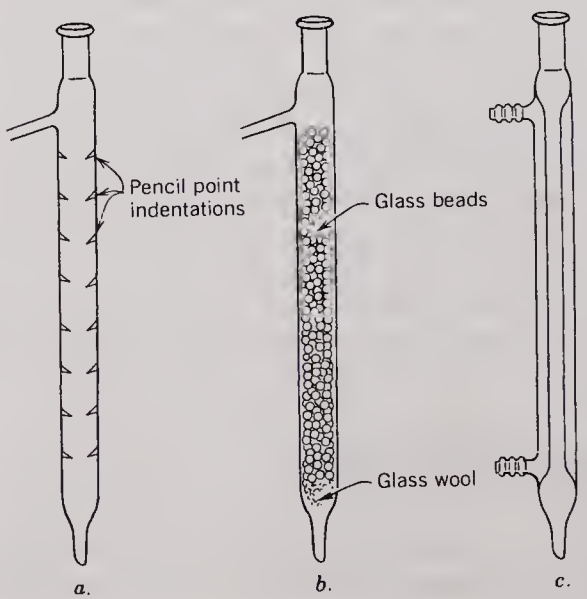


FIGURE 7.14 Three common types of fractionating column, which might be with or without sidearm. (*a*) Vigreaux. (*b*) Hempel. (c) Jacketed.

by heating a small spot on an ordinary glass column until the glass softens, then pushing the glass inward with a pencil point. A 20-cm Vigreux column has a relatively low efficiency rating of two to three theoretical plates (HETP 10–7 cm). It is convenient to use, however, because of its low holdup (ca. 1 ml) and its potentially high takeoff.

A more efficient column is known as the Hempel column, shown in Figure 7.14*b*. It consists of a simple distillation column filled with some kind of column packing to within about 1 or 2 cm of the sidearm. Common types of packing are glass beads, glass rings, glass helices, stainless steel beads or rings, or stainless steel turnings. If the liquids being distilled do not react with copper or aluminum turnings they also are suitable. Small-diameter (3–5 mm) glass tubing cut into approximately 1-cm lengths also can be used. The basic idea, of course, is to provide a large surface area on which many successive condensations and vaporizations can take place. A 20-cm Hempel column packed with glass helices has a theoretical plate rating of about 5 (HETP 4 cm per plate) and a holdup of 4 ml.

Notice that at the lower end, your distilling column has three finger-like projections which act as supports for packing.

To introduce loose packing like beads or rings, hold the column horizontally and put in about one-third of the packing; then hold the bottom of the column closed and quickly raise it to a vertical position. If the packing starts to fall out the bottom of the column, return the column to the horizontal and again set it upright. When the packing is stabilized in the vertical position, fill the remainder of the column. If this method is unworkable, first put a *thin* layer of glass wool (angel's hair) over the finger supports; then add the loose packing. Use the smallest possible amount of glass wool because a wad of it will encourage **flooding,** the collection of a pool of condensate in the column.

If you are using metal turnings, take care not to pack them too tightly into the column. Using 2–3 g of copper turnings for a 20-cm column, push them into the column with a stirring rod so that the packing density is reasonably uniform. Tight wads of turnings encourage flooding. Remember that many organic compounds, notably halides, will corrode metal packings.

If glass wool must be used as a support for column packing wear gloves while working with it. Tiny fragments can imbed themselves in your skin and cause irritation.

Insulation

The temperature at the sidearm of the column must be maintained always at the boiling point of the lowest boiling liquid present. Vigreux or Hempel columns usually need to be insulated from drafts and even normal air currents in order to work properly. Insulation is *essential* for distillation of liquids boiling over 100 °C. To insulate the column and still head, surround them with a glass tube jacket held in place by bored corks, loosely wrapped aluminum foil, or a blanket made of glass wool held between two sheets of aluminum foil. Sometimes, for very high boiling liquids or long columns, evacuated jackets are installed on the columns, or electric heating tape is used so that heat loss is balanced by application of heat to the column.

Column Holdup

The holdup depends on column length and on the amount and kind of packing. The longer the column and the more packing of a given kind, the greater is the holdup. The ratio of the initial amount of liquid in the distilling flask (the charge) to holdup should be as large as possible because the holdup represents liquid that will not be discharged from the column into the condenser. A general rule is that the still charge to holdup ratio should be at least 20 to 1.

The holdup can be approximated by pouring a known amount of the liquid in the top of the column and measuring how much does not run out the bottom. The holdup will vary some depending on the temperature of the apparatus and the viscosity and boiling point of the liquid.

Reflux Ratio The more difficult the separation of components (the closer their boiling points), the greater is the reflux ratio necessary to effect a good separation. Separation of compounds differing only a little in boiling point might require a reflux ratio of 50 to 1, whereas a separation involving a wider boiling point spread might demand a reflux ratio of only 5 to 1. In any case, the number of drops returning to the pot will be at least several times as great as those going into the receiver. To check the reflux ratio, count the drops returning to the pot and the drops going into the receiver; then divide pot drops by receiver drops. Adjust the heat input so that the reflux ratio is about the same as the number of theoretical plates in your column plus pot.

Flask Size As for simple distillation, use a flask size no larger than necessary. However, keep it large enough so that at the beginning of the distillation it is no more than one-half to two-thirds full.

Flooding Flooding most often results from columns which are too tightly packed or which are subjected to drafts or rapid heating. If your column floods, remove the heat source until all of the liquid pool has returned to the pot. Begin distillation again, starting with a lower heat input than before.

Collection of Fractions In separate, labeled, stoppered vials or test tubes, collect and save fractions of distillate coming off at various steady temperatures or temperature ranges. Label the containers 1, 2, 3, . . . or a, b, c, . . . , in accord with the record being kept, as shown in Table 7.2. The volume of individual samples collected depend somewhat on the initial charge. In general, 1- or 2-ml samples are likely to be satisfactory for samples of the size you are likely to have in beginning organic laboratory. Pour together all samples coming over at the same temperature or within a narrow temperature range and save them as one fraction. The range depends on desired purity, of course, but in general for liquids whose boiling points are separated by perhaps 30–50 C°, a 2–3 C° range probably is satisfactory. If weights of fractions is desired rather than volumes it is a good idea to have preweighed (tared) flasks ready.

Conducting the Distillation Put liquid in the flask and add a couple of boiling chips. Raise the heat source into place and heat the solution to a gentle boil.

As soon as boiling begins, you might see a ring of condensate rising up the column. Make the rise of the ring very gradual so that a steady temperature gradient from the bottom to the top of the column is attained. It should take 5 or 10 min to move up a 20-cm column. Open column insulation slightly from time to time so you can watch for the rise of the condensate ring and for potential flooding. When the ring has risen to just below the bottom of the thermometer bulb, keep it there for a few minutes; then increase the heat input slightly so that distillation begins. Record the temperature at the still head when the first drop of distillate comes over. Adjust the heat to maintain the desired reflux ratio and a takeoff of no more than 1 or 2 drops/s (3 to 6 ml/min). If a forerun is observed, change receivers when the temperature rises to the boiling point of the lowest boiling liquid or when the distillate is no longer turbid.

If you have the heat input properly adjusted and are getting a sharp fractionation, when the distillation of the first liquid is complete, the temperature at the head will drop and distillation will cease. If you are going to collect another fraction, change receivers and increase the temperature of the pot so as to initiate distillation of the next higher boiling liquid.

If the temperature rises gradually throughout the distillation, you are not getting a good separation. The problem might be that you are distilling too rapidly and/or that the column is not efficient enough. If you are not getting a sharp separation because of

a too rapid heating, it is probably best to start over. If the problem is due to low efficiency, collect fractions within temperature ranges and redistill them later.

Sometimes liquid refluxes in the still head without discharging to an appreciable extent into the sidearm. Wrapping the top of the head will force more vapors into the sidearm before condensation.

At the end of distillation, terminate heating before the flask is dry. In general, distillation to dryness is a bad practice because when there is no more liquid to evaporate, the flask temperature can rise very quickly. You can damage a heating mantle by overheating it. Disassemble the apparatus, returning the dry packing to its container.

If peroxides (often found in conjunction with ethers, alkenes, and aldehydes) should be present in the residue of a dry flask, an explosion might result.

Distillation Chasers

Because there is a holdup associated with every distillation apparatus, the last highest boiling substance to be distilled cannot be fully distilled over. The yield of the final distillate can often be improved by ensuring that it is not the highest boiling substance present. To accomplish this an even higher boiling liquid (which will not form an azeotrope) is introduced into the pot. This liquid is referred to as a **chaser** because it "chases" the desired vapors from the distillation apparatus and then itself occupies the volume associated with the holdup. Add at least enough chaser to equal the column and boiling flask holdup. It is, of course, necessary to do the final fractionation carefully so as to avoid contamination of the product with chaser.

Review the operational hazards related to simple distillation.

7.8 EXPERIMENTAL PART
Fractionation and Identification of a Binary Mixture

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Adding chemicals to reaction vessels	(0.8)
Storing products	(0.12)
Labeling	(0.13)
Boiling points	(3.5)
Simple distillation	(7.2)

You will be given 20 ml of unknown binary mixture (5/15 by volume) consisting of one of the following pairs: methanol/water, methanol/chloroform (IUPAC trichloromethane), methanol/isopropyl alcohol (IUPAC 2-propanol), methanol/2-methyl-2-butanol, ethanol/2-propanol, ethanol/2-methyl-2-butanol, pentane/hexane, pentane/heptane, pentane/octane, hexane/heptane, hexane/octane.

Preparation of a Hempel column. Pack a 15-cm distilling column or short jacketed condenser with a packing material suggested by your instructor. If a jacketed condenser is used, do not introduce water into the jacket. If no prepared packing is available, use a loose 2-g packing of copper turnings or cut enough 1-cm lengths of 4-mm glass tubing to fill the column to the required height. Wrap the column and upper part of the flask loosely with aluminum foil; if a jacketed condenser is used you will not need to wrap the column.

Setup of apparatus. Set up a distillation apparatus like that in Figure 7.13. Because of the volatility of the liquids, you might want to collect the distillate in a cooled receiver, open to the atmosphere but connected to the condenser. A vacuum adapter inserted

between condenser and receiver works well (Figure 7.13). Use a 10-ml graduated cylinder or test tube as receiver. If a test tube is used, mark the tube at 0.5- and 2.0-ml intervals, employing masking tape or a felt marker. It is best to have two tubes so marked, the second one being kept in the cooling bath when not in use. Introduce your mixture of liquids into a 50-ml round-bottom flask along with one or two boiling chips. Connect the flask to the distillation apparatus.

Conducting the distillation. Heat the flask using an appropriate heat source. If you are using a heating mantle, set the rheostat initially at about 50 V. Do not allow heating to be too rapid. As soon as boiling begins, turn the rheostat control back a little and watch for a ring of condensate to rise up the column. (A condensate ring is not always observable.) Increase the rheostat setting slightly if the ring definitely stops moving upward. Do not hurry it. Considering the equipment you probably have in your laboratory, you should probably distill at a rate of about 0.5 ml/min or, depending on drop size, about 1 drop every 2 or 3 s. Collect 1-ml fractions (**cuts**). Watch the thermometer carefully, and when the temperature drops, increase the heat input a little. When the temperature begins to rise sharply record the temperature at the end of each half-milliliter fraction. You can put all fractions together which come over at the same temperature or between temperatures that do not vary by more than 2 or 3 degrees.

Prepare a table of data as you work. Record the number of the cut, the time, the lapsed time, the temperature, the volume collected, and the cumulative volume at the end of each 2.0-ml cut. Please refer to Table 7.2 for an example.

As soon as the temperature of the higher boiler has been reached and you have ascertained that the temperature is constant during collection of a few milliliters of the higher boiling liquid, you can stop. Pour the contents of the pot, along with the higher boiling distillate, into a graduated cylinder to measure the total volume of the higher boiling liquid; then pour it into a container and cover it. △

Put distillate, pot residue, and the combined fractions (those collected while the temperature was rising rapidly) into separate, labeled vials and submit them to your instructor. Be sure to indicate on the labels the number of your unknown as well as your identification of the fraction. Determine and record the barometric pressure. Calculate and record the boiling points corrected for pressure. Make a distillation curve like that of Figure 7.8. Use the ordinate for temperature and abscissa for milliliters of cumulative distillate collected.

Determine and record the takeoff for each section of the curve by dividing milliliters collected for each section by the corresponding time elapsed for that section. Calculate the percent yield for each purified component of the mixture.

Writing the discussion. Identify your unknown mixture and explain your conclusion. Based on the shape of the distillation curve, discuss how well you separated the two components of the mixture. Suggest how you might improve separation and yield by altering your personal technique.

7.9 EXERCISES

Prelaboratory

1. Make a complete labeled drawing of the still you will use for your fractional distillation.
2. Should there be a temperature gradient from bottom to top of a fractionating column? Would a proper temperature gradient be likely to be established if the condensate ring rises rapidly? Explain.
3. A student was separating 20 ml of pentane mixed with 30 ml of octane. She used a fractionating column and set a graduated cylinder on the bench top for a receiver. The temperature at the still head thermometer was 36 °C for a while, then rose rapidly to 126 °C. She obtained 28 ml of octane but only 5 ml of pentane. Explain. Suggest an appropriate modification of apparatus which would give better results.

Postlaboratory

1. If the vapor pressures of two pure liquid components of a mixture are the same, could they be separated by fractional distillation?
2. If, on mixing together of two liquids, the energy of making nonbonded interactions is greater than the energy of breaking nonbonded interactions, which kind of azeotrope is more likely to form? Will the mixing produce an exotherm or an endotherm?
3. Mole% is often used instead of mole fraction in phase diagrams. How do you change X to M%?
4. Using Figure 7.4, determine P_b, P_t, and total P when $X_b = 0.20$.
5. Using Figure 7.4, determine whether there is any composition of benzene-toluene that will boil at 60 °C.

7C Vacuum Distillation

When liquids decompose at their atmospheric boiling points we commonly use vacuum distillation, also called distillation at reduced pressure, to purify them. We also often use vacuum distillation to purify liquids that have atmospheric boiling points above 200 °C, even if they do not decompose, because (1) the heating device we must use is not able to supply the required temperature; (2) we do not want to use a Bunsen burner flame around flammable organic compounds; (3) it is more likely that an organic compound will air-oxidize at a higher temperature; (4) very hot equipment is more troublesome and hazardous to work with; and (5) condensers are more difficult to cool as high-temperature vapors pass through them.

7.10 DISCUSSION OF VACUUM DISTILLATION

A liquid boils when its vapor pressure is equal to the ambient pressure (usually atmospheric pressure). Decreasing the ambient pressure allows the liquid to boil at a lower temperature because less energy is required to produce a vapor pressure that equals the reduced ambient pressure. For example, methyl anthranilate (IUPAC Methyl 2-aminobenzoate—artifical grape flavor) boils at 256 °C at a pressure of 760 torr but boils at 135.5 °C at 15 torr.

A useful generalization for estimating reduced pressure boiling points is that above 25 torr halving the pressure reduces the boiling point by about 25 C°. By this rule we predict that methyl anthranilate should boil around 231 °C at 380 torr, or 131 °C at 24 torr ($256 - 5 \times 25 = 131$, the factor of 5 resulting from halving the pressure five times). We see that this predicted boiling point is not quite correct, the reason being that reduction in boiling point is not a linear function of pressure.

The nomogram of Figure 7.15 usually enables you to make a closer estimate. A **nomogram,** or nomograph, is a graph that permits finding with a straightedge the value of a dependent variable when the value of an independent variable is given. Let us find the boiling point of methyl anthranilate at 24 torr by using the nomogram. Lay a straightedge on the nomogram so it rests on 256 °C on the vertical normal boiling point scale and on 24 torr (the independent variable) on the oblique curved line, thereby producing line A–B. This line crosses the vertical reduced-pressure boiling point scale at 142 °C (the dependent variable).

You can use the nomogram for estimating (1) reduced-pressure boiling points from normal boiling points, (2) normal boiling points from reduced-pressure boiling points, and (3) one reduced-pressure boiling point from another reduced-pressure boiling point by finding as an intermediate the normal boiling point. The nomogram applies best to non-hydrogen-bonded liquids.

Measurements of reduced-pressure boiling points are somewhat more difficult and not as accurate as measurements at atmospheric pressure for several reasons: First, superheated vapors are more likely to reach the thermometer bulb because in vacuo

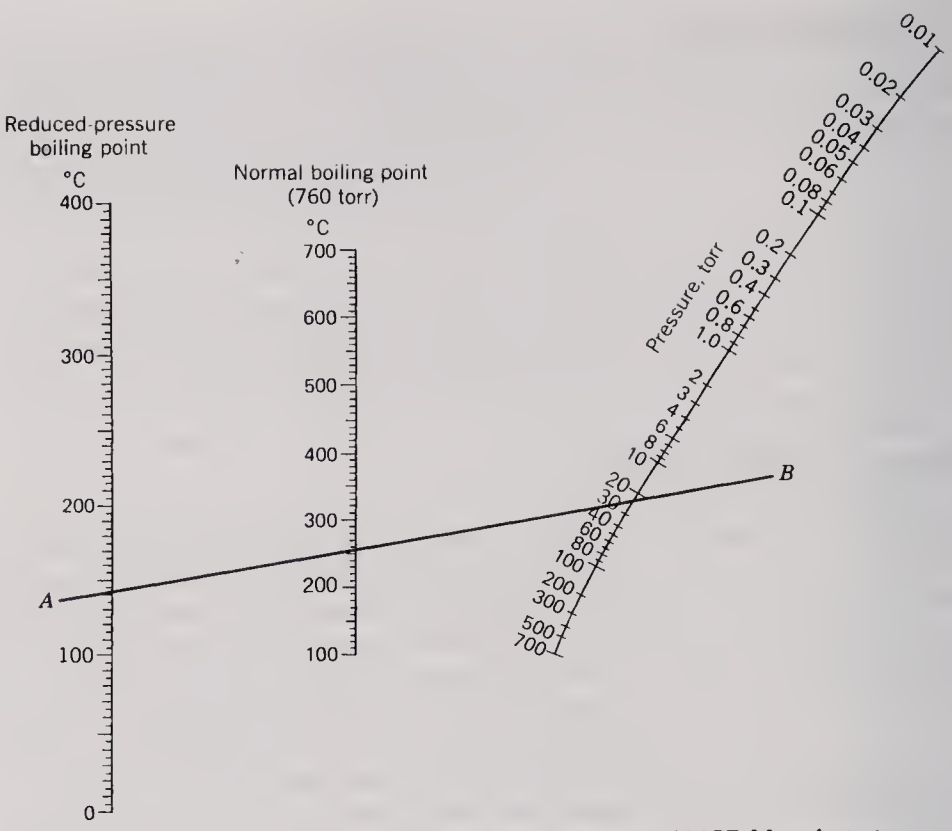


FIGURE 7.15 Pressure-temperature nomogram. Courtesy of MCB Manufacturing Chemists, Inc.

the molecular velocity toward the sidearm is vastly increased when there are fewer molecules to collide with each other and impede forward motion; this leads to reporting a temperature that is too high. Second, the greater velocity toward a highly evacuated center permits a greater vapor pressure at the surface of the liquid than nearer the vacuum source. Therefore the pressure at the manometer is likely to be lower than the pressure where evaporation is actually occurring. Third, to produce smooth boiling, one often uses an ebulliator to introduce a fine stream of air bubbles into the boiling liquid; this tactic disturbs vapor equilibria and leads to an erroneous indication of pressure at the boiling surface. Finally, because vapor bubbles generated by boiling at 15 torr expand rapidly to 40 or 50 times the size of bubbles at atmospheric pressure, one often observes severe bumping. For the same reasons just noted it is also more difficult to get a good fractionation at reduced pressure than at atmospheric pressure.

7.11 TECHNIQUES OF VACUUM DISTILLATION

The Apparatus

We carry out vacuum distillation in generally the same manner as other distillations but with modifications made to accomodate use of reduced pressure. Figure 7.16 illustrates an ordinary distillation apparatus which has been made air tight and attached to a vacuum source. The vacuum line hoses must have thick walls so they will not collapse when evacuated. If tubing exhibits cracks when stretched, you should replace it because it is essential that there be no air leaks in the system. Keep vacuum hose lengths short and make all connections of rubber hose to glass tight. Carefully inspect all glassware for stars or cracks. Lightly grease all ground glass joints and make all rubber stopper connections snug. Do not forget to insulate the column for high-boiling distillates.

Figure 7.17 illustrates the kind of apparatus you can sometimes use if the distillate readily condenses at the pressure of operation. The sidearm must extend well into the cool region below the side spout of the test tube. In addition to simplicity, this sort of apparatus reduces losses due to holdup.

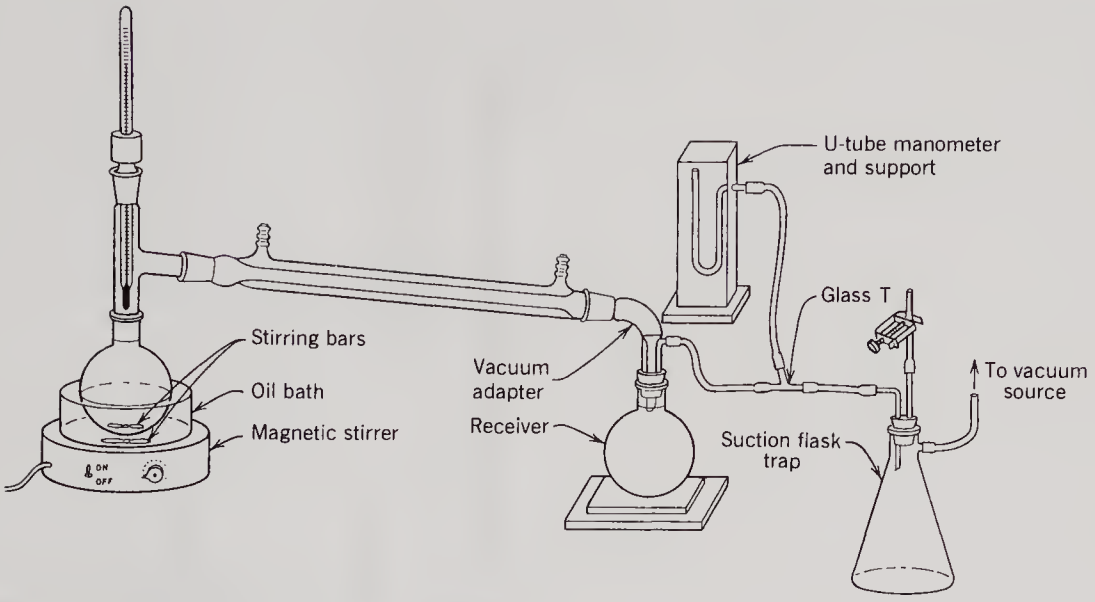


FIGURE 7.16 Vacuum distillation apparatus.

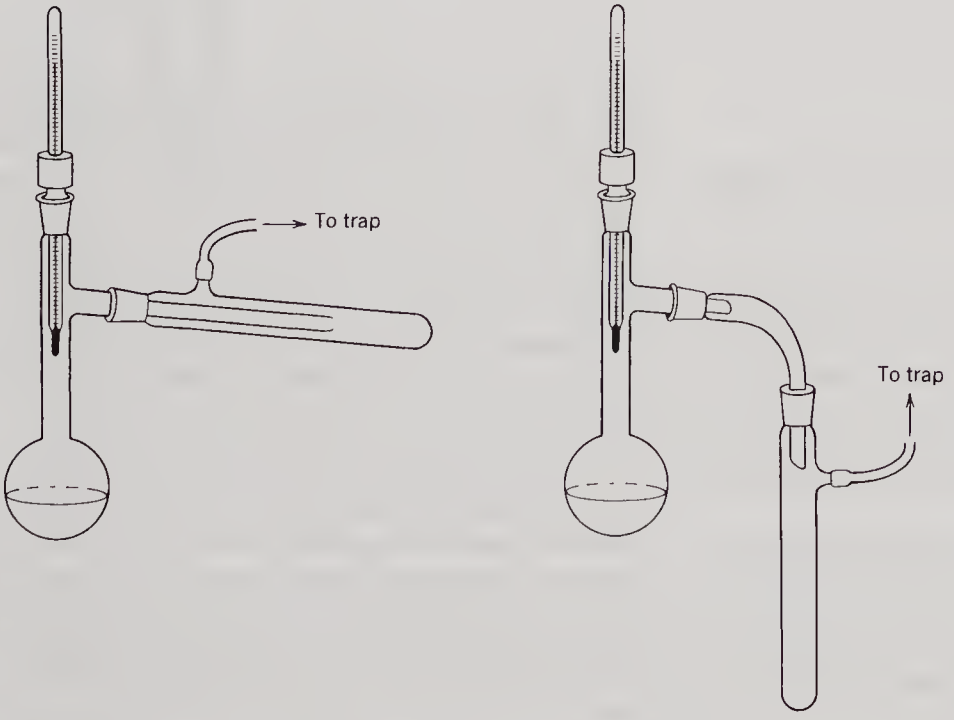


FIGURE 7.17 Vacuum distillation apparatuses without condensers.

Review the hazards for simple and fractional distillation.

Place a safety shield between you and highly evacuated equipment, or at least wear a face and throat mask. Danger comes not only from flying glass during implosion but hot chemicals as well.

Check all glassware for stars and cracks. Do not use thin-wall glassware.

Sometimes, to help prevent bumping into the sidearm, a Claisen head is employed, as shown in Figure 7.18.

Use a water-cooled condenser unless the temperature of the vapors entering it are above 150 °C; then you should use air for cooling. For the sake of the condenser (and your pocketbook!) estimate the reduced-pressure boiling point from Figure 7.15.

A trap is necessary between the receiver and vacuum source. If you are using a water aspirator to create vacuum, the trap protects the manometer and product from

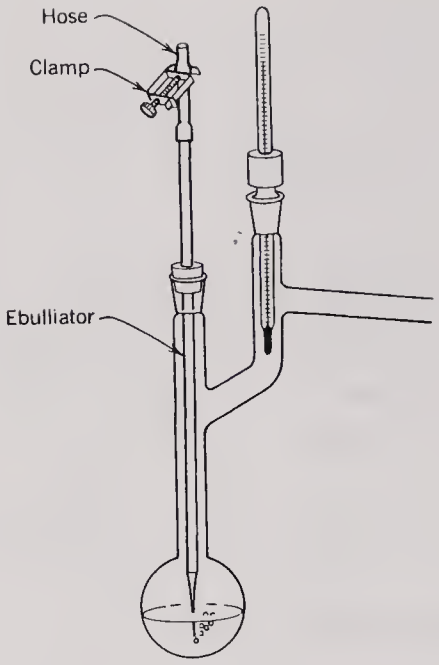


FIGURE 7.18 Distilling flask with Claisen head and ebulliator.

water should the water pressure fluctuate during distillation. The trap is the same one you use for vacuum filtration. Use the clamp on the trap to regulate the pressure in the still and to slowly release vacuum at the end of distillation. If you employ a vacuum pump for evacuation, you must replace the water trap of Figure 7.16 with the cold trap of Figure 7.19. The trap causes many vapors to liquefy or solidify, thereby keeping them from getting into the pump oil or corroding the pump. Make the Dewar flask thermos about one-third full of acetone, then cautiously add small pieces of dry ice to the acetone. It will bubble violently at first. When dry ice chunks remain without rapidly evaporating in the acetone, *slowly* insert the cold trap and clamp it in place. Maintain the height of the dry ice acetone bath about 2 cm below the rim of the Dewar flask by adding small chunks of dry ice or cold acetone as required.

Wear insulated gloves and use a tongs when working with dry ice.

Be certain that moving belts of vacuum pumps are adequately guarded. Tie back long hair and avoid wearing loose clothing, especially sleeves.

Enclose evacuated Dewar flasks in a wood box or wrap them completely with friction tape to help prevent flying glass in case of implosion.

Always keep the open end of a U-tube manometer sealed when it is not in use.

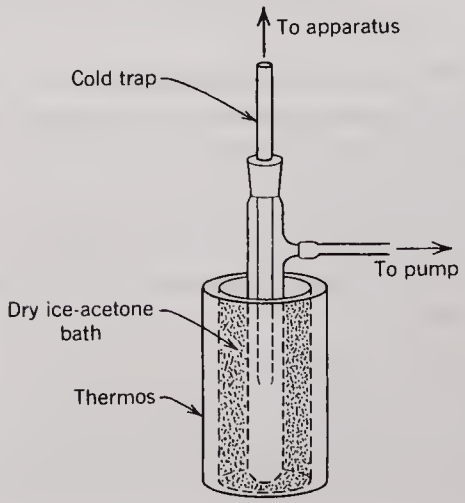


FIGURE 7.19 Cold trap.

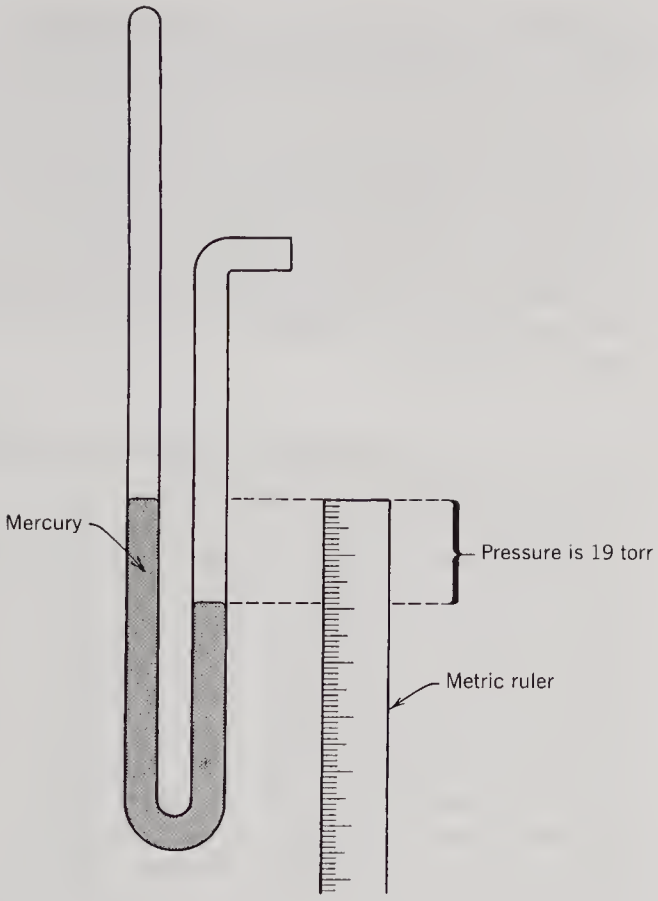


FIGURE 7.20 U-tube manometer.

Reporting a boiling point without also reporting pressure is of little value so it is customary to include a manometer somewhere in the system. The type of manometer you are most likely to have in your laboratory is the closed-end U-tube manometer, shown in Figures 7.15 and 7.20. As pressure within the system decreases, the mercury moves down from the closed end and rises in the right-hand tube until evacuation is at its maximum. The distance in millimeters between the levels of mercury in the right and left tubes is the pressure in the system. If there is no scale attached to the manometer, find the difference in height with a metric ruler.

The handiest vacuum source is the water aspirator. The maximum attainable vacuum by this system depends on the vapor pressure of water, which in turn depends on water temperature. To a close approximation, the vapor pressure in torr of water between 5 and 30 °C is numerically the same as its temperature. If the water temperature is 20 °C, the best vacuum attainable would be about 20 torr. Typically, attainable pressures are higher in the laboratory because aspiration is less efficient when many students are using aspirators at once.

A vacuum pump in good repair and containing good pump oil is able to decrease pressure down to 1 torr. The pressure can not be any lower than the vapor pressure of the pump oil, which depends on its purity. This is one reason why it is important to protect the pump with a cold trap.

Promoting Smooth Boiling

It is more difficult to prevent bumping during vacuum distillation than during atmospheric pressure distillation. Ordinary boiling chips are not satisfactory because in vacuo (under vacuum) they rapidly lose the tiny air bubbles trapped in their porous structures. The most convenient method to ensure smooth boiling is to use a rapidly rotating stirring bar in the still pot driven by a larger stirring bar in the heating bath (Figure 7.16).

A second method to induce smooth boiling makes use of an **ebulliator,** a drawn out tube that continually releases a fine stream of air bubbles into the boiling liquid. Many ground glass kits contain an ebulliator. If one is not available, you can make one

by selecting a piece of glass tubing which snugly fits available rubber hose, heating and drawing out the center about 6 cm to the diameter of a hair, and cutting it in the middle of the drawn out section. Put a 3-cm length of rubber hose and a screw clamp on the large end and attach the tube to the flask so the fine tip end extends to within 2 mm of the bottom. See Figure 7.18. By adjusting the tightness of the screw clamp, regulate the amount of air drawn into the liquid. Use a Claisen head with the ebulliator. The Claisen head serves two purposes: It holds the ebulliator in place, and it helps to prevent the bumping of liquid over into the condenser. Although an ebulliator is usually quite effective for inducing smooth boiling, its use poses two disadvantages: The introduction of air increases likelihood of oxidizing the hot materials in the pot and makes pressure monitoring less accurate.

Procedure Remove low-boiling solvents by simple or fractional distillation at atmospheric pressure prior to purification by vacuum distillation.

Assemble an apparatus incorporating the features that best suit your purpose. Securely clamp it to ringstands or other supports and make sure that all joints are air tight. Add the liquid to be distilled until the pot is no more than half-full and raise the heat source into position. Open the screw clamp(s) and, after maximum vacuum has been attained, read the manometer. Use Figure 7.15 to estimate the boiling point. If an ebulliator is being used, adjust its screw clamp until a fine stream of bubbles emerges from its tip. Watching the manometer, adjust the trap clamp if you want to conduct the distillation at a specific pressure other than maximum attainable vacuum. Turn on the heat source, controlling it so that the takeoff is about 1 drop/s. After distillation is under way, record the temperature and pressure; then check them occasionally. If pressure changes, adjust the heat input accordingly. When you have collected the distillate, turn off the heat source and lower it; then wait a few minutes while the system cools. Next, *slowly* open the trap screw clamp to release the vacuum. If you are using an ebulliator, slowly open its clamp simultaneously.

If a forerun must be removed, or if you are collecting fractions, you must break the vacuum and change receivers. Shut down the distillation as we have just described,

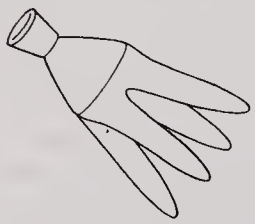


FIGURE 7.21 Cow.

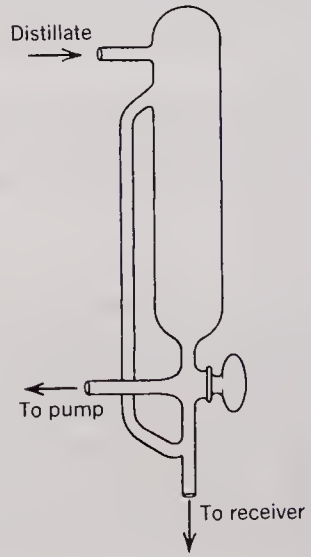


FIGURE 7.22 Fraction cutter.

change the receiver, and start it up again. You must cool *the pot* when the receiver is changed or sudden violent boiling or frothing might occur when you reestablish the vacuum.

A more convenient way to collect fractions is to use a cow (Figure 7.21) or a fraction cutter (Figure 7.22). With a cow you can collect several fractions before breaking vacuum; with a fraction cutter you need not break the vacuum at all.

Release vacuum so slowly that the manometer is not broken by a sudden surge of mercury toward the closed end. Set the manometer in a tray that will contain the mercury in case of breakage.

7.12 EXPERIMENTAL PART
Separation of Methyl Salicylate, Salicylic Acid, and Methylene Chloride

Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Filtration	(4.2)
Simple distillation	(7.2)
Boiling points	(3.5)
Melting points	(3.3)
Storing	(0.12)
Labeling	(0.13)

You will be given a mixture containing 5.0 ml of the methyl salicylate (IUPAC methyl 2-hydroxybenzoate), 10.0 ml of methylene chloride (IUPAC) dichloromethane), 0.5 g of salicylic acid (IUPAC 2-hydroxybenzoic acid), and a few floor sweepings. Your task is to separate the chemicals from each other.

Filtration. Using a fluted fast filter in a glass funnel, filter the mixture into a 50-ml distilling flask. Discard the filter residue. △

Recovery of methylene chloride. Assemble a simple distillation apparatus and collect methylene chloride at ca. 40 °C in a cooled, tared vial. Weigh the vial, cap it, and label it. Transfer the pot residue to a 25-ml distilling flask. △

Recovery of methyl salicylate and salicylic acid. Adapt the simple distillation apparatus for vacuum. Insulate the column and still head. If you are using a water aspirator for reduced pressure, you will have to use an oil bath, heating mantle, or flame as a heat source. If you are using a vacuum pump, a hot water bath or steam bath should be sufficient. Draw as much vacuum as you can, read the manometer, and from the nomogram and normal boiling points of methyl salicylate estimate the reduced-pressure boiling point. Distill at a rate of about 1 drop/s until dripping into the receiver ceases. Be sure to record the boiling point and pressure. Remove the heat source and slowly release the vacuum. Transfer the distillate into a tared vial, weigh it, label it, and cap it. While it is still hot, pour the pot residue onto a watch glass. Rinse the cooled flask with 1 ml of methylene chloride and pour the rinse onto the watch glass. Allow the methylene chloride to evaporate, obtain a melting point, and then transfer the product into a tared vial. Weigh the vial, label it, and cap it. △△ Based on the manometer reading during distillation, determine the normal boiling point of methyl salicylate from the nomogram.

Writing the discussion. Report the percent yield of each of the chemicals. Explain where and how (1) losses of each occurred, and (2) procedure and/or apparatus could be modified to give higher yields without sacrificing purity. Compare the literature boiling

point of methyl salicylate with the normal boiling point obtained with the nomogram; explain fully any variations.

7.13 EXERCISES

Prelaboratory

1. What methods are satisfactory for promoting smooth boiling during vacuum distillation? Which one will you use in this experiment?
2. (a) Make a list of the equipment required for the simple distillation of this experiment. (b) Make a list of the additional equipment you will need to modify the apparatus for vacuum.
3. What is the purpose of the trap during vacuum distillation using (a) a water aspirator; (b) a vacuum pump?
4. Write a stepwise summary of the experimental procedure for vacuum distillation.

Postlaboratory

1. Using the temperature-pressure nomogram, determine theoretical normal boiling point of strychnine, which boils at 270 °C and 5 torr. At what temperature would it boil at a pressure of 0.5 torr?
2. Butanoic acid boils at 163.5 °C at 757 torr. At what temperature would it boil if reduced pressure is created by a well-operating water aspirator with 25 °C water?
3. The normal boiling point of pentadecane is 270.5 °C. What would the pressure have to be in order for it to boil at 95 °C?
4. A student set up an apparatus to vacuum distill 20 ml of pentyl 2-hydroxybenzenecarboxylate (amyl salicylate). He set up the apparatus shown in Figure 7.16, employing a hot water bath, water aspiration capable of attaining a pressure of 30 torr, and a water-cooled condenser. Using this chapter and a handbook of chemistry and physics as source materials, critique the student's procedure.

7D Steam Distillation

Although fractional distillation techniques apply only to miscible mixtures, it is also possible to distill liquids that are immiscible. The distillation of such mixtures can be called **immiscible codistillation,** codistillation meaning distilling together. When one of the immiscible phases is water, the codistillation process is known as **steam distillation,** which has the advantage that liquids with boiling points well over 100 °C can be made to distill below 100 °C.

Steam distillation is widely used to isolate liquids and solids from natural sources. It is an important method for removing a reaction product from a nearly intractable or tarry mixture, for removing a product from an aqueous mixture containing inorganic salts or other organic solids, and for purifying a compound that decomposes at its boiling point. It is an excellent technique to use with compounds that are difficult to isolate or purify in any other way, and usually results in yields of high purity.

7.14 DISCUSSION OF STEAM DISTILLATION

For two miscible liquids, Q and R, which form an ideal solution, the total vapor pressure is the sum of the vapor pressures of the pure liquids as modified by their mole fractions:

$$P_{\text{total}} = P^0_Q X_Q + P^0_R X_R \qquad (7\text{-}10)$$

In the case of two *im*miscible liquids, A and B, the total pressure depends only on the vapor pressures of the pure liquids and is independent of their mole fractions:

$$P_{\text{total}} = P_A^0 + P_B^0 \tag{7-11}$$

Two immiscible liquids distill together at constant temperature and mole ratio. This is because the composition of the vapor above an immiscible mixture depends only on the individual vapor pressures, the mole ratio of the two components in the vapor state being the same as the ratio of the vapor pressures of the pure liquids A and B:

$$\frac{\text{moles A}}{\text{moles B}} = \frac{P_A^0}{P_B^0} \tag{7-12}$$

As an example, let us look at a benzene-water mixture, for which the boiling point is 69.4 °C. At this temperature the vapor pressure of water (from a handbook of chemistry and physics) is 228 torr; the vapor pressure of benzene at this temperature must be 760 − 228 = 532 torr. The mole ratio therefore is

$$\frac{532 \text{ moles benzene}}{228 \text{ moles water}} \quad \text{or} \quad \frac{2.36 \text{ moles benzene}}{1 \text{ mole water}}$$

Notice that the boiling point of the mixture (69.4 °C) is less than that of benzene (80.1 °C) or of water (100.0 °C). Notice also the similarity to minimum-boiling azeotropes; and indeed such immiscible mixtures do represent extremes of the molecular incompatibilities that produce azeotropic mixtures. The extreme incompatibility causes a higher total vapor pressure than would be predicted from Raoult's law, resulting in a lower boiling point for the mixture than for either component.

This discussion applies to combinations of all immiscible liquids. However, in practical separations by immiscible codistillation, water is used as one of the liquids because it is usually readily available and inexpensive, and its solubility characteristics are far different from those of a wide variety of organic substances.

Actually, all real liquids have at least slight compatibility. In a benzene-water mixture, two layers will form with benzene lying above water. The upper layer is a solution of a tiny bit of water in benzene and the lower layer is a solution of a very small amount of benzene in water. For very dilute solutions like these, Raoult's law applies fairly well and the combined vapor pressures of the two liquids in either layer are nearly equal to the vapor pressure of the major component in that layer. This is because the mole fraction of the major component is very nearly 1. Therefore, for practical purposes, mixtures like benzene and water behave in codistillation as if the liquids were completely immiscible.

The higher the vapor pressure of the organic compound relative to water, the shorter the distillation time will be. This is because when the organic vapor pressure is high (low boiling point), the ratio of organic compound to water is high, as we see in equation 7-12 and more specifically in equation 7-13:

$$\frac{\text{moles organic compound}}{\text{moles water}} = \frac{P^0_{\text{organic compound}}}{P^0_{\text{water}}} \tag{7-13}$$

This means that in the time required for a *small* amount of water to distill, a relatively *large* amount of organic compound will codistill along with it, the codistillate boiling point being well below that of water. On the other hand, if the organic vapor pressure is low (high boiling point), only a small amount of organic component will codistill along with a large amount of water. A long distillation time will therefore be necessary to obtain a substantial amount of product. The lower the organic vapor pressure, the more closely the codistillate boiling point will approach, but never exceed, the boiling point of water.

Two methods of steam distillation are commonly used: the direct process, and the live steam process. In the **direct process,** steam is generated in the still pot by boiling water and the other immiscible liquid together. In the **live steam process,** steam from a steam line is introduced into the pot. The live steam method is probably more widely used. It requires somewhat more complex apparatus, but reduces bumping. It is generally recommended when distillation involves a substance of low vapor pressure, such as

liquids of high molecular weight and/or polarity. You can even distill relatively volatile solids by this method.

Because water has a large molar heat of vaporization, it takes a considerable amount of heat to evaporate the large amounts of water necessary to steam distill substances of low vapor pressure at a reasonable rate. This requires an intense heating source, often causing superheating of liquid and the consequent violent bumping. The effects of bumping can be lessened in two ways: first, by using live steam, and second, by using a Claisen head. The former is the more effective control.

7.15 TECHNIQUES OF STEAM DISTILLATION

In order for the process to be feasible, the organic compound must have a vapor pressure of at least 5–10 torr at 100 °C.

The Direct Process

Set up the distillation apparatus of Figure 7.23, using a round-bottom flask and a Claisen distilling head. We use the Claisen head to help prevent the bumping of slurries over into the sidearm. You might want to wrap the flask and Claisen head with aluminum foil and/or fiberglass to minimize premature condensation of steam. Use the dropping funnel to add water to the still pot, thereby keeping the liquid level constant. In other ways proceed as you would for simple distillation.

The Live Steam Process

Assemble an apparatus like that shown in Figure 7.24 and securely fasten it to ringstands. If ground glass joints are used, lubricate them. The Claisen head is not essential but helps prevent bumping over of flask contents into the sidearm. Make the lines from the steam source to flask as short as possible so that cooling of steam and subsequent condensation in the lines are minimal. The steam inlet tube must extend well into the mixture to be distilled. If a three-neck flask is not available, insert the steam inlet tube down through the portion of the Claisen head directly over the bulb of the flask, as shown in Figure 7.25.

Be certain that steam lines are securely fastened at all points. A blast of steam from a loose steam line could cause thermal burns or startle you, causing you to upset equipment.

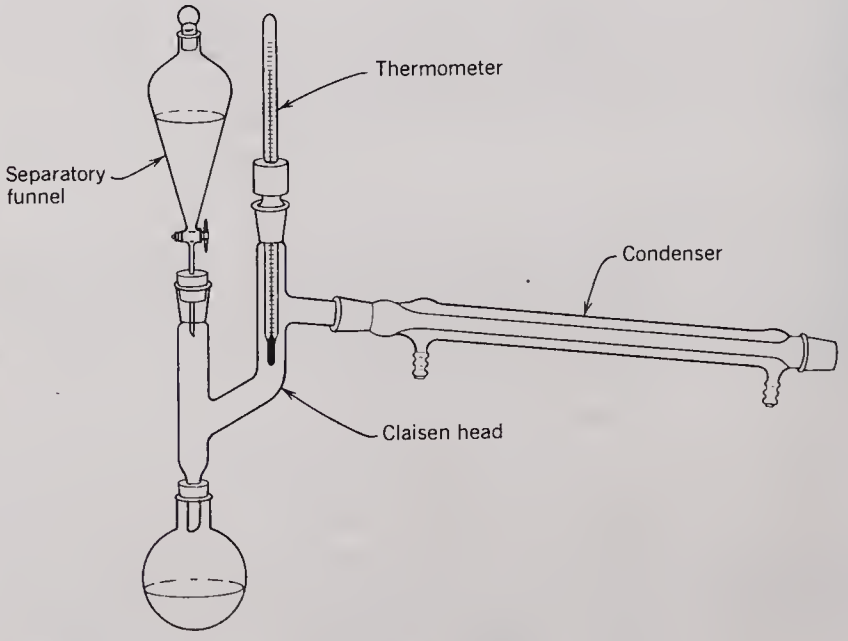


FIGURE 7.23 Direct steam distillation apparatus.

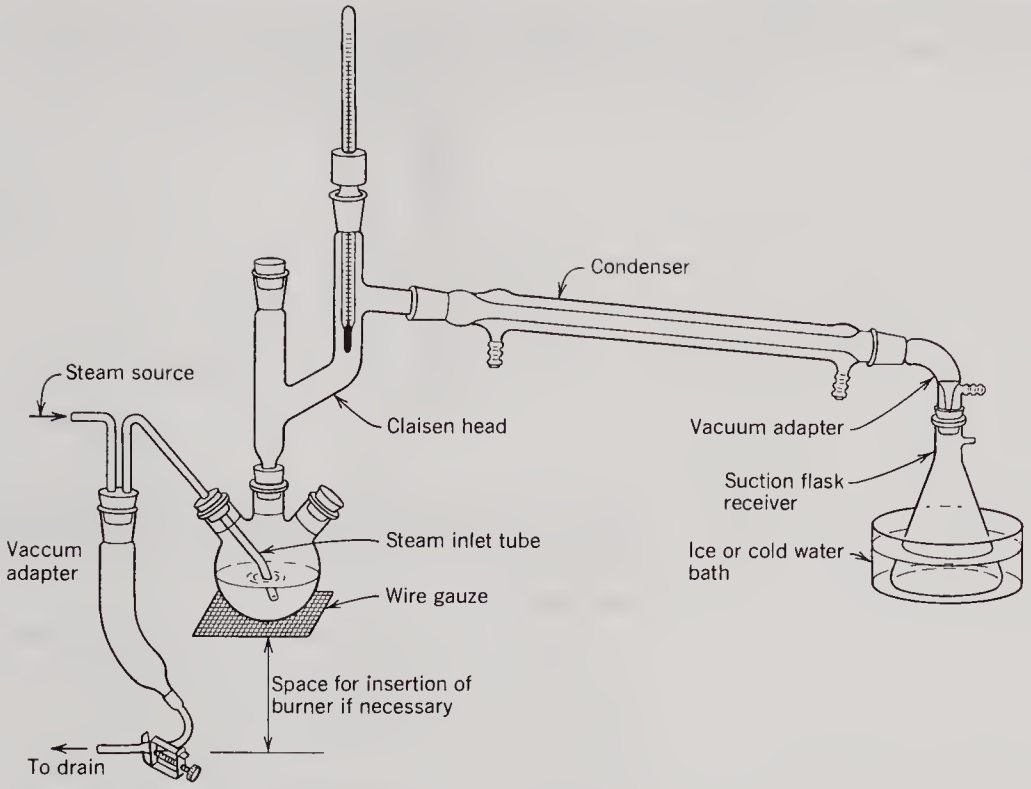


FIGURE 7.24 Live steam distillation apparatus.

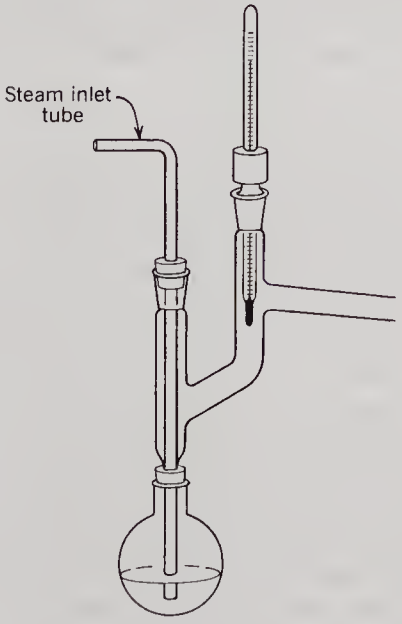


FIGURE 7.25 Steam distillation with a single-neck flask.

The flask should be no more than half-full throughout the distillation. It is ordinarily not necessary to use an external heat source, but if the flask begins to fill with condensed water during distillation, gently heat the flask with a heating mantle or Bunsen burner. If a burner is employed, use wire gauze under the flask to help distribute the heat evenly. You might find it advisable to wrap the flask and Claisen head with aluminum foil and/or fiberglass in order to minimize premature condensation of steam. You can get the distillation underway more quickly if you heat the contents of the flask to near 100 °C just before steam is introduced into the flask.

Use of the hot water trap shown in Figure 7.24 is advisable because when the steam valve is first opened, all of the condensed water in the pipe line must be removed before

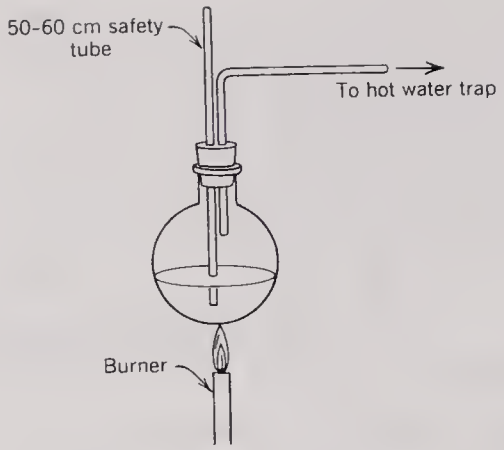


FIGURE 7.26 Steam generator.

steam can be supplied. Use a vacuum adapter to construct the trap. Keep the screw clamp on the drain hose open until the steam begins to enter the pot; then close it. Check the trap occasionally during distillation to ensure that water is not condensing and filling it.

You should adjust the steam flow rate so that steam heats the liquid in the flask, vaporizes it, and codistills with it as rapidly as possible without preventing condensation in the condenser. The flow of cooling water in the condenser will probably have to be a little faster than usual for simple distillation. To keep the receiver-end adapter and receiver cool to the touch throughout the distillation, you can use an ice bath around the receiver. When distillation is complete, open one of the screw clamps on the hot water trap and remove the steam inlet tube from the flask so that as the system cools, liquid from the flask will not back up into the steam line.

If no external steam line is available, you can construct a simple steam generator with a Bunsen burner heat source, as shown in Figure 7.26.

Determining the Point of Completion

There are three ways to determine when codistillation is complete. (1) If the compound to be distilled has a boiling point much below that of water, the boiling point of the codistillate will also be substantially less than 100 °C. In this case you will see the temperature at the sidearm rise to 100 °C when all of the organic compound is distilled over. However, in most cases of steam distillation, the boiling point of the organic compound is well above that of water. (2) You can observe the distillate to see that no more water-insoluble phase is distilling. As long as oily droplets are present or the distillate appears milky or cloudy, organic material is still distilling. In the case of a low-melting, solid organic compound, solid might be collecting in the condenser. When these conditions are no longer observable either in the condenser or in a separate test vial, the distillation is complete. (3) You can calculate the mole ratio or organic substance to water from equation 7-13. Then, based on the anticipated product yield, you will be able to estimate the total volume to collect. In the example of the benzene-water codistillate boiling at 69.4 °C we saw that the benzene-water mole ratio was 2.36 to 1. Assuming a 20.0-ml expected yield of benzene, and using the molecular masses and densities of benzene (bz) and water (w) at 20 °C, the milliliters of water and then the total volume can be calculated:

$$\frac{(1.00 \text{ mole w})}{(2.36 \text{ moles bz})}\left(\frac{\text{mole bz}}{78.1 \text{ g bz}}\right)\left(\frac{0.879 \text{ g bz}}{\text{ml bz}}\right)\left(\frac{18.02 \text{ g w}}{\text{mole w}}\right)\left(\frac{\text{ml w}}{0.998 \text{ g w}}\right)(20.0 \text{ ml bz})$$

$$= 1.72 \text{ ml w}$$

$$1.72 \text{ ml w} + 20.0 \text{ ml bz} = 21.7 \text{ ml total codistillate to be collected}$$

It will not hurt anything if you distill beyond the point of codistillation.

If a solid organic substance deposits in the condenser during codistillation, be certain that it does not plug the sidearm or condenser, thereby creating a closed system.

Review the operational hazards related to simple distillation.

7.16 EXPERIMENTAL PART
Purification of Aniline

Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Gravity filtration	(4.2)
Glassware	(0.3)
Heating	(0.5)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Simple distillation	(7.2)
Boiling points	(3.5)
Storing products	(0.12)
Labeling	(0.13)

You will be given a total of 100 ml of liquid containing 2.0 g of aniline (IUPAC benzenamine), 98.0 ml of water, and a small amount of floor sweepings.

Aniline is highly toxic. See Appendix C. Work in a hood when vapor can escape from reaction vessels.

Filtration. Using a fluted fast filter in a glass funnel, filter off any insoluble residues into a round-bottom flask of appropriate size. △

Distillation. Using the direct steam distillation method, steam distill the mixture. Grease the ground glass joints well because aniline is basic. Heat the mixture with a Bunsen burner and distill to the point of completion. Determine the point of completion by one of the methods described in Section 7.15. To prevent frozen joints, disassemble the apparatus immediately. △

Isolation of aniline. To isolate the aniline from the distillate, add 10 g of sodium chloride per 50 ml of distillate and stir the mixture well to dissolve the salt. Then extract the mixture twice with methylene chloride (IUPAC dichloromethane). △ Dry the extract over anhydrous sodium sulfate, △ and decant or filter the liquid into a distilling flask. Distill off the methylene chloride and then collect the aniline that comes over between 180 and 185 °C. Use a small-scale distillation apparatus if necessary (Section 7.18). Put the dichloromethane in its recovery container. △△ Turn in your final product. Calculate the percent yield.

Writing the discussion. Here are several suggestions as to what should be included in your discussion. Not all of them are appropriate. Review Section 1.4 and decide which to use:

1. Why the percent yield was less than 100%.
2. Why ground glass joints must be greased in presence of a base.
3. How insoluble impurities are filtered from a solution before distillation is begun.
4. Why insoluble impurities were filtered from your solution before distillation was begun.

5. Criticism of your technique relative to your percent yield.
6. Raoult's law.

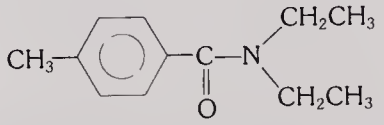
7.17 EXERCISES

Prelaboratory

1. Why do you use water as the codistillate for aniline?
2. During the second distillation the dichloromethane will distill at about 40 °C; then the benzenamine will distill at about 184 °C. For the sake of your condenser, what precaution should you take after the dichloromethane is distilled and before the benzenamine distills?
3. What precaution should be taken with regard to use of steam lines?
4. Why is sodium chloride added to the steam distillate in the experiment of Section 7.16?
5. During extraction in the experimental section do you expect the benzenamine to be in the upper or lower phase? Why? How can you experimentally determine this for certain?

Postlaboratory

1. If a codistillate containing water has a boiling point of 95 °C at 760 torr, what is the mole ratio of the second substance to water?
2. If a codistillate containing water has a boiling point of 90 °C at 760 torr, and 40.0 ml of the organic compound (mol mass 124 g/mole, specific gravity $1.2^{20/4}$) is anticipated, how many milliliters of codistillate in the receiver at 20 °C should be collected?
3. In the experimental section, ethoxyethane (ether) could have been used in place of dichloromethane to help extract benzenamine from water. For what reason of a precautionary nature was ether not used? If the ether had been used, would the top, or bottom, phase in the separatory funnel have contained the benzenamine? Why?
4. A student was purifying the odiferous solid, *N*,*N*-diethyl 4-methylbenzenecarboxamide,



by direct process steam distillation. Bumping was a constant problem. Analyze the reason for the bumping and suggest means for eliminating it.

7E Small-Scale Distillation

There are many times when a chemist is faced with having to distill small quantities of liquids, perhaps less than 1 ml. The obvious problem is that the holdup of usual distillation equipment might be greater than the sample size; therefore, special small-scale equipment is necessary. In this section, we will take a look at several varieties of small-scale distillation methods which might be useful to you. Keep in mind, however, that these small-scale distillations, often called **microdistillations,** will not give good fractionations.

7.18 TECHNIQUES OF SMALL-SCALE DISTILLATIONS

Small Distilling Flask

You can use a 5- or 10-ml distilling flask in a setup like that shown in Figure 7.27. The sidearm test tube acts both as condenser and receiver. The rubber stopper must fit tightly to the test tube mouth and sidearm of the flask. If the liquid boils at less than 100 °C, you will have to cool the sidearm test tube. In general, a bath 50 C° below the distillation temperature is about right. The drying tube is to prevent condensations of moisture (from the air) inside the receiver when cooling baths are used. You can also use the test tube sidearm as a point for attaching a vacuum line. If a small distilling flask is not available, a sidearm test tube can be used in its place, as shown in Figure 7.28. You must lengthen the sidearm of the test tube used as the still pot by adding a section of glass tubing which extends down into the sidearm test tube receiver. Hold together the glass tube and sidearm by a tight sleeve of *clean* hose. An obvious disadvantage to this arrangement is that plasticizers or other contaminants might leach from the hose during distillation. You need to keep at a minimum the exposure of the hose to the distillate and its vapors.

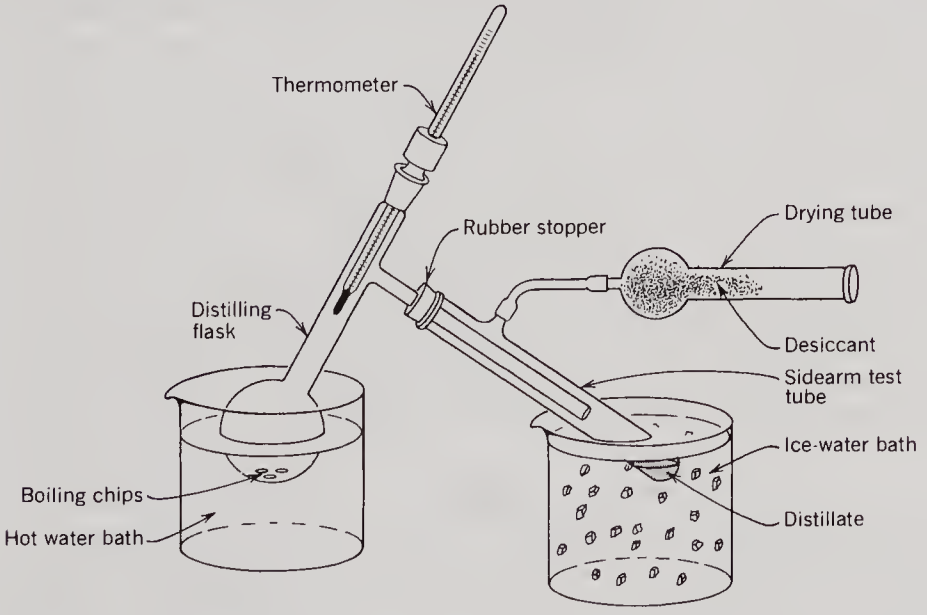


FIGURE 7.27 Small-scale still.

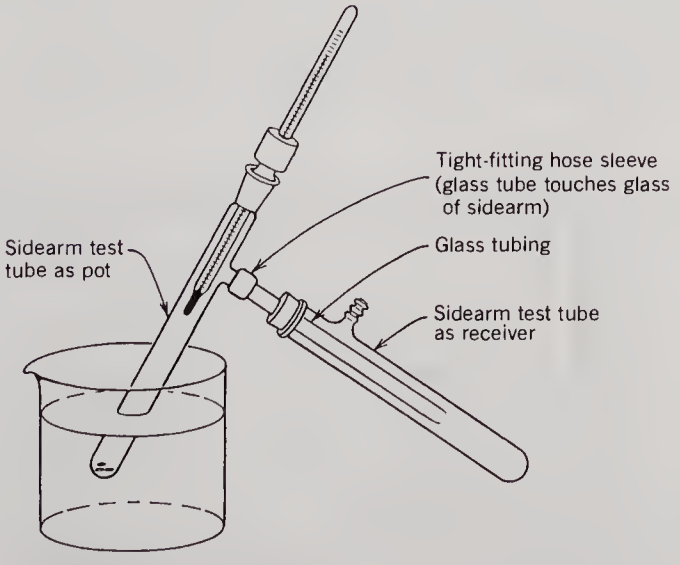


FIGURE 7.28 Small-scale sidearm test tube still.

Promote smooth boiling by use of boiling chips. For small samples, put a loose pad of glass wool into the liquid as a substitute for boiling chips.

The apparatuses of Figures 7.27 and 7.28 are practical for a charge of as little as 2 and 1 ml, respectively. The distillate yield would of course not be very large.

Equipment with Special Heads and/or Flasks

Special distillation heads are commercially available or can be made by a glass blower. Figure 7.29 illustrates the use of a pear-shaped flask to hold a very small amount of liquid and a head which is designed to have minimum holdup. The apparatus would be satisfactory for as little as about 2 or 3 ml.

The Hickman unit of Figure 7.30 distills liquid from a pear-shaped flask up through the neck into the cylindrical condenser. The walls of the condenser are kept cold by a piece of cloth continually damp-wetted with ice water or by a piece of cloth from which acetone continually evaporates. Insulation keeps the neck region warm. Glass wool is used to prevent bumping. You remove the distillate through the top of the apparatus with a medicine dropper. This unit can satisfactorily distill as little as 1 or 2 ml.

The same precautions apply as for simple distillation and for vacuum distillation. If glass wool is used in the place of boiling chips, gloves should be worn while handling it.

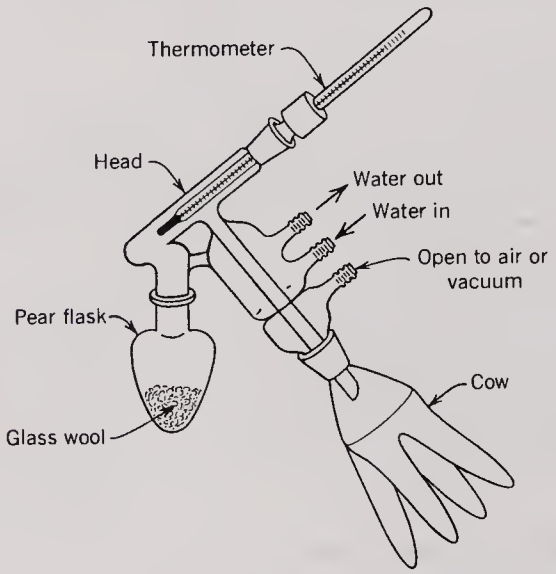


FIGURE 7.29 Pear flask and small head.

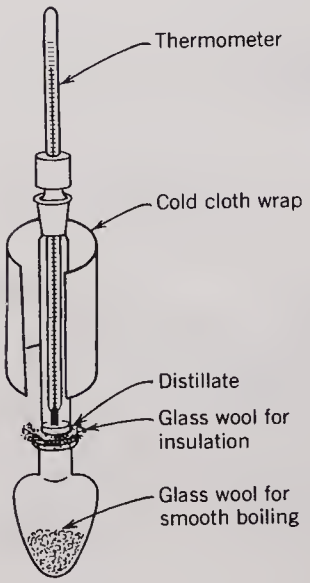


FIGURE 7.30 Hickman still.

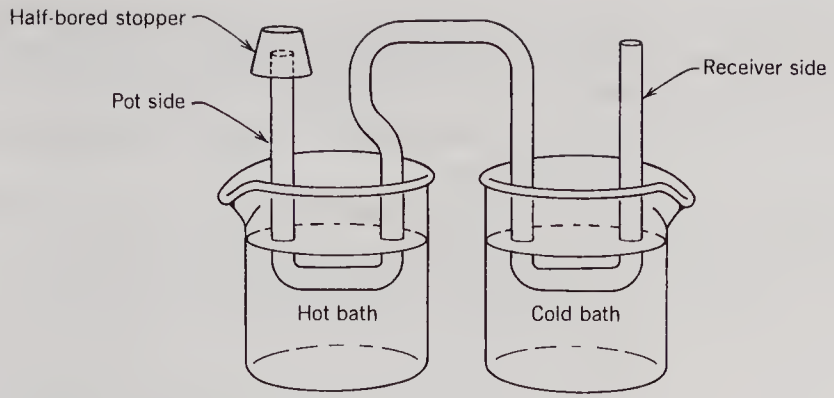


FIGURE 7.31 Microdistilling U-tube apparatus.

Microdistilling Tube

A very simple device that any "worthy organiker" can make is the double U tube shown in Figure 7.31. Choose a section of glass tubing of a diameter that seems appropriate for the size of sample to be distilled (the larger the sample the larger the tubing diameter). The dimensions of a 0.6–0.8 ml double U tube still are given in the experimental section. You must calculate the dimensions so that the pot side of the still holds the required volume of liquid without being filled deeper than about three-quarters of the tubing diameter. If you make the calculated dimensions for about two times your anticipated volumetric need it should be about right. Tubing diameters of less than 5 mm i.d. are generally unsatisfactory for making microdistilling tubes because even with very small samples the attraction between glass and liquid causes the liquid to occlude the entire diameter of the tubing. The bend in the tube on the pot side is to help prevent bumping and to eliminate mixing of distillate with residue when the distillate is poured out. If you want to distill at reduced pressure attach a vacuum hose to the receiver side. For liquids with boiling point above 75 °C, you might need to insulate the column portion of the tube all of the way across the top to where the tube bends downward toward the receiver (the region between the arrows on Figure 7.31). The apparatus is satisfactory for as little as ½ ml of sample. Introduce the sample into the pot side of the still with a micropipet, eyedropper, or buret.

Never draw a sample into the tube by suction with your mouth.

Put the sample into the pot side and seal it with a half-bored rubber stopper. The liquid in the pot side must not fill the pot. There must be an air space above the liquid all the way across the pot portion of the tube. Prior to distillation, you can cool the pot side by a cold bath of appropriate temperature; then apply a vacuum to remove any residual low-boiling solvent you do not want. When you are ready to distill, apply heat to the pot side using a water bath, steam bath, oil bath, or microburner. Increase the temperature of the pot bath gradually so that you do not cause flooding or excessive bumping. Remove the distilled sample from the apparatus by decanting.

7.19 EXPERIMENTAL PART
Construction and Use of a Microdistilling Tube

Time Required: 2 1/2 hr

Review Techniques and Principles:

Lab notebook	(1)
Simple distillation	(7.2)
Storing products	(0.12)
Labeling	(0.13)

Preparation of the tube. Obtain a 50-cm section of 7-mm-i.d. soft glass tubing. Bend it to the shape shown in Figure 7.31. Remember to anneal the bends by using a luminous

flame. The vertical portions should be about 10 cm high, the horizontal portions about 6 or 7 cm. Fire polish the ends. Bore a small rubber stopper halfway through. Twist off and pull out the plug with pliers. Make the stopper fit your tube snugly. △

Be sure to check with your instructor regarding flame-permit times and areas for your laboratory.

Do not work with flammable solvents in the area where flames are in use.

To approximate the holdup of the apparatus, weigh the double U tube along with the stopper to the nearest tenth of a gram, then pour a known amount of tetrachloromethane (carbon tetrachloride) at room temperature in one end of the apparatus and allow it to run out the other. Permit it to drain until it does not drip. Shake off any drop at the end of the tube, attach the stopper, and weigh the apparatus again immediately. Put the CCl_4 into a recovery container. The difference between and first and second weighing is the approximate holdup for CCl_4. Using the density of CCl_4, obtain the volume of the holdup. This volume will also be the approximate holdup for other liquids. Blow the tube dry with the laboratory compressed air source. △

Remember that work with toxic substances should proceed in an adequately ventilated area.

Distillation. You will be given from a buret 1.0 ml of methanol (methyl alcohol) colored by a small amount of methyl orange dye. Protect your sample from evaporation. Set up the double U tube apparatus as shown in Figure 7.31 and put your sample in the tube. Remember not to *fill* the horizontal section of the pot side. Use a hot water bath or steam bath as the heat source and bring the bath temperature up slowly. When distillation is complete, dry the outside of the receiver and decant the product into a tared vial. Cap it and weigh it to determine the recovery. Clean your microdistillation tube with wash grade acetone and put the rinsings in the acetone recovery container. Gently blow the apparatus dry and save it for future use. △△

Using the density of methanol, calculate the percent yield based on (1) initial 1.0-ml charge and (2) the amount possible to collect, knowing the holdup, (charge − holdup). Turn in the labeled product to your instructor.

Writing the discussion. In your discussion of results, be sure to mention your percent yield relative to your technical performance and how it might be improved in future use of the microdistilling apparatus. Compare your results with some of your coworkers. Relate your percent recovery to loss due to holdup.

7.20 EXERCISES

Prelaboratory

1. What are the purposes of the bend of the pot side of the double U tube microdistilling apparatus?
2. If you are going to construct a microdistilling tube, draw a diagram of the one you will make, including dimensions.
3. During use of the double U tube at atmospheric pressure, should the receiver end be left open? Why?
4. A student made a double U tube apparatus like that of Figure 7.31. However, he made the pot side bend in the opposite direction. To what difficulty could this lead?
5. What is the boiling point of methyl orange? Do you think it will distill along with the methanol?
6. What solvent do you know will remove residual methyl orange from the still pot?

Postlaboratory

1. Calculate the diameter of glass tubing to use for making a double U tube still that could handle 2 ml of sample. Use the lengthwise dimensions for the still pot described in this chapter along with the formula $V = \pi r^2 l$, wherein V is the volume, r is the tubing radius, and l is the horizontal length of the still pot. Remember that the diameter is twice the radius.
2. Assuming holdup is largely due to wetting the inside surface of the double U tube, calculate the approximate holdup of the still made of the tubing size you arrived at in postlab exercise 1. Base your calculations on $A = 2\pi rl$ and on your experimental work with your own double U tube and tetrachloromethane.

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1. van Winkel, M. *Distillation;* McGraw-Hill: New York, 1967.
2. Malesinski, W. In *Azeotropy,* Ridgway, K., Ed.; Interscience: New York, 1965.
3. Swietoslawski, W. In *Azeotropy and Polyazeotropy;* Ridgway, K., Ed.; MacMillan: New York, 1963.

Chromatography

Chromatography is the separation of the components of a complex mixture by distributing them between a stationary phase and a mobile phase. Chromatography has its origin in separations of mixtures of colored pigments extracted from plants. What might appear to be a single-colored plant leaf extract is generally a combination of pigments. The chromatographic process separates these pigments from each other and deposits them on a solid phase in a series of colored bands or spots. The word "chromatography" is a combination of "chromato," a prefix meaning "color," and "graphy," which refers to writing; and relates to the record of leaf extract "written in color." Actually, chromatographic techniques today are used most often for noncolored substances.

Chromatography has grown in science and technology into three classes: First, there is **partition chromatography,** which involves distribution of solutes between a moving solvent and an immiscible stationary liquid held in place by a solid support; second, there is **adsorption chromatography,** in which solutes are distributed between a moving solvent and a solid adsorbent (a material that attracts chemicals to its surface and holds them there more or less securely); finally there is **molecular sieve chromatography,** which separates molecules according to size by passing the solute through a porous cross-linked polymeric stationary phase. Sometimes molecular sieve chromatography is called **gel permeation chromatography.**

Separations by partition chromatography are theoretically similar to liquid-liquid extractions, since both techniques distribute solute between two phases. In actual practice, the physical methods are quite different. Partition chromatography includes paper chromatography, which involves liquid-liquid phase distribution and gas-liquid chromatography (GLC), which is characterized by gas-liquid phase distribution.

Adsorption chromatography encompasses several types which depend on liquid-solid phase distribution: ion-exchange chromatography, high-pressure liquid chromatography (HPLC), thin-layer chromatography (TLC), and column chromatography. Ion-exchange chromatography involves separations of ions with an electrically charged polymeric stationary phase (ion-exchange resin) and is used for water softening. High-pressure liquid chromatography is a form of column chromatography in which pressure forces a solution through a fine, tightly packed adsorbent.

In this book we shall examine in some detail thin-layer, paper, column, and gas-liquid chromatography.

TECHNIQUE 8

THIN-LAYER CHROMATOGRAPHY

Thin-layer chromatography (TLC) is a very useful laboratory technique. It can be used to separate mixtures, to identify compounds, to determine how many components are present in a mixture, to find out what solvents should be used in column chromatography, and to determine the purity of a sample.

TLC is useful for working with small amounts of substance. Usually, relatively large fractions of milligrams are used, but it is even possible to use microgram quantities. On

the other hand, with large TLC plates one can make separations involving half-gram quantities. In addition to qualitative TLC procedures, quantitative TLC analyses are becoming increasingly important.

8.1 DISCUSSION OF TLC

For a stationary phase, TLC utilizes a thin layer of an adsorbent on a glass or plastic plate. In a process called **spotting** a solution of the compounds to be separated is applied as a small spot near the bottom of the coated plate. The spotted plate is put into a closed vessel containing a shallow pool of liquid called the **developer** which ascends the slide by capillary action within the adsorbent. As the developer moves upward it carries some of the spotted compounds farther than others, thereby separating them in a process known as developing. As shown in Figure 8.1, a vertical row of spots is produced, one spot for each compound if the separation is complete. This array of spots is called a **chromatogram.** The spots are visible if colored compounds are in the mixture, but usually the compounds are not visible and must be submitted to some kind of visualization technique.

The rate at which a compound ascends the thin-layer plate depends on polarity of the adsorbent, polarity of the developing solvent, and polarity of the compound.

The Adsorbent

Many adsorbent are available, but most commonly the adsorbent is finely ground silica ($SiO_2 \cdot nH_2O$) or alumina (Al_2O_3). Silica, also known as silica gel or silicic acid, is relatively polar, in large part because of the considerable electronegativity difference between silicon (1.8) and oxygen (3.5).

Silica by itself does not bind well to the glass plate. Therefore you will use Silica Gel G, the G designating gypsum ($CaSO_4 \cdot 2H_2O$). Silica Gel G contains about 10% by weight calcium sulfate or calcium sulfate half-hydrate which, as it absorbs water from solution or from moisture in the air becomes gypsum, setting up solidly and binding the silica gel particles together and to the glass plate. An additive like calcium sulfate is called a **binder.**

Alumina is more polar than silica and will be discussed in more detail in Technique 10.

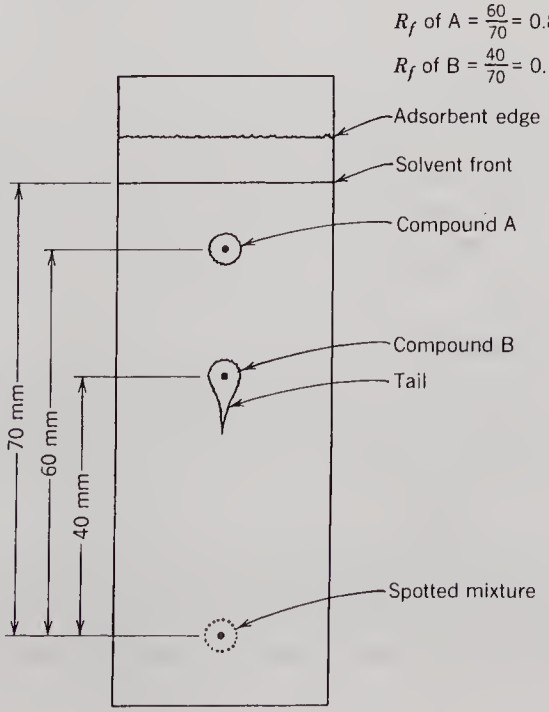


FIGURE 8.1 Developed TLC plate.

TABLE 8.1 TLC Developers

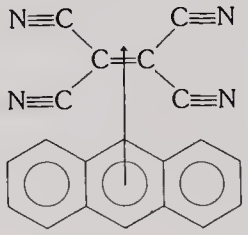
High Polarity	*Low Polarity*
Acetic acid	Toluene
Methanol	Carbon tetrachloride
Ethanol	Pentane
Anhydrous acetone	Hexane
Ethyl acetate	Ligroine
Anhydrous ether	
Chloroform	
Methylene chloride	

The Developer

Because the developer's function as the mobile phase is to selectively desorb (remove from the adsorbent) and transport some compounds farther than others, its polarity is very important. If it is too polar, it will carry all of the spotted materials about the same distance, therefore giving a poor separation. Conversely, if the developer is too nonpolar, none of the spotted compounds will be moved. In general, the desorbing and transporting capability of a solvent increases with increasing polarity. Table 8.1 lists a number of TLC developers in order of polarity. As we shall soon see, the ability of a solvent to act as an effective developer depends not only on its polar interactions with the compounds but with the adsorbent as well.

Interactions Among Adsorbent, Developer, and Spotted Compounds

Most types of intermolecular interactions can arise when a mixture of chemicals comes in contact with an adsorbent. Table 8.2 lists these nonbonded interactions in approximate order of binding strength, an approximate binding strength, and an example of each. The order and binding strengths are necessarily approximate because there is considerable overlapping in the various categories. For example, a dipole-induced dipole attraction can be so strong that a new chemical species is formed, viz., the interaction of tetracyanoethylene and anthracene to form a charge transfer complex:



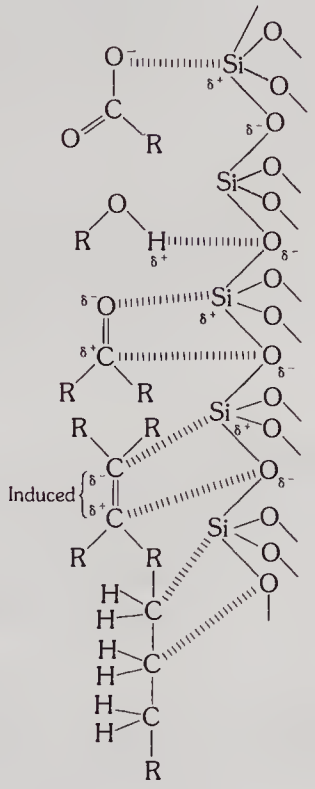
Furthermore, it is not always easy to assign an interaction to one class or another: van der Waals forces are always in operation and become relatively more important when very weak polar forces are operating; therefore van der Waals and weak dipole-dipole forces could be similar in strength and both contribute significantly to binding. Also the division between covalent and ionic bonds is not clear cut, the 1.7 electronegativity difference rule meaning only that there is 51% ionic character and not that a bond is completely ionic.

Notice from Table 8.2 that you would not expect nonpolar hydrocarbon molecules to be very attracted to silica because they become bound to silica primarily by van der Waals interactions. However, the larger the hydrocarbon, the stronger the binding, since the larger size gives more opportunity for a multitude of interactions. Remember Gulliver and the Lilliputians? He was bound by many tiny threads as tightly as if he had been bound by one big rope!

Roughly, binding of compounds to silica follows the order acids and bases > amides > alcohols > aldehydes, ketones > halides > esters > unsaturated hydrocarbons > saturated hydrocarbons. The distances traveled by the compounds would of course be in reverse order. In general, the stronger the binding forces, the shorter the distance traveled.

TABLE 8.2 Nonbonded Interactions

Interaction Type	*Approximate Strength, kcal/mole*	*Examples of Solutes*	*Portion of Silica Structure*
Ion-dipole	15		
Dipole-dipole H-bonds	5		
Dipole-dipole Other	1–5		
Dipole-induced Dipole	1		
van der Waals	0.5		



Initially a compound is adsorbed by the silica or other adsorbent by one of the forces noted above during the spotting process. When the developer passes by the compound, it competes with the silica for that compound. How successful the competition is depends on the interactive strength between solvent and compound, on the interactive strength between adsorbent and compound, and on the interactive strength between adsorbent and solvent. Imagine the path of an adsorbed pigment molecule: First it is bound to the adsorbent; then the developer attracts it and desorbs it. The developer then takes up residence at the site that the pigment molecule had just occupied, thereby helping to prevent readsorption of the pigment at that site. However, becoming dissolved in the solvent does not preclude the readsorption at some point farther upstream, and the molecule continually is adsorbed and desorbed as the solvent moves up the plate. If the adsorbed molecule is very soluble in the developer and not tightly bound to silica, it will be relatively easily desorbed and will spend more time in the developer than on the adsorbent. But if it is tightly bound to silica it will spend relatively more time on the adsorbent and will not be carried along as far in a given time period. In order for it to be carried along faster, a more polar solvent could be used because a more polar solvent is more strongly attracted to silica and will be more tightly bound itself, thereby more completely preventing readsorption of the pigment molecule. Because the number of silica particles is great and they are packed closely together, and since fresh developer is continuously sweeping over a given spot on the plate, the number of times the solute is adsorbed and desorbed is tremendously large.

As you can see, the TLC process is a complex interaction of all three components of the system; solvent, adsorbent, and adsorbed solutes (pigments).

In order to obtain the many adsorption-desorption equilibrations necessary for separating solutes in a mixture, the ratio of adsorbent to sample must be high. Therefore, on a small plate, the amount of sample must be small, usually less than a milligram.

TLC is therefore used primarily as an analytical technique rather than as a preparative method.

The distance traveled by solute relative to the distance travelled by the **solvent front** (the point of farthest advance of solvent at any given time) depends on molecular structures of the solvent and solute. Therefore TLC can be used to identify compounds as well as to separate them. The ratio of the distance traveled by solute to the distance traveled by solvent front is characteristic of each solute and is called the R_f, a symbol meaning "ratio to front."

$$R_f = \frac{\text{solute distance}}{\text{solvent front distance}}$$

R_f is always reported as a decimal fraction. R_f is very dependent on the exact conditions of moisture content, thickness of adsorbent, purity of solvent, and so on. Therefore, comparison of literature values with your experimental values is subject to considerable uncertainty. Identities of compounds are usually established by spotting the TLC plate with known compounds as well as the unknown mixture.

8.2 TECHNIQUES OF TLC

The techniques involve preparation of the adsorbent slurry, preparation of the plates, spotting the plates, selecting the developer, preparing the development chamber, developing the chromatogram, and visualizing the spots.

Preparation of the Adsorbent Slurry

You can prepare the slurry conveniently in a wide mouth screw cap jar. You might be instructed to prepare your own slurry, or your instructor might make one slurry for everyone to use. For about 10 students, mix 80 ml of chloroform (IUPAC trichloromethane) with 40 ml of methanol (methyl alcohol) in an 8-oz jar. While stirring constantly, slowly add *to this solution* 45 g of Silica Gel G. Lumpiness generally results if you add the liquid to the silica. Cap the jar and shake it vigorously. You can make an individual portion by using proportionately lesser amounts.

Preparation of the Plates

For qualitative TLC analysis of organic mixtures, you will probably use microscope slides because they are of a convenient size and easy to use.

Wash the plates thoroughly with water and soap or a cleanser such as Old Dutch, Ajax, or the like. Rinse them well with water, then rinse them with 50% aqueous methanol, and thoroughly dry them on paper towels. Once they have been washed, handle them only by the edges since fingerprints are oily and will prevent tight binding of adsorbent to glass. Put two slides back to back as shown in Figure 8.2 and dip them together into

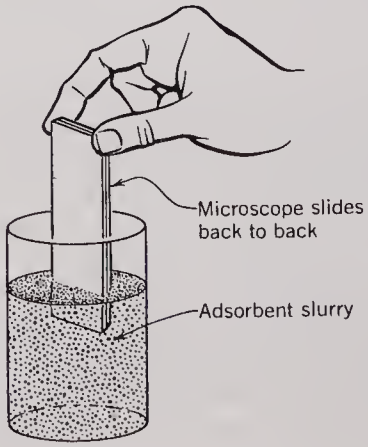


FIGURE 8.2 Dipping slides.

the adsorbent slurry until only about 1 cm remains uncoated. Then, slowly and steadily withdraw them from the slurry over a period of about 2 s so that a nonbroken layer of uniform appearance is produced. Mix the slurry thoroughly just prior to use by shaking it vigorously, and cap it immediately after use to prevent solvent evaporation. There should be no streaks or lumps and the coating should be thick enough so that the glass does not show through. You can wipe unsatisfactorily coated plates with a paper towel and redip them. It might be necessary to adjust the rate and smoothness of dipping and/or the thickness of the slurry by dilution or addition of more silica gel (if necessary ask your instructor for help). Next air dry the slides for 5 min. Finally, put them in an oven and dry them at 110 °C for a minimum of one-half hour to remove water that may be adsorbed on the silica surface. Do not remove them from the oven until just before use. Allow them to cool to room temperature before spotting.

TLC plates are also commercially available in a ready-to-use form with silica gel or alumina coated on glass, aluminum, or plastic. The plastic plates are somewhat flexible and can be cut to size with a scissors.

Making a Micropipet

You spot the plates with a micropipet, which can be easily made from a melting point capillary or similar tubing. Rotate and heat the tubing at its center with a microburner until the glass is soft, then remove it from the flame and draw it out until the portion of the tubing with a reduced diameter is about 4 cm in length. After cooling, place the constricted portion in a fold of paper towel and break it in the center to yield two micropipets. The pipets are fragile and should be kept in a stoppered vial.

Place the drawn out capillary in the fold of a paper towel before breaking it so that chips do not fly at yourself or others.

The tip of the pipet capillary will be very sharp since you will not be able to fire polish it. Handle and store it with this in mind.

Do all work with flames in another room or in a designated flame-permit area of the laboratory.

Spotting the Plates

Dip the narrow end of the micropipet into the solution of chemicals to be separated. The solution will be drawn into the capillary by capillary action. Touch the tip of the pipet to the adsorbent on the thin-layer plate 1 cm from the lower end in such a manner as to leave the adsorbent undisturbed. The solution will be removed by capillary action of the adsorbent. The pipet should touch to the adsorbent only momentarily so that the spot remains no more than 2 mm in diameter. You can make the spot contain more of the mixture by repeated applications to the same spot, allowing the solvent to evaporate each time. You can put two or three horizontally and equally spaced spots on one microscope slide. Using a sharp pencil or spatula, score a small mark at the side of the plate to note the position of the original spots (Figure 8.3). Clean the pipet by repetitively dipping it into fresh solvent and discharging it by capillary action onto a piece of paper towel. You can then save it and reuse it.

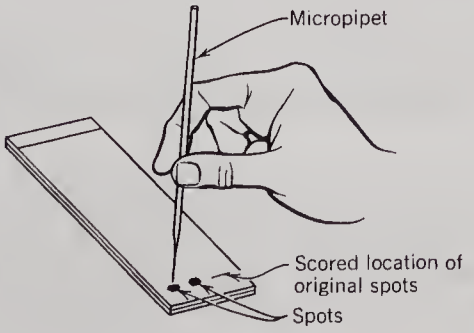


FIGURE 8.3 Spotting slides.

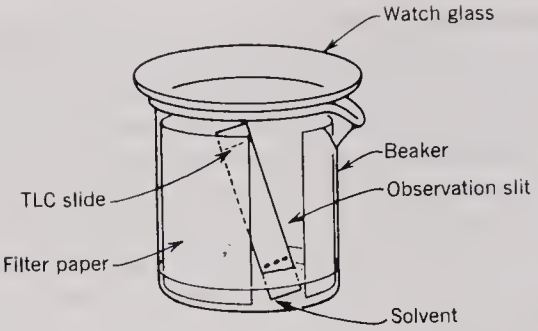


FIGURE 8.4 TLC development chamber.

Selecting a Developer

To obtain the best separations, you want the least polar solvent that will do the job. Spot a plate with the mixture you are going to separate, using as many spots spaced 2 cm apart as you have developers to test. Next draw developer into one of your micropipets and lightly touch it to one of the spots. The solvent will move outward, creating a disc of wetness on the adsorbent. Mark the solvent front with a spatula or pencil before the developer evaporates. Apply a different developer to each spot, using enough developer on each spot to make the disc about 1 cm in diameter. After visualization (please see below), you will see that each properly developed spot has become a tiny chromatogram of concentric rings. Choose the developer that produces major rings between one-third and two-thirds of the distance to the solvent front. If a single solvent will not do the job, use mixtures.

For hydrocarbons and other relatively nonpolar solutes, try the developers near the bottom of Table 8.1. For compounds of moderate polarity try those in the middle of the table; and for more polar materials, try developers near the top. If you do not know the character of the solutes, start with developers at the bottom of the table and, by trial and error, work toward the top.

The Development Chamber

To make a development chamber, you can use a small watch-glass-covered beaker or a small cork-stoppered bottle. Line the inside with a piece of filter paper cut so that it forms a cylinder around the inside walls, and rests on the bottom of the chamber (Figure 8.4). The paper cylinder should be incomplete so that a vertical observation slit is left. To prevent evaporation of solvent from the slide during development, saturate the paper in the chamber with solvent. Then immediately pour solvent into the chamber until the pool at the bottom is about 5 mm deep. The pool must not be deep enough to touch the spots on the TLC plate when it is put into the chamber. Cover the chamber and set it aside until you are ready to use it.

Developing the Chromatogram

Remove the top of the chamber and, as quickly as possible, carefully put the slide in so that the spotted end is in the pool and the upper end rests against the wall. Replace the cover immediately so that the vapor-saturated chamber atmosphere is disturbed as little as possible. It will be obvious to you that the solvent front is advancing up the plate. That part of the adsorbent wetted by developer will look like wet snow. When the solvent front has advanced to about 5 mm from the end of the adsorbent-covered area, promptly remove the plate from the chamber. While the solvent front is still visible, mark it with a sharp pencil or spatula. When the solvent has evaporated, outline the visible spots by carefully scoring around them. If spots are not visible, or if you think there are others besides the visible ones, you will need to use a visualization method.

Spot Visualization

A simple chemically nondestructive way to visualize certain spots is to go into a dark room and shine an ultraviolet (UV) light on the developed plate. The UV energy will cause some chemicals to fluoresce so you can mark their spots on the chromatogram. Silica Gel G and most commercially prepared TLC plates contain a **phosphor** (a com-

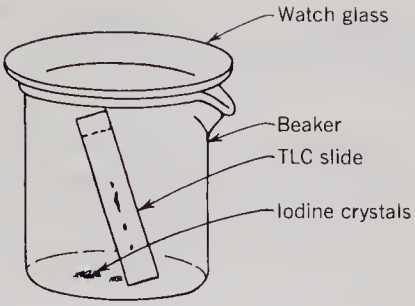


FIGURE 8.5 Iodine visualization chamber.

pound that emits light when irradiated), often a mixture of cadmium and zinc sulfides. When irradiated, the entire plate fluoresces, leaving darker spots where the compounds are located.

Another relatively simple nondestructive method is to use an iodine chamber. Put the slide in a covered beaker with a couple crystals of iodine, as shown in Figure 8.5. Then heat the chamber gently on a hot plate or over a steam bath. The iodine forms a reversible complex with most organic compounds except saturated hydrocarbons and alkyl halides. The spots fade rapidly after removal from the beaker and must be marked at once. If the entire adsorbent turns brown, remove the slide from the chamber and allow the iodine to evaporate from the silica gel until only the spots remain. The iodine method is the most common form of visualization.

To make a permanent chromatogram by a chemically destructive method, you can spray the developed plate with concentrated sulfuric acid. Heat the TLC plate in an oven to about 120 °C; then using a tongs, remove it into a hood. Spray the hot TLC plate from an atomizer with sulfuric acid that has been heated to about 50 °C. This treatment oxidizes and chars the compounds of the chromatogram, leaving brown to black spots. If necessary to complete charring, put the plates back in the oven after spraying them.

Avoid looking at the ultraviolet source. It can damage the retina of your eyes.

Iodine vapors are quite toxic. Work only in a hood.

The hot concentrated H_2SO_4 method is quite dangerous. Use it only if specifically approved by your instructor. Wear gloves and a face shield and work in a well-ventilated hood.

In addition to the methods just given, there are others that are specific for certain kinds of compounds or functional groups.

Calculation of R_f Measure the distance that a solute travels from the center of the original spot to the center of the migrated spot. Sometimes a spot becomes elongated during migration and exhibits tailing, as shown in Figure 8.1. For a tailed spot, measure to the point that seems to be its center of area. For the distance of solvent travel, use the distance from the center of the original spot to the point of farthest advance of the solvent front. Establish an R_f value for each spot, calculating as shown in Figure 8.1.

8.3 EXPERIMENTAL PART
Detecting the Presence of Vanillin and Ethylvanillin

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook (1)
Drying solids (2.2)

In this experiment you will be analyzing pure vanilla extract and/or imitation vanilla flavorings to detect the presence of vanillin and ethyl vanillin, both of which are components of vanilla beans.

TLC spotting and development. Prepare two TLC slides as described in Section 8.2, or use readymade plates such as Baker-flex Silica Gel 182. Spot each slide with a 0.1% alcoholic solution of vanillin 0.6 cm from the left side. Next spot one slide with pure vanilla extract and the other with an imitation vanilla flavoring in the center of the slide. Finally spot each slide with a 0.1% alcoholic solution of ethyl vanillin 0.6 cm from the right side.

Dry the spots under a gentle stream of air or in an 80 °C oven for 2 or 3 min to remove all solvent. (If the water present in the solvent is not evaporated from the slide, it will cause streaking.) Develop the slides in a 50/50 mixture of ethyl acetate (IUPAC ethyl ethanoate) and cyclohexane by volume. Allow the developer to evaporate from the slides. △

Visualization. Put the slides in an iodine chamber and observe the development of spots. Remove the slides from the chamber and mark the location of each spot. Carefully observe, and record your observations. Allow the spots to fade (you can hasten the process by putting the slides on a warm hot plate or by holding a lighted incandescent bulb over them.) Next lean the slides against a vertical surface and gently spray them with a freshly prepared 50/50 mixture by volume of 5% aqueous ferric chloride and 5% aqueous potassium ferricyanide. Make observations that allow you to compare the two methods of visualization. △ Measure the positions of the spots, calculate R_f values for each spot, and make a sketch of the slides in your notebook. This should all be done on the same day as the spraying because the entire slide will darken after about one day.

Spray the slides in a fume hood.

Writing the discussion. Discuss (1) the relative merits of the two methods of spot visualization; (2) the presence or absence of vanillin and ethyl vanillin in the samples and, based on the darkness of spots, their relative concentrations in the samples; and (3) the relationship between R_f and polarity of vanillan and ethyl vanillin.

8.4 EXERCISES

Prelaboratory

1. Write the equation that defines R_f.
2. Why should the TLC plate be thoroughly washed before coating it?
3. How will you handle the plates after washing?
4. Why are the TLC plates oven dried before use?
5. What is the maximum size a spot should be allowed to attain during spotting?
6. What is the purpose of the filter paper inside the developing chamber?
7. How deep should the pool of solvent in the developing chamber be?
8. How far should the solvent front be allowed to advance?
9. Why can there be no thin patches or breaks in the surface of the thin layer of silica gel?
10. A student applied to a TLC slide one spot for each of three substances. During development he went to the chemistry library to get melting point data on the substances. When he returned he removed the slide from the development chamber and allowed it to dry. He observed no spots, so visualized it with iodine. Three horizontally elongated spots appeared at the end of the silica coating farthest from

the original spots. Measuring from the centers of area, he calculated and reported the same R_f value for each substance. Critique his method and explain his results.

11. Why are TLC plates dried before spotting?
12. Why are the TLC slides in Section 8.3 dried after spotting?
13. Is iodine visualization a destructive or nondestructive method of visualization? What leads you to think that spraying with ferric chloride-potassium ferricyanide might be a destructive method?
14. Prepare a flow diagram for the entire experimental part.

Postlaboratory

1. How do you think lumps in the path of the advancing spots would affect the R_f value? In devising your answer, try to visualize the path of the molecules moving in the region of a lump.
2. Ten percent presence of calcium sulfate dihydrate in the adsorbent must also affect adsorptive properties to some extent. What kinds of adsorbent-organic compound intermolecular attractions can you visualize because of the presence of the binder?
3. Water is strongly attracted to silica gel. If the plates are exposed to a humid laboratory atmosphere, do you think water would become bound? Would this affect the performance of the plate? Explain.
4. Your supervisor at the pharmaceutical company where you work wants you to prepare a hydroxy-functional drug by reduction of a ketone. Suggest how you might tell when the reaction has gone to completion.
5. A student reduced 1-phenylethanone (acetophenone) to form the enantiomeric pair of secondary alcohols. She knew that two enantiomers should be present, but upon TLC analysis was perplexed to find only one product spot. Explain.
6. Draw the structures of vanillin and ethyl vanillin; give them systematic names.

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TECHNIQUE 9

PAPER CHROMATOGRAPHY

Paper chromatography (PC) is a technique closely resembling that of thin-layer chromatography (TLC). But whereas TLC involves liquid-solid adsorption, PC is a liquid-

liquid partitioning technique. Although PC can be used quantitatively, we shall concentrate on its use in qualitative analysis.

9.1 DISCUSSION OF PC

It will help you to understand the following discussion if you have already read Technique 8, Thin-Layer Chromatography.

Separation of mixtures of compounds by PC depends on adsorption, ion exchange, and partitioning between the solvents used. However, the major factor by far in most PC work is partitioning between two nearly immiscible phases. In this sense, the action is just like the partitioning process in a separatory funnel. Water is usually the stationary phase in PC, and an organic solvent is the mobile phase.

Filter paper serves the same purpose in PC that glass plates do in TLC. The filter-paper strip on which spots are deposited acts like a **support** for the stationary aqueous phase. That is, the filter paper acts like a blotter, adsorbing the water and holding it in place. The strong attraction of paper for water is due to its cellulose content. Cellulose contains many hydroxy groups with which water can form hydrogen bonds. The attraction of cellulose for water is so intense that a solvent that is normally appreciably miscible with water might be rendered immiscible with the cellulose-water complex.

As in TLC, one end of a dry spotted strip is placed in a mixture of developer solvents. The developer then moves up the paper by capillary action. As solvent flows past a spot of solutes, partitioning takes place between the moving organic phase and the stationary aqueous phase. The various solutes are separated because of their differences in K_D between the two phases. The solutes with highest K_Ds move the greatest distances in a given time. The same factors that affect solubilities and partition coefficients affect separations by PC: van der Waals forces, dipole-induced dipole, dipole-dipole, and ion-dipole interactions.

R_f values are calculated for PC just as for TLC. Here also, the reliability of R_f values is not always high under ordinary conditions, but generally is better than that in TLC.

9.2 PC TECHNIQUES

In general, PC involves the following steps: (1) selection and preparation of the paper support, (2) preparation of the sample, (3) spotting the paper, (4) choosing the developer, (5) developing the chromatogram, and (6) visualization. We shall examine each of these areas in turn.

The Paper Support

There are many grades of paper from which to choose. They differ in texture, uniformity, and speed of solvent travel. When undertaking a major chromatographic program, make preliminary tests on several grades of paper to determine which best suits the separation you are making.

Handle the paper with a tongs or forceps, or cut off the parts of the paper which are touched by fingers. Fingerprint spots can be developed just like any other spots and might show up in the final chromatogram.

Chromatographic grade filter paper comes in sheets or strips, usually with an arrow or other symbol in a corner to indicate the direction of the paper's grain. You can determine the grain direction by holding the paper in front of a light, or by putting a small drop of water on and observing the way the drop spreads: The water spot will elongate in the direction of the grain. During use, orient the paper so that solvent flow is in the direction of the grain.

Sample Preparation You usually prepare the sample to be analyzed by simply dissolving it in a suitable solvent at a concentration of from 0.1 to 1%. Recommended sample sizes vary from one class of compounds to another, but the chromatographic literature is replete with suggestions.

Spotting the Paper Spotting is probably the most important single factor for producing a successful chromatogram. Lay the filter paper flat on a clean glass plate (if a glass plate is not available, a clean paper towel or sheet of notebook paper can be used). Lightly make pencil (not ink) marks where the spots are to be applied. Place the spots 2–3 cm from the lower edge of the paper and about 2 cm apart from each other, using a micropipet constructed as described in Section 8.2. For best results apply no more than 2–3 μl at one time. If the spot needs to be more concentrated, make successive small applications over the same spot, drying each application before the next. Strive to keep the spot size at a minimum, no larger than 3 mm in diameter. If the applied spot is too large, the developed spots will be diffuse and indefinite. You can keep spot size small and hasten drying between applications by using a blow dryer, infrared lamp, hot plate, or even a common light bulb. Be careful not to scorch the paper, especially if you place it on a hot plate.

The Developer Most developing solvents in paper chromatography are two-phase organic-aqueous systems or are organic solutions. The solubilities of the solutes to be separated suggest what solvent system to use. Slower moving solvents generally produce more circular, less diffuse spots. Surface tension, density, and viscosity all play a role in speed of development. Suggested solvent systems for various kinds of solutes are quite extensive in chromatographic literature.

Development Use the same basic method for development as you would use for TLC. To obtain even, horizontal solvent fronts with well-separated, symmetrical spots, you must presaturate the chamber with solvent, control the temperature carefully, and develop the chromatogram slowly. To saturate the chamber with vapors, line its walls with filter paper resting in solvent (see Section 8.2). Sometimes, in a chamber with a tight lid, a small container of developer is put into the chamber 24 hr prior to development.

Figure 9.1 illustrates a simple chamber which will give reasonably good results for rapid qualitative work. The R_f values obtained will, of course, not be very reproducible. The chamber of Figure 9.1 consists of a 250-ml Erlenmeyer flask with one-hole rubber stopper. The paper strip should be 4 cm wide and about 8 cm long. Touching only the ends, lay the strip on a clean sheet of paper; then fold it up the center by creasing it with a spatula so that it will fit inside the flask neck in a semifolded manner. Cut off the ends touched by fingers and mark the position for the spots with a pencil (not a pen!). Hold the strip with forceps alongside the flask and cut it so that it is about $1\frac{1}{2}$ cm shorter than the distance from the bottom of the stopper to the floor of the flask. Now, completely

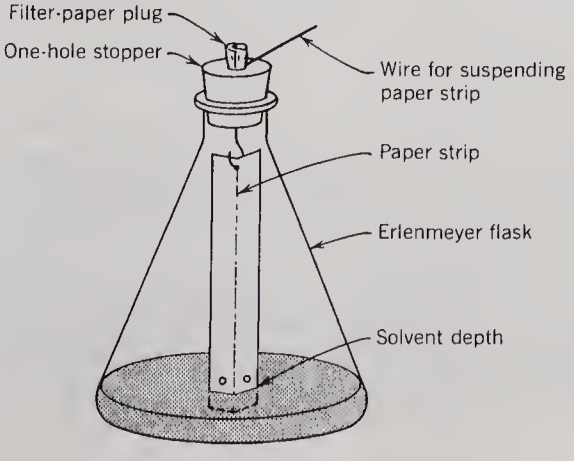


FIGURE 9.1 Paper chromatography development chamber.

straighten a paper clip, then bend one end into a small hook. With the hook, pierce the paper strip about 0.5 cm from the end which is opposite the spots and suspend it on the hook. Slip the straight end of the wire through the hole in the stopper, and try the stopper and strip for size in the flask. The paper should hang freely about 1½ cm above the bottom of the flask when the wire is drawn all the way up. Lower the strip so it barely touches the bottom, and bend the wire 90° over the top of the stopper. Now, remove the stopper and strip. Pour developer into the flask to a 1-cm depth and put a solid stopper on top. Spot the strip, remove the solid stopper from the development chamber, and insert the strip and one-hole stopper far enough so that the strip hangs *above* the solvent. (Hold the wire up in the hole with a plug of filter paper.) After 10–30 min, depending on solvent volatility, the chamber will probably be reasonably saturated with vapor. Then push the wire down to its 90 °C bend so that the strip dips into the solvent. Allow solvent to ascend the strip to a point a bit below the wire hole. Remove the strip and mark the solvent front with a pencil while it is still visible.

Dry the chromatogram of developer thoroughly before visualization. You can use a forced-air oven if the solutes are not heat sensitive. Dry at room temperature if phenol is one of the solvents.

Because of variations in temperature, type, and quality of paper support, and exact solvent composition from one run to another, R_f values are often not exact enough to use in identifications. It is therefore customary to run samples of known substances along with unknowns so that R_f values found under identical conditions can be compared. Because K_D is a function of temperature, you should report temperature along with R_f.

During drying, use a hood or vent vapors out of the laboratory.

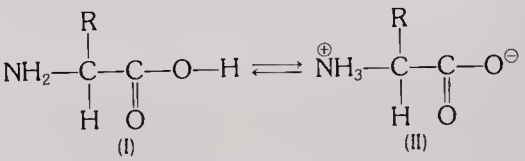
Keep oven temperatures below flash points of solvents.

Visualization Most spots are noncolored and some method of visualization is necessary. The literature abounds with visualization techniques for various classes of compounds. Sometimes a UV source will produce fluorescence, but most often chemical reactions are used to produce colored spots.

Looking at a UV source can damage the retina of your eyes.

9.3 DISCUSSION OF SEPARATING AND IDENTIFYING AMINO ACIDS

Recall that an amino acid is at least bifunctional, possessing a carboxyl group and an amino group. The alpha-amino acids of biological importance have the generalized structure



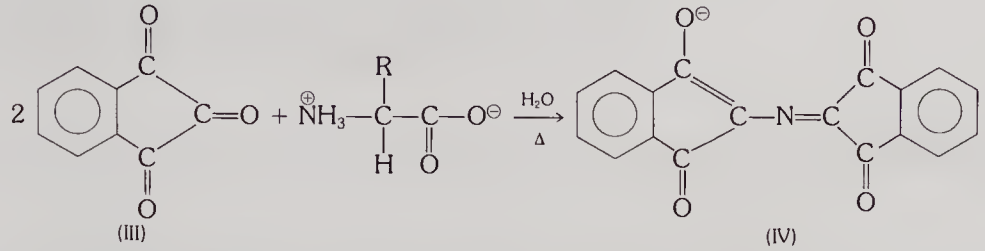
(9-1)

(I) (II)

wherein R is alkyl or aryl. Notice that the alpha carbon is chiral and that the acid possesses both acidic and basic functional groups. Therefore, in the solid state and at certain pH in aqueous mixtures, the amino acid exists as the *zwitterion* (II). For more information about chirality and pH-dependent equilibria of amino acids you should consult your lecture textbook.

There are a number of chemical reagents that will visualize amino acids. For example, ninhydrin produces mostly blue to violet colors on a chromatogram, isatin reacts to yield compounds with a variety of colors depending on the individual amino acid, and 1-fluoro-2,4-dinitrobenzene produces yellow spots.

In the experimental part for this technique, we shall use ninhydrin because of the color intensity that it imparts to the developed spots and the easy procedure that it provides. The reaction of an amino acid with ninhydrin (III) is



(9-2)

Notice in IV the highly conjugated structure which is responsible for its blue color. The reaction requires heat to complete the process.

9.4 EXPERIMENTAL PART
Separating and Identifying Amino Acids

Time Required: 2–3 hr

Review Techniques and Principles:

Lab notebook	(1)
TLC	(8.1, 8.2)

You will be given 1 ml of a 50% aqueous alcoholic solution 0.05*M* in each of two or more amino acids which will be chosen from the following: leucine (leu), threonine (thr), tryptophan (try), or tyrosine (tyr). There will also be available in the laboratory 0.07*M* standard solutions of the same amino acids.

Preparation of the developing chamber. Make a development chamber like that of Figure 9.1. Pour into it, to a depth of 1 cm, developer consisting of a 1/4/5 mixture by volume of glacial acetic acid (IUPAC ethanoic acid), *n*-butyl alcohol (IUPAC 1-butanol), and water respectively. Cover the flask with a solid stopper.

Preparation of the chromatogram. Wash your hands thoroughly with soap and water to remove skin oils. Obtain a piece of Whatman No. 1 or comparable filter paper and, being careful not to touch the paper except with a forceps, determine the direction of the grain. Cut from the paper two 4 × 8 cm strips, with the 8-cm measurement along the grain. Put three light pencil marks 1 cm up from the bottom and spaced 1 cm apart from each other and from the side edges. Spot one of the strips with two drops each of leu, unknown, and threo; spot the other strip with try, unknown, and tyr. Allow the first drop to dry before adding the second drop. Use a new pipet for each kind of solution or clean the pipet after spotting each kind in the following way: Dip the pipet into a small amount of 50% aqueous alcohol then touch the tip to a piece of paper towel or filter paper; dip, touch; dip, touch. After spotting, permit the spots to dry before developing. △

Visualization. After development, remove the strip from the developing chamber, flatten it, and allow it to air dry for 5 min. When the strip is dry, spray it lightly from an atomizer bottle with a 0.1% solution of ninhydrin in 95% ethanol. Heat the strip in a 100 °C oven, on a 100 °C hot plate, or under a heat lamp for about 20 min, by which time the spots should be readily visible. △△ Discard leftover samples down the drain. Calculate the R_f values (Section 8.2) for each of the spots obtained from the unknown sample and for each reference spot. Fasten the chromatograms permanently in your notebook with tape and/or glue.

Do the ninhydrin spraying in a hood with the glass as far down as possible. Because of the irritating nature of the developer, work in a hood if possible.

Writing the discussion. Identify the unknown amino acids in your sample, explaining by specific reference to standards how you arrived at your conclusions.

9.5 EXERCISES

Prelaboratory

1. Why should applied spots be kept small?
2. Look up the structure of cellulose. Show how hydrogen bonding occurs between cellulose and water.
3. In which chamber would saturation by vapor take longer: one with a solvent system of acetic acid and water, or one with a solvent system of 95% ethanol? Explain.
4. Why should ink not be used to mark positions for spotting?
5. If Whatman No. 1 paper is not available, what other comparable filter paper could you use?

Postlaboratory

1. If the partition coefficient of A is 20, and that of B is 15, which will be likely to have a higher R_f when developed in an aqueous-organic solvent? Explain.
2. Look up the structure of the four amino acids and explain on a structural basis the order in which they are found in a chromatogram.
3. A student developed a chromatogram for a sample containing only two unknowns. After visualization, he was surprised to find at least five spots. Suggest a possible technical error that might have led to these erroneous results.

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TECHNIQUE 10

COLUMN CHROMATOGRAPHY

Like TLC, column chromatography is a liquid-solid adsorption chromatographic technique. But, whereas TLC is primarily an analytical technique, column chromatography is largely a product isolation technique.

As you study this technique you will be continually reminded of the principles you

learned in the TLC process. Whereas we concentrated on use of silica as the adsorbent in TLC work, we shall now turn our attention primarily to another important adsorbent, alumina.

10.1 DISCUSSION OF COLUMN CHROMATOGRAPHY

The adsorbent is a solid phase and takes the form of a column contained in a vertical tube, as shown in Figure 10.1. In column chromatography we separate a mixture by first putting it on the top of the column where the components of the mixture, the **elutants,** become adsorbed. Next, we **elute** the column, that is, pass a series of solvents called **eluants** of increasing polarity and/or solubility parameter down through the column. As an eluent flows past the adsorbed elutants it carries them along to varying degrees, depending on the same principles we discussed for development of a TLC slide. This process is called **elution.**

The Adsorbent

We can use many adsorbents, such as silica (SiO_2), alumina (Al_2O_3), charcoal (C), magnesium silicate ($MgSiO_3$), magnesia (MgO), and carbohydrates $(CH_2O)_n$, of which the first two are most popular. The adsorbent used in ordinary column chromatography must be coarser than that used for TLC because the eluant must flow through it freely. But despite its coarseness 1 g of column chromatographic grade alumina has a surface area of about 100 m^2!

Alumina is more strongly adsorptive than silica because of the strong aluminum-oxygen dipole and the empty *p* orbital on aluminum. The empty *p* orbital is at the same energy level as the bonding orbitals of aluminum, and hence gives aluminum very strong Lewis acid properties. Table 10.1 illustrates the ways that elutants and eluants can bind to alumina. Alumina is most useful for chromatographing compounds that are not too polar because very polar and ionic elutants bind so tightly that they are eluted with difficulty.

There are two kinds of alumina useful for chromatography: basic and neutral. **Basic alumina** contains some carbonates and some hydroxy functions. It, of course, can not be used for separations of mixtures that are base-sensitive. The **neutral alumina** is prepared by neutralizing the basic alumina with acid and then washing it thoroughly with water. Alumina is further classified as **activated** or **deactivated** depending on whether

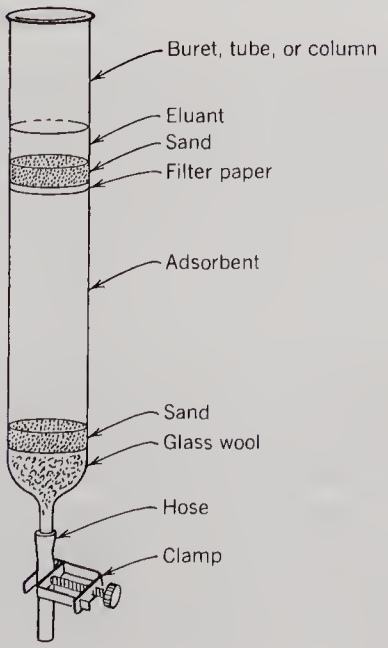
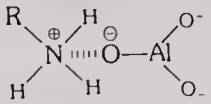
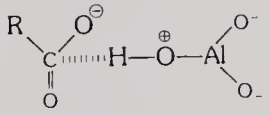
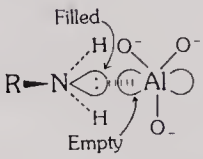
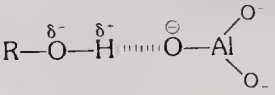
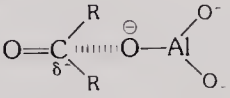
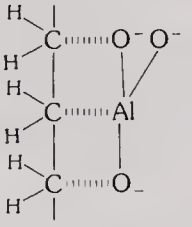
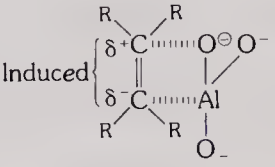


FIGURE 10.1 Chromatographic column.

TABLE 10.1 Bonded and Nonbonded Interactions

Interaction Type	*Approximate Strength, kcal/mole*	*Examples of Elutants*	*Portion of Alumina Structure*
Cationic salt formation	150		
Anionic salt formation	150		
Lewis acid-base salt formation	100–150		
Ion-dipole, hydrogen bonds	15–20		
Ion-dipole, other	15		
van der Waals	0.5		
Ion-induced dipole	5–10		

it is anhydrous or heavily hydrated. To indicate degree of activation, alumina is assigned to activity grades depending on the percent water it contains: grade I (0%), grade II (3%), grade III (6%), grade IV (10%), and grade V (15%). The greater the amount of water present, the poorer are the adsorptive capabilities because when water occupies binding sites, the elutants cannot. Basic and activated alumina are not often used because of their abilities to cause molecular rearrangements of the kinds illustrated below in the section on eluants.

The Column You can conveniently prepare a column in a buret. The disadvantage of a Geisler buret, with ground glass stopcock, is that stopcock grease is dissolved to some extent and carried out with the elutant. A Teflon stopcock, however, is quite satisfactory since there is no need for grease. You can fit the type of buret which has no stopcock with a short piece of rubber hose, through which you control elution rate with a screw clamp (Figure 10.1). You can also prepare a column in a distilling column, condenser, or glass tubing. You can use even a medicine dropper for small trial samples.

Figure 10.1 depicts the prepared column. The glass wool at the bottom keeps

granular material from being eluted. The sand forms a base on which the finely divided adsorbent can rest and not be drawn through the glass wool by the eluant. The filter-paper disc keeps the top of the column level while the top layer of sand is added, although the disc is often omitted. The upper sand layer is to keep the adsorbent from being disturbed when new solvent is added to the column. The process of filling the glass tube with the various components of the column is called **packing.** The column is packed wet, that is, in a liquid, and remains wetted throughout the entire chromatographic procedure.

The amount of adsorbent to use is important, and depends on the polarities of the compounds to be separated. It might require a mass anywhere from 20 to 100 times the mass of the mixture requiring separation. Commonly we take the mass of alumina to be about 30 times the mass of the elutant mixture. We must also consider the ratio of adsorbent height to radius. A short, large radius adsorbent column would not give much separation, and a long, very slender column would be unwieldy and slow. The height/radius ratio should be between 6:1 and 20:1, and is commonly about 16:1. Based on sample size you can calculate the height and radius by equation 10-1, in which r is the column radius in centimeters:

$$(\pi r^2)\left(\frac{\text{height}}{\text{radius}}\right) r = \frac{(\text{adsorbent mass in g})}{(\text{adsorbent density in g/cm}^3)} \qquad (10\text{-}1)$$

For example, if the amount of sample is 0.10 g, the amount of adsorbent is 30 times greater, or 3.0 g. Using a height/radius ratio of 16:1 and assuming an adsorbent density of 1.1 g/cm^3, the radius of the column would be

$$(\pi r^2)\left(\frac{16}{1}\right) r = (3.0\text{ g})\left(\frac{\text{cm}^3}{1.1\text{ g}}\right)$$

$$16\pi r^3 = 2.73\text{ cm}^3$$

$$r^3 = 0.054\text{ cm}^3$$

$$r = (0.054\text{ cm})^{1/3}$$

$$= 0.38\text{ cm for column radius}$$

$$16r = 6.0\text{ cm for column height}$$

You can use this equation for silica columns also. Table 10.2 shows the results of several such calculations and can be used for selecting buret or glass tubing sizes. Of course, you will probably have to make the selection for your column in accord with the nearest standard size.

Sometimes it is advisable to add a filter aid like diatomaceous earth to the adsorbent in order to increase the elution rate to a more acceptable level. This is especially a consideration when laboratory time is limited. Of course, you should expect adsorption characteristics to be changed somewhat; so it is important to note what filter aid you use and the amount relative to the adsorbent.

Elution

The dissolved mixture to be separated is initially adsorbed at the top of the column, as a **band** (or zone) of elutants. As the eluents pass downward over the column, the various elutants are moved along at differing rates depending on their relative affinities for eluant and adsorbent. If the proper eluants are used, distinct bands of separated elutants form.

TABLE 10.2 Column Sizes and Adsorbent Amounts

Sample amount, g	*Adsorbent amount, g*	*Column radius, g*	*Column height, cm*
0.10	3.0	0.38	6.0
0.50	15.0	0.65	10.4
1.00	30.0	0.82	13.0

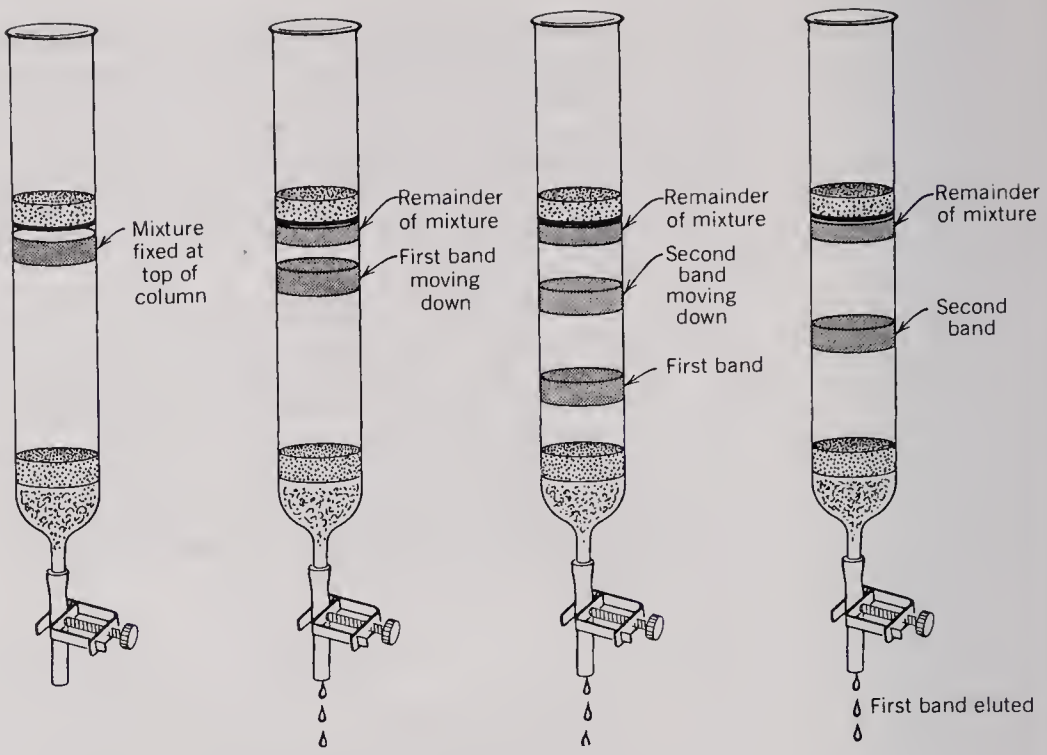


FIGURE 10.2 Formation and elution of bands.

Continued elution will cause each band in turn to pass out of the column. Figure 10.2 illustrates banding and elution.

To obtain distinct bands, the column must be free of trapped air or vapor bubbles around which elutants must migrate. The column should also be free of surface irregularities and channels through which elutants can be rapidly carried along by the eluent. Figure 10.3 illustrates these conditions, which cause **streaming** (also called channeling), wherein a portion of the band advances more rapidly than the remainder. The result is likely to be a poor separation of elutants.

During elution it is important that the bands be horizontal and well separated from each other. Otherwise the elutants will remain mixed or only partly separated. Good separation is a function of column height and radius, the correct amount of adsorbent, and proper choice of eluent. It the column is not held vertically, as shown in Figure 10.4, or if the top of the column is not horizontal, the bands might be in such positions relative to each other that elution of the second band will begin before elution of the upper part of the first band has been completed.

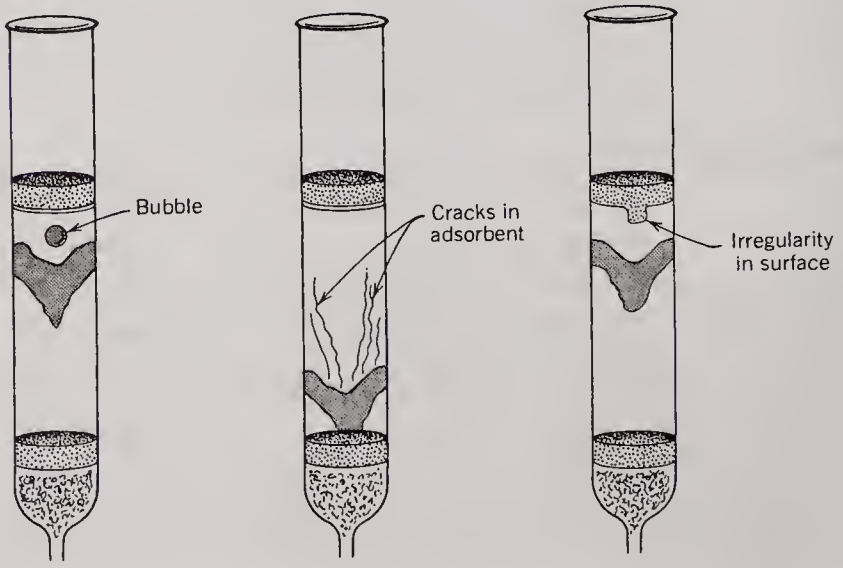


FIGURE 10.3 Channeling and its causes.

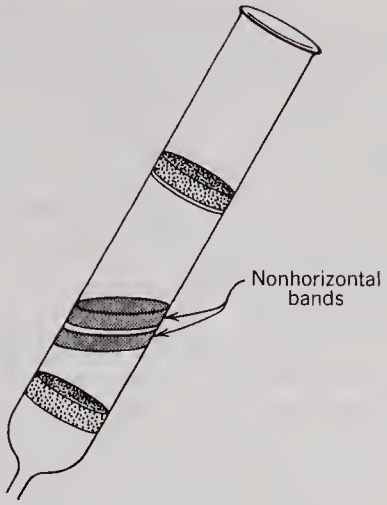
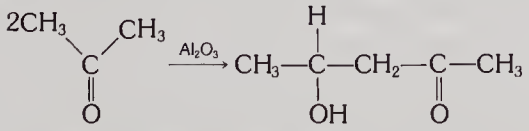


FIGURE 10.4 Nonhorizontal bands.

We use the same common solvents as eluants in column chromatography as for developers in TLC, and, since the same basic principles apply, the order of elutive capability is the same as the order of TLC developing capability. Please see Table 8.1. We also use mixtures of solvents, and addition of as little as 1 or 2 vol% of a more polar (more elutive) eluant to a less polar one can lead to a large increase in eluting capability. This is because increase in elutive capability is a very strong function of adsorption of the eluant itself on the column. The eluant takes the place of the adsorbed elutants and shifts their adsorbent-eluant equilibrium toward the eluant side. Because water is strongly attracted to polar adsorbents, it has a considerable elutive ability and you must take care to exclude even small amounts of it from solvents to be used as eluants.

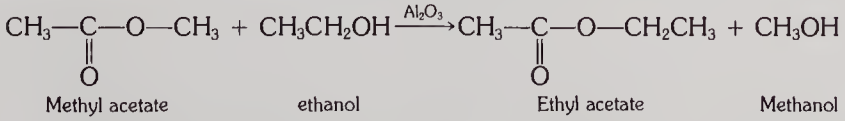
You should not suddenly change from one eluant to another because sudden replacement of a solvent can result in exothermic solvation changes on alumina which cause appearance of bubbles and/or cracks in the column. Make the change from one eluant to another gradually, beginning with just a little of the new solvent mixed with the old solvent. Gradually increase the new solvent concentration over several additions of eluant to the column until the desired concentration of new solvent is achieved.

Some solvents are unsatisfactory for use in chromatography because they react with the adsorbent. This is particularly a problem with basic or activated alumina. For example, acetone (IUPAC propanone) dimerizes *via* an aldol condensation catalyzed by alumina:



(10-2)

Transesterification is another catalytic reaction that occurs when an alcohol is used as the eluant during separation of esters. Catalyzed by alumina, the alcohol eluant exchanges places with the alcohol portion of the ester:



Methyl acetate ethanol Ethyl acetate Methanol

(10-3)

Another problem occurs with very polar solvents: Some eluants like methanol, water, and small carboxylic acids will dissolve some of the adsorbent.

10.2 THE TECHNIQUES

Preparation of the Column

You can quite easily convert grade I alumina (activated alumina) into other grades by simply weighing the required amount of alumina and water, putting them into a relatively

large screw cap jar, and shaking or rolling the jar for several hours. You can make activated alumina from other grades by heating it at 200 °C for several hours.

Clamp the buret or other cylindrical glass tubing securely at the top and bottom in a vertical position. A tube with Teflon stopcock is preferable. Alternatively, attach a piece of clean flexible hose to the bottom of the column, and use a screw clamp to regulate the flow. It is important at this point to use a hose that will not be degraded by the solvents to be used. Polyethylene should be your first choice because it is relatively unaffected by most solvents. Rubber is degraded by tetrachloromethane (carbon tetrachloride) and benzene; the plasticizer of tygon will be removed by many solvents commonly used in chromatography.

Pack the column in a solvent of low polarity, usually the first eluant. The liquid used for packing must have no greater elutive capability than the first eluant to be used. Using a small beaker, soak glass wool in the liquid used for packing. Use an amount of glass wool which when put at the bottom of the column will make a relatively loose plug about 1 cm high. Mash the glass wool in the beaker with a spatula until there are no bubbles. Put a few milliliters of the packing liquid into the buret. With a glass rod, push the glass wool to the bottom of the buret, then tamp it gently to pack and ensure that all bubbles have been removed. You must pack the glass wool enough to support the sand, but no more than necessary. Otherwise, you might restrict eluant flow.

Glass wool can be very irritating to the skin. Handle it carefully, preferably with rubber gloves.

Next, pour onto the glass wool enough clean, dry sand to make a $\frac{1}{2}$ cm column of it. Tap the glass tube gently with your finger to level the sand and remove any bubbles which appear. Wash down any grains sticking to the side of the column with a little packing liquid.

You can often pack in the adsorbent by partially filling the buret with packing liquid and then by slowly adding the dry, powdered adsorbent so that it settles evenly. However, bubbles often form and become trapped by this method, perhaps not appearing until the column is packed and standing ready for use. This is particularly a problem if other than the very nonpolar solvents are used for packing. It is especially a problem with alumina and silica gel.

The **slurry method** obviates the bubble difficulty. Prepare a moderately thick slurry of adsorbent and the packing liquid in a separate container by adding the adsorbent *slowly*, with stirring, to the liquid. Never add the solvent to the adsorbent because heat of solvation is released, causing bubbling and evaporation of solvent, and resulting in a lumpy slurry. In order to obtain a slurry of the right consistency, try a ratio of about 10 g of solid (adsorbent and filter aid, if any) to 20 ml of solvent. Use enough liquid so that the slurry can be poured conveniently. Stir the slurry and allow it to sit for about 5 min; then stir it again to remove any bubbles that might have formed. Measure the amount of solvent used for preparing the slurry.

Because of the toxicities of commonly used eluants, keep all containers closed except when they are in a hood.

Put a short, wide stem funnel in the top of the buret. Drain the buret to the top of the sand. Swirl the slurry in the beaker and pour small portions into the buret. If the adsorbent settles out of the chosen liquid easily, you will have to spoon the wet adsorbent into the column. Take care to keep the adsorbent wet at all times. Periodically rinse the spooned adsorbent into the column with small measured amounts of packing liquid. While filling the column, allow liquid to drain slowly from the bottom of the column into another beaker. The draining establishes a slowly moving eluant current within the buret which helps to settle the adsorbent uniformly in place. *Never* allow the column to run dry by draining! During addition of slurry, continuously gently tap the buret with a finger or short section of vacuum hose in order to promote even packing and prevent trapping of bubbles. Then recycle the drained liquid through the column once or perhaps twice to ensure that the column is well settled and to rinse down particles of adsorbent adhering to the inside of the buret. Tap the column gently to level the top surface of the adsorbent.

Next, allow a disc of fast filter paper slightly smaller than the column diameter to gently float down onto the column surface.

Finally, add a layer of clean, dry sand to a depth of about 2 or 3 mm. Wash down sand adhering to the inside of the buret with a small amount of solvent. Then drain down to a point about 1 cm above the top of the column.

Measure the amount of solvent used in preparing the slurry and the amount of solvent initially put in the buret. When the column is completely prepared, drain off and measure the excess solvent. Subtract the drain-off amount from the total initial amount to obtain the amount left on the column. The eluant volume left on the column is called the **chromatographic column holdup.** It is useful to know the holdup so that the eluant on the column can be changed completely by addition of the holdup amount of new eluant.

Stopper the top of the buret with a clean cork in order to prevent liquid evaporation. Do not allow the column to dry out or the column will crack, and subsequent use would result in channeling!

The best practice is to avoid preparing the column long in advance of its use because it might settle too much or with some adsorbents might swell, in either case decreasing the flow rate capability of the column.

Adding the Sample

A liquid mixture can be directly applied to the column, whereas a solid mixture must be dissolved in a solvent of elutive capability as near to that of the packing liquid as possible. Use a volume of solvent as small as possible so that the very narrowest band attainable can be formed at the top of the column.

Remove the cork from the buret and drain the liquid to the top of the adsorbent (but absolutely no lower!). Apply the sample preferably with a long enough pipet to reach near the surface of the column, so as to form a shallow layer on the top of the adsorbent. Then drain the column until the sample solvent is down to the top of the adsorbent. Pipet a small amount of sample solvent onto the column and again draw it down. Repeat this process a couple of times to ensure that all of the sample is adsorbed on the column. If the sample is colored and fresh solvent applied to the column becomes colored, it is obvious that all of the sample is not adsorbed.

Allow the system to sit 5 min to help establish a true equilibrium of elutant between adsorbent and eluant. This often helps to give a better separation.

Put all unused solvents into their recovery containers.

Never pipet by mouth. Use a rubber bulb for suction.

Elution

After the sample mixture is fixed on the column, elute it with an eluent or series of eluents as recommended or determined by prior experimentation. In general, start with solvents of lowest elutive capability and progressively increase the elutive capability either by using pure solvents or solutions. You can separate the majority of organic compounds on silica or alumina columns using hexane, toluene, and ether combinations, and then trichloromethane (chloroform). For best work, use only pure reagents. But for most general laboratory purposes the small amounts of impurities present in commercial grade solvents will be of negligible importance.

Begin elution by adding a portion of the first eluant and drain the eluant back down again to the top of the column.

In order to prevent bubble formation and channeling, make the change to a second eluant very gradually. For example, the following eluant systems in volume parts might be used in changing from hexane to toluene: 99 hexane/1 toluene; then 98 hexane/2 toluene; then 95 hexane/5 toluene; then 90 hexane/10 toluene; then 85 hexane/15 toluene; then 75 hexane/25 toluene; then 50 hexane/50 toluene; then 100% toluene. The amount of eluant to use each time should be equal to the column holdup.

The rate of flow through the column should be slow enough to allow good equilibration of elutants between eluant and adsorbent, but not so slow that diffusion spreads

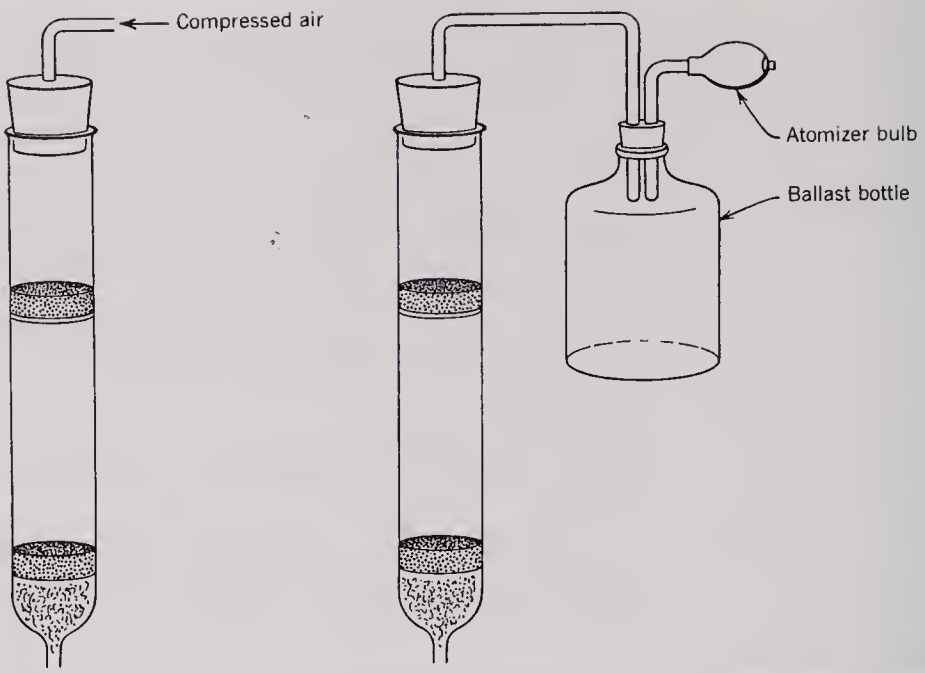


FIGURE 10.5 Application of air to column.

the size of bands. Generally a flow rate of about 2 ml/min is satisfactory. If the flow rate is too slow, you can increase it by filling the column to a higher level to give a greater pressure head, or by applying a slight air pressure from a compressed air source or an atomizer bulb connected through a large bottle for ballast volume. Please see Figure 10.5.

Use care in adding pressure to the column from an air hose. Too much pressure could fracture glassware. Work behind a shield.

Sometimes when a single eluant is used, an elutant band does not move cleanly along, but leaves a lower concentration of elutant at the trailing edge of the band. Such a phenomenon is called **tailing.** Tailing can result in overlapping of bands during collection. It can be rectified by constantly increasing the polarity (elutive capability) of elutant mixtures, thereby causing the trailing edge to move faster than the front and catch up.

Monitoring and Collecting Elutants

Monitoring in the sense used here means keeping track of the elutants. Monitoring elutants is easy when only colored compounds are involved. Most often however, compounds are colorless. Sometimes you can use ultraviolet (UV) light because some organic compounds will fluoresce. The room must be at least semidarkened in order for UV lamps to be useful; the smaller the amount of compound, the darker the room must be. In most cases you collect volume fractions, as in producing data for a fractional distillation

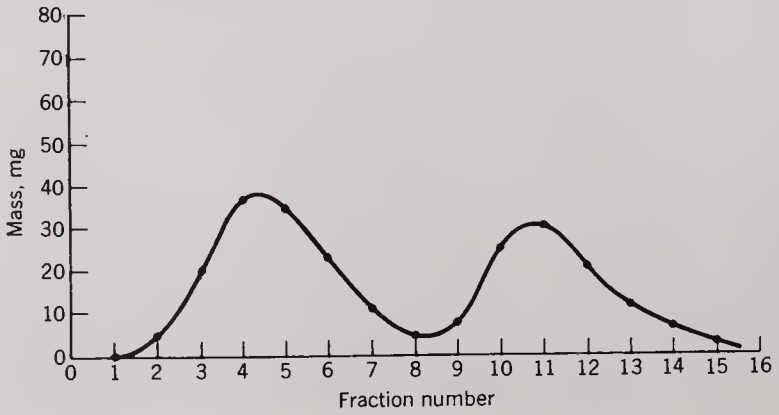


FIGURE 10.6 Typical elutant plot.

curve. Collect the fractions in tared (preweighed) flasks, remove the solvent by distilling or evaporating, and weigh the flasks to determine the mass of residue. A plot or fraction number (abscissa) versus mass (ordinate) yields a curve that shows which fractions belong together and the degree of separation obtained. Please see Figure 10.6.

Avoid looking into a UV source. It can cause retinal damage.

Emptying the Buret

Allow the buret, or other difficult-to-empty column, to drain until dripping is quite slow. Working in a hood, hold the column upside down and shake it. If this method does not suffice, attach an air hose to the constricted portion at the bottom of the buret. Hold the buret at an angle to horizontal of about 30°, with the open end on the bench top. Carefully apply air with just enough pressure to push the contents gently out. As the column exits, move the buret continuously so that the contents is laid in cylinder form on the bench top. The adsorbent can then be sectioned out and put in a container with solvent, where it can perhaps be saved and cleaned up for recycling.

Apply only minimum pressure when blowing contents out of the buret during clean up. Work behind a shield if you can.

10.3 EXPERIMENTAL PART
Separation of Methylene Blue and Methyl Orange

Time Required: 2 hr

Review Techniques and Principles:

Storing liquids	(0.12)
Labeling	(0.13)
TLC	(8.1, 8.2)
Lab notebook	(1)
Simple distillation	(7.2)
UV–VIS	(14.4)

Preparation of the column. Prepare a chromatographic column in a buret of 1½-cm diameter using 10.0 g of 80–100 mesh neutral alumina of Brockman activity 1. Use 95% ethanol as the packing solvent.

Separation of methylene blue and methyl orange. Put 2.0 ml of a stock solution consisting of 0.100 g of methylene blue and 0.100 g of methyl orange in 100.0 ml of 95% ethanol. Elute the column with 95% ethanol. If it is necessry to increase the rate of elution, attach a rubber hose to the laboratory air supply and turn on the air until a *gentle* stream of air emerges. Then hold the hose firmly enough on the top of the buret so that the desired rate of elution is attained. Collect the eluant until the lower part of the alumina column is white and the eluant is only very slightly blue. Note the color of the sand at the top and bottom of the column.

Using the buret-emptying technique described above, *gently* blow the column to the top of the buret; then remove and discard the upper sand layer and filter paper. Blow the alumina part of the column into a beaker and add 20 ml of 40 °C distilled water to extract the dye. Filter off the alumina and rinse it with 40 °C distilled water until the dripping filtrate is nearly colorless.

Analysis. Using an appropriate aqueous dilution of the stock solution of the dye mixture, and of the two elutants, obtain their visible spectra. After analysis, pour the ethanolic solution into a recovery container and discard the aqueous solution down a drain.

Writing the discussion. Report the percent yields and justify losses. Discuss the order of elution in terms of elutant polarities. Discuss λ_{max} relative to color of the mixture and

elutants. Propose a reason for the color of the sand layers at the top and bottom of the column.

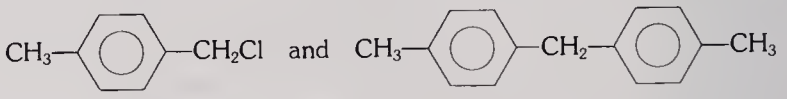
10.4 EXERCISES

Prelaboratory

1. Make a sketch of a chromatographic column using alumina. Label the various layers, and assign a function to each.
2. Make a step by step list of directions as to how you will prepare the column for separation of methyl orange and methylene blue.
3. Why must the column not be allowed to become dry once it has been prepared?
4. Why is a Teflon stopcock more satisfactory for chromatography than a ground glass one?
5. Describe how a change in eluent should be conducted.

Postlaboratory

1. What intermolecular interactions cause the dry pack method often to be plagued with bubbles in the column?
2. Discuss the relative polarities of silica and alumina on the basis of the electronegativities and atomic orbitals of the elements involved in each.
3. A student decided to purify a sample containing small amounts of methylbenzene (toluene). He assembled an alumina column and eluted with dichloromethane (methylene chloride) as eluant. No methylbenzene was ever recovered. However, analysis showed compounds of the following structures to be present in the eluent fractions:



Explain.

REFERENCE

1. Heftmann, E. *Chromatography*, 3rd ed.; Van Nostrand Reinhold: New York, 1975.

TECHNIQUE 11

GAS-LIQUID CHROMATOGRAPHY (GLC)

We usually refer to gas-liquid chromatography as GLC. It also goes by several other names: gas phase chromatography (GPC), vapor phase chromatography (VPC), gas-liquid partition chromatography (GLPC), or simply gas chromatography (GC). GLPC is the most descriptive term since the process involves a partitioning of the components to be separated between a gas phase and a liquid phase.

Gas-liquid chromatography is a separations technique, and is used to separate and

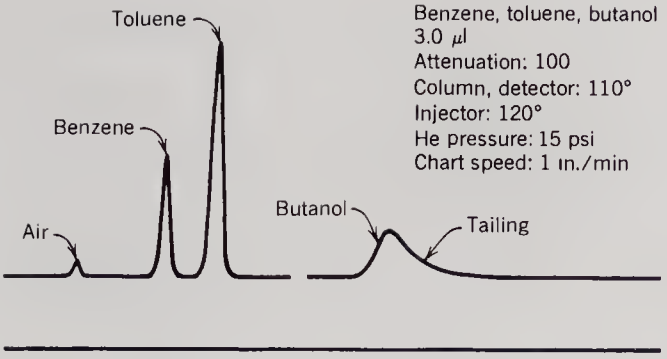


FIGURE 11.1 GLC chromatogram.

isolate components of a mixture, to help determine the purity of substances, to aid in identifications, and to make quantitative analyses.

GLC is not an adsorption process like TLC or column chromatography. It belongs to that general area of chromatography known as partition chromatography because each component in a mixture is partitioned between a gas phase and a liquid or semisolid phase.

GLC is limited to compounds that can be vaporized without decomposition at temperatures generally below 300 °C. However, this limitation is more than offset by the capability of analyzing parts per million quantities. Common sample sizes are in the neighborhood of from 1 to 5 μl (millionths of a liter)!

The instrument used for GLC is called a **gas chromatograph**. The recorder of the instrument traces a series of peaks like that shown in Figure 11.1, a printout called the **GLC chromatogram.** Each peak on the chromatogram corresponds to the presence of a single substance if a good separation is obtained.

11.1 INSTRUMENTATION

The gas chromatograph is a much more complex apparatus than those used for paper, TLC, and column chromatography. A schematic diagram of a commonly used instrument is shown in Figure 11.2.

The Injection Block

The injection block contains a heated cavity into which the sample is injected with a microsyringe through an **injection port** which is covered by a silicone rubber **septum** (a thick membrane). The sample is vaporized in the injection block and then carried into the column by an inert gas under pressure. This moving gas phase is called the **carrier gas,** and is usually helium or nitrogen. Helium is the carrier gas of choice because it is inert and has a greater thermal conductivity than any gas other than hydrogen.

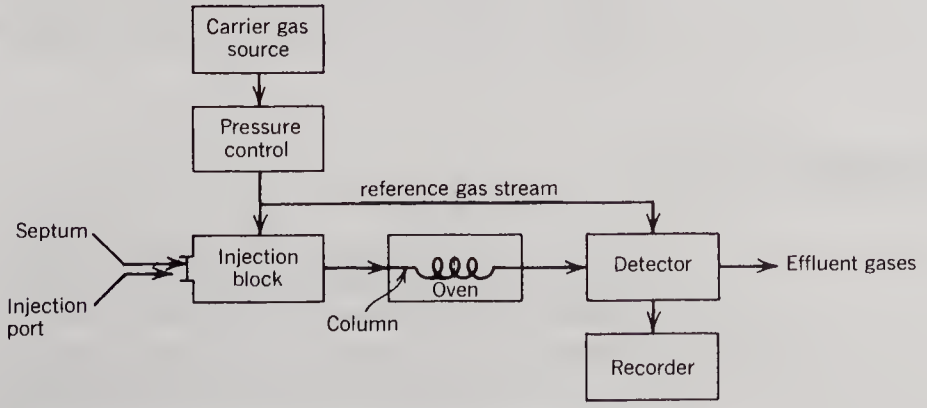


FIGURE 11.2 Schematic diagram of gas-liquid chromatograph.

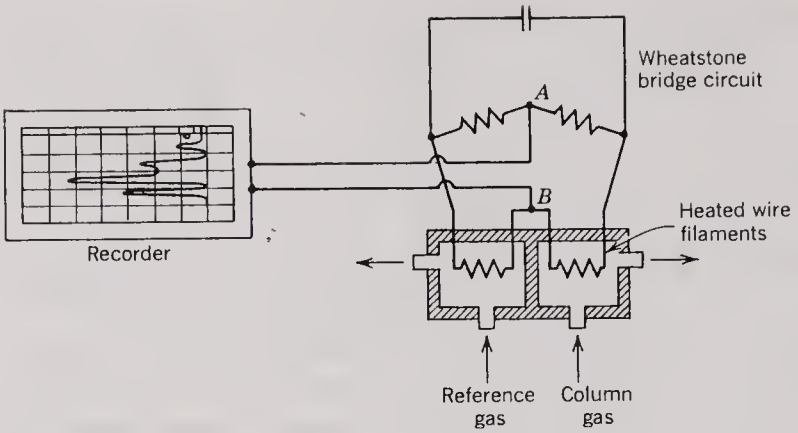


FIGURE 11.3 Thermal conductivity detector.

The Column The column, the most fundamental part of the gas chromatograph, consists of a long stainless steel or copper tube containing the stationary phase. The tube is usually 3 to 6 mm in diameter and as long as 100 m. A common length is 3 to 4 m. Because of the length, the column is usually coiled or in some way folded so that it takes up less room and will fit in the oven which carefully controls its temperature. The tubing is fitted with connectors on each end so that it can be easily attached to and removed from the instrument.

The **stationary phase** is a high-boiling liquid of low volatility, a low-melting solid, or a wax, sometimes coated only on the inside walls of the column tube, but usually adsorbed on a high surface area, solid **support** like diatomaceous earth, crushed firebrick, or alumina.

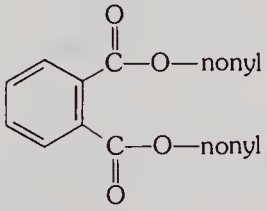
The Detector After the substances separated in the column are swept from it by the carrier gas, they enter the detector. Detectors are commonly of two types: flame ionization and thermal conductivity. Flame ionization detectors are generally far more sensitive and useful for analyses involving extremely minute amounts of compounds. However, most student models of gas chromatographs employ a thermal conductivity detector. Figure 11.3 illustrates a thermal conductivity detector. It basically consists of a Wheatstone bridge circuit and two, similar, electrically heated wire filaments. When streams of pure carrier gas at a constant temperature are passed over the wire filaments, the temperatures and the electrical resistances of the filaments are equal. The voltage at junction *A* is the same as that at junction *B* under these conditions. The **reference gas** stream always maintains a constant resistance in the reference filament. However, when the column gas stream contains molecules of some substance in addition to the carrier gas, its thermal conductivity is decreased and it conducts heat from the column side wire filaments less efficiently. Therefore the temperature and electrical resistance of the filament increase. Now the voltage at point *B* is higher than that at point *A*. This difference in voltage is printed out by the recorder as a peak on chart paper. The area of the peak is proportional to the difference in voltage, hence to the amount, and to some extent the kind, of substance present.

11.2 DISCUSSION OF GLC

The separation of the mixture by GLC is a partition process, and is similar to the separation that occurs in a separatory funnel wherein a mixture is separated by the differential solubilities in the two liquid phases. In the case of GLC, the distribution (or partitioning) takes place between a liquid-like phase and a gas phase.

GLC is also similar to paper chromatography. Both GLC and paper chromatography involve partitioning between phases. But whereas in the latter the moving and stationary

TABLE 11.1 Stationary Phases

Stationary Phase	*Type*	*Composition*	*Temperature Limit, °C*	*Relative Polarity*	*Used Typically for*
Apiezon	Hydrocarbon grease	$CH_3—(CH_2)_n—CH_3$	250–300	Non	Hydrocarbons (hydroxylic compounds tail)
Carbowax	Polyethylene glycol	$HO—(CH_2CH_2O)_n—CH_2CH_2OH$	150–250	Medium high	Polar compounds; alcohols, ethers, amines, aldehydes, ketones, etc.
DC-200	Polysiloxane	$(CH_3)_3Si—O\left(\begin{matrix}CH_3\\ \vert\\ Si—O\\ \vert\\ CH_2\end{matrix}\right)_n Si(CH_3)_3$	200–250	Medium low	General; aldehydes, ketones, alkyl halides
Diethylene glycol succinate	Polyester	$\left(CH_2CH_2—O—\overset{\overset{O}{\Vert}}{C}—CH_2CH_2—\overset{\overset{O}{\Vert}}{C}—O\right)_n$	225	High	Polar compounds; esters, acids
Dinonyl phthalate	Ester		150	Medium	General

phases are both liquids, in GLC the mobile phase is a gas. Moreover, the vaporization of a compound into the GLC gas phase is a function of its vapor pressure and does not depend so much on the intermolecular nonbonded interactions which are so important in paper chromatography. One further difference is the carefully controlled high temperature of the GLC column.

In a GLC column, each component of the mixture being separated becomes partitioned between the nonmobile stationary phase and the moving gas phase. Because the various kinds of molecules spend different amounts of time in the two phases, they become separated from each other. The rate of a component's travel through the column depends on (1) its solubility in the stationary phase, (2) its vapor pressure at the temperature of the column, and (3) the carrier gas flow rate.

The chosen stationary phase is often critical for obtaining good separations. The functional groups, polar characteristics, and even molecular weights of compounds help to determine what stationary phase is generally selected. The components to be separated must have reasonable solubility in the stationary phase. For example, for separation of esters and acids, dinonyl phthalate could be used because dinonyl phthalate, being itself an ester, is likely to dissolve esters and acids reasonably well. Table 11.1 lists some commonly used stationary phases along with some of their properties and uses. The separation of a two-component mixture is schematically shown in Figure 11.4, which

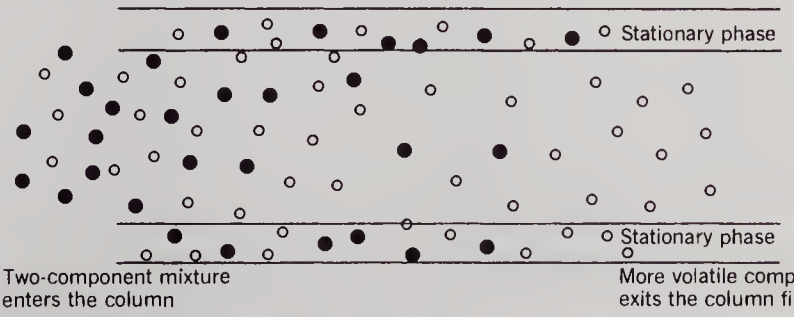


FIGURE 11.4 GLC separation schematic.

for simplicity illustrates a column in which the stationary phase is coated on the walls of the tubing. In this schematic drawing, the molecules illustrated by the solid dots are more soluble in the stationary phase and/or have a lower vapor pressure than the molecules depicted by the white dots. As the two components are pushed through the column at a steady rate by the carrier gas, the molecules come in contact with the stationary phase and dissolve in it. However, at the temperature of the column, the molecules vaporize from the stationary phase into the gas phase again and move farther down the column. But fewer of the more soluble, less volatile molecules (solid dots) vaporize into the gas phase. This process is repeated thousands of times throughout the long length of the column, allowing for thousands of equilibrations. Therefore the more soluble, less volatile molecules are gradually left behind. GLC equilibration is the situation that pertains when equilibrium is established between the dissolving of molecules in the stationary phase and their evaporation back into the gas phase. Actually equilibrium is continually shifted toward the gas phase because the gas is always in motion toward the end of the column where the components are **eluted** from it (come out from it). The more time a given component spends dissolved in the stationary phase, the longer it will take to be eluted. Now you can understand why the GLC column must be so long. The more similar the compounds to be separated are, the longer the column must be.

The rate of carrier gas flow must not be so great that the gas passes over the stationary phase so rapidly that there is insufficient time for components of the mixture to equilibrate between the gas and stationary phase.

The amount of compound that can be in the gas phase is primarily a function of the compound's vapor pressure: the higher the temperature, the greater the vapor pressure, and the greater the amount of compound in the gas phase. Within a homologous series (like hexane, heptane, octane; or methanol, ethanol, propanol) components of a mixture will elute in order of decreasing vapor pressure. The temperature of the column must be kept high enough so that individual compounds will be vaporized from the stationary phase after they have dissolved in it, but not so high that concentration of all compounds in the mixture will be about the same in the carrier gas. The temperature of the column must also be kept low enough so that the stationary phase does not vaporize and become desorbed from the solid support. The temperature is normally adjusted to be at about the boiling point of the lowest boiling component of the mixture.

The lapse in time from injection of a compound to its exit from the column is called the **retention time,** often symbolized by t_R. It is measured from time of injection to the production of a maximum of the recorded peak. Each compound has a characteristic retention time depending on the length of the column, carrier gas flow rate, column temperature, injection block temperature, and stationary phase. The retention time can therefore be used to help identify compounds in GLC much the same way that R_f can be used in TLC. Actually, t_R, like R_f, is difficult to duplicate from day to day.

Under good operating conditions and with relatively short retention times, sharp peaks will be observed. The longer the retention time is, the flatter and broader the recorded peaks will be.

Resolution is the extent of separation between two components of a mixture. The best resolution will produce peaks that are completely separated from each other,

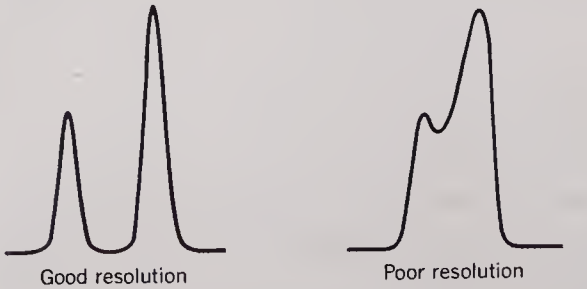


FIGURE 11.5 Resolution.

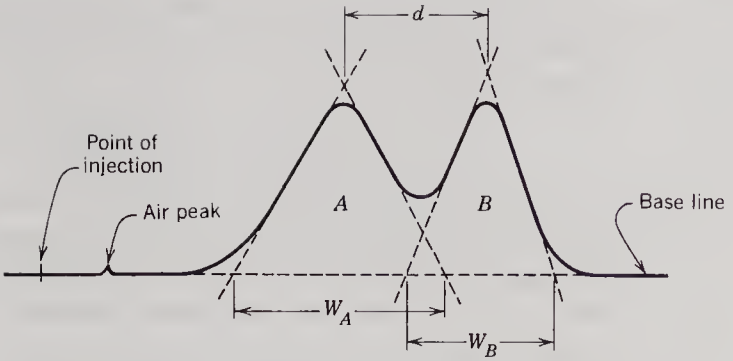


FIGURE 11.6 Measurements for calculating resolution.

like those in Figure 11.5*a*. Poor resolution results in incomplete separation of peaks (Figure 11.5*b*) which can arise by using too much sample for the capacity of the column, too high a temperature, the wrong choice of stationary phase, too short a column, too wide a column, or combinations of the same. Small-diameter columns give best resolution, but then sample size must also be small.

In GLC, resolution is mathematically defined as;

$$R = \frac{2d}{W_A + W_B} \tag{11-1}$$

wherein d is the distance between the maxima of the two peaks and W_A and W_B are the peak widths along the base line. Please refer to Figure 11.6. This equation is valid only when the peaks are of the same height, as shown in Figure 11.6. If the heights are different, the concentrations of the components in the solution must be changed in order to use equation 11-1. Complete separation of peaks will give a resolution of 1 or greater.

11.3 GLC TECHNIQUES

The Sample

It is important to remember that the sample should consist largely of components with boiling points generally somewhat below that of the stationary phase. If the components are too high boiling, they will not be eluted from the column at ordinary operating temperatures but will remain there and change the partitioning characteristics of the stationary phase. If the temperature is increased to help elute them, you might elute the stationary phase as well! Nonviscous liquids are injected *neat* (are not mixed with a solvent). Viscous liquids and solids must be dissolved in a volatile solvent like ether.

Preparing the Gas Chromatograph

In your initial work, your instructor will probably have prepared the gas chromatograph. Later, after reading the manual for the operation of your instrument, you might have to do some of the following things yourself:

1. Select and install a column that is appropriate for the separation. Refer to Table 11.1 in selecting the proper stationary phase.
2. Bring the injection block, column, and detector up to temperature. The temperature of the injection block is usually maintained at 40–50 C° above the boiling point of the highest boiling component of the mixture. The column and detector are maintained at a temperature at or somewhat below the boiling point of the highest boiling substance of the mixture. Sometimes the detector is maintained at a higher temperature than that of the column to keep the detector clean.
3. Set the carrier gas flow rate by adjusting the pressure regulator and needle valve. The flow rate depends on the column diameter, and for a $\frac{1}{8}$ (0.125) in. i.d. column

should be about 25 cm^3/min, attained by a pressure of 10–15 psig. To obtain the same velocity of gas down the column for a $\frac{1}{4}$ (0.25) in. i.d. column, calculate the flow rate by

$$25 \text{ cm}^3/\text{min} \frac{(0.25 \text{ in.})^2}{(0.125 \text{ in.})^2} = 100 \text{ cm}^3/\text{min}$$

4. Set the bridge current (filament current) at the appropriate value for the instrument.
5. Set the attenuator so that the pen deflection stays on the chart paper. The attenuator regulates the sensitivity of the recorder. If the largest peak is less than 50% of a full scale deflection, the peak can be made larger by resetting the attenuator.
6. Set the base line by adjusting the recorder zero.
7. Set the chart speed as desired, usually 1 in/min or 2 cm/min. But it depends on the retention times of the sample components. If the retention time is short, a greater chart speed might be in order; conversely if the retention time is long, a lesser chart speed should be used.

Injecting the Sample

Fill a microliter syringe by placing the tip below the surface of the liquid sample; then draw the liquid in by slowly pulling the syringe plunger part way up. Usually some air, which you will observe as a bubble, will be drawn in along with the sample. Sometimes you can remove air by holding the syringe tightly to the side of the sample container and pushing the plunger in rapidly and then slowly pulling the plunger part way up. (Since the needle is fine and easily bent or sealed, the needle must not be allowed to strike the bottom of the container.) Draw the sample in slowly and expel it rapidly in this manner several times. Then draw the sample in again and adjust it to the desired level by pointing the syringe upward and pushing the plunger. Sometimes you can remove air bubbles by drawing in the liquid, inverting the syringe, gently tapping the syringe with your finger until the bubbles are seen to rise up to the needle end, and then pushing the plunger in until liquid runs out of the needle and the desired amount is contained. You will usually use a sample size of 1 to 5 μl.

Hold the charged syringe by the barrel in one hand with the little finger gently but firmly against the side of the plunger to keep it from being blown out by the carrier gas pressure. Please see Figure 11.7. Guided by the other hand, next insert the syringe at a right angle carefully but quite rapidly through the rubber septum as far as it will go into the injection port (the chamber of the injector block). Immediately depress the plunger, hesitate 1 or 2 s, then withdraw the needle straight back through the septum as rapidly and smoothly as possible. Keep the plunger depressed during withdrawal.

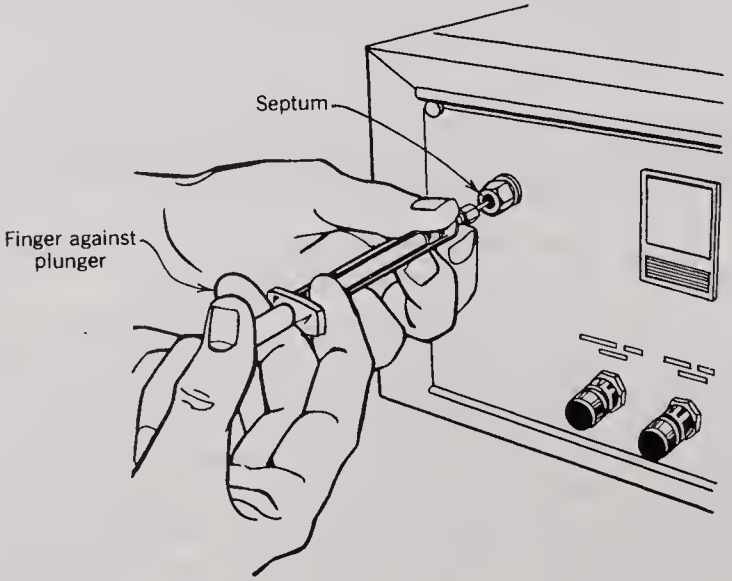


FIGURE 11.7 Injection of sample into gas chromatograph.

Marking and Labeling the Chart Paper

Before the injection is made, label the GLC chart paper in ink with the following information: identification of the sample; size of the injected sample; attenuation setting; column, injection block, and detector temperatures; identity of stationary phase; chart speed; and carrier gas pressure and/or flow rate. A common practice is also to give each instrumental plot an identifying number, such as GLC-1, GLC-2, and so on. This makes it easy to refer to individual plots in writing observations and conclusions.

Set the recorder pen at the zero line on the chart paper. Set the chart speed you want to use and let the recorder run to a vertical line on the chart paper. Stop the recorder and mark the vertical line with the recorder pen by moving the zero knob. Rezero the chart paper after moving the knob. The mark you made will be the starting point of the chromatogram and fixes time zero for calculating retention times. At the time the plunger sends the sample through the injection port, you must set the chart paper into motion. Obviously, since both of your hands are busy with the syringe, you can not start the chart at exactly the same time of injection. At a slow chart speed the error will be negligible if you flick the chart switch as soon as possible after injection. At the faster chart speeds, you can ask a classmate to turn on the chart for you at the time of injection.

Cleaning the Syringe

As soon as you have made the injection, clean the syringe! Many syringes have become irreparably stuck because they were not cleaned immediately. Cleaning is especially important when a viscous liquid or solid dissolved in a solvent has been injected.

Clean the syringe by drawing in a solvent for the materials just injected, and then squirt it into a waste solvent container. Two or three repetitions should suffice.

Immediate cleaning is not necessary only if the samples are known to consist solely of simple solvents, such as chloroform, benzene, methanol, water, and so on. However, before each succeeding injection you must rinse the syringe by drawing in some of the next sample to be analyzed and injecting it into a waste solvent container. This process should be repeated two or three times before the syringe is filled for an injection.

Gas chromatographs release vapors of the substances that were injected into them. The amount of vapor is quite small per sample. However, continued use and/or injection of particularly toxic materials could be hazardous. A hose can be run from the chromatograph outlet into a hood.

Never cross a busy laboratory with an unsheathed syringe. Move slowly, and keep the work area clear.

Fill and rinse syringes in a hood if toxic materials are used or suspected.

Be careful about touching the injection port of the chromatograph. It is likely to be very hot.

Obtaining and Storing the Chromatogram

Depending on the sample injected, the chromatogram might take less than a minute or more than an hour. For analysis of a new mixture it is necessary to assume a very long retention time to be sure all components have been eluted from the column, but for most mixtures that you will analyze, 5 or 10 min should be sufficient. When the chromatogram is finished, turn the recorder chart control to "Standby."

The chromatograms should be safely stored or securely taped or glued into your notebook, thereby becoming a permanent part thereof. Record the make and model of the GLC instrument and of the recorder.

11.4 QUALITATIVE GLC ANALYSIS

The purpose of qualitative GLC analysis is to determine the identity of the components of a mixture.

GLC qual is based on the premise that each component of a mixture has a different retention time, t_R. A given retention time pertains to a specified column operated at a stated temperature and gas flow rate. Under specified operating conditions, t_R is a constant. Therefore, if a sample is injected into a column several times, the resulting chromatograms should be identical.

The retention time of a component of a mixture should be the same whether injected alone or in a mixture, and this is generally the case as long as the sample is very small. However, this assumption must be made with caution.

There are two general methods by which identifications of components of a mixture are obtained: (1) measurement of t_Rs; (2) addition of a standard to the mixture.

Method 1. Measurement of t_Rs

GLC chart paper is divided horizontally into standard units, like centimeters or inches. Your first task in measuring t_R is to make a time-distance calibration of the chart paper. That is, you must determine, for example, how many centimeters on the chart paper represent a minute at a given chart speed. Actually, in order to make efficient use of your time, you can make the calibration at the same time you are running a sample through the GLC instrument.

First, select and set the recorder's chart speed. Adjust the base line to the zero position on the vertical scale. The **base line** is that portion of a chromatogram when only the carrier gas emerges from the column and passes through the detector. Now run the chart paper through the recorder until the needle rests on a vertical line. Mark this line with your pen as the point of injection and time zero. Inject the sample mixture and turn on the chart, simultaneously starting a stopwatch or noting the time. Allow the chromatogram to be recorded. When the pen rests on a line, simultaneously stop the chart paper and the stopwatch. Calculate the number of seconds or minutes per division or subdivision of the chart paper, obtaining a time/distance ratio, *TD*, such as seconds/centimeter.

The t_R of each peak can now be determined by measuring the distance from the injection point to the top of the peak, then multiplying that distance, *d*, by *TD*:

$$t_R = TD(d) \tag{11-2}$$

Note that each peak has its own t_R.

Now choose reference standards for making GLC chromatograms with which you can compare the chromatogram of the unknown sample. A **standard** is a known pure substance believed to be in the unknown mixture.

Make chromatograms for each standard and determine the t_Rs. Inject reference standards soon before or after the mixture to be analyzed so that conditions are as nearly alike as possible.

Compare the t_Rs of unknown and standard peaks to identify the components of the mixture.

If a mixture of unknowns is being analyzed, you might find it advantageous to chromatograph a mixture of reference standards because retention times might be somewhat influenced by the presence of the other components.

Method 2. Addition of Standard to the Mixture

This method can be used to confirm the identity of an unknown determined by method 1 or in lieu of method 1.

Prepare a GLC chromatogram of the unknown sample. Now, take about 1 ml of the unknown and add to it two or three drops of a standard. (If the sample is very volatile, relatively larger amounts of unknown and sample will have to be used.) Make a chromatogram of the new mixture. The peak of the new chromatogram which appears larger than in the original chromatogram belongs to a substance with the same identity as that of the standard.

11.5 QUANTITATIVE GLC ANALYSIS

In general, you can relate the ratio of areas under the GLC peaks to the molecule ratio of components if the components of a mixture are very similar. The more different compounds are, the less applicable this generality is. The only way to be certain about the weight/area is to analyze known mixtures.

There are four common methods of quantitative GLC analysis: integration, peak area or height, peak width at half-height, and weight of peak. In most cases, standards should be used to produce peaks with which you can make comparisons.

Integration

If the recorder has an integrator built into it, the area under a peak is automatically measured. You should be so lucky!

Peak Area or Height

The area of a peak of a gas-liquid chromatogram is proportional to the number of gaseous molecules of any one chemical species reaching the detector. The peak area is the area enclosed by the peak and the peak base, the peak base being an interpolation of the base line between the extremities of the peak, line *AE* in Figure 11.8. Only roughly is the ratio of peak areas of *different* kinds of components equal to the ratio of their molar concentrations in the mixture, however. Nevertheless, comparing the approximate areas of the peaks gives a pretty good idea about how much of each component is present in the mixture. If the peaks are all very symmetrical and of the same general sharpness, you can use peak heights instead of areas. This is easier than trying to measure areas. Neither of these approximations would, of course, suffice for a really precise quantitative analysis.

Peak Width at Half-Height

You can use geometric approximation (triangulation) when the peaks are quite symmetrical and well resolved. The height of the peak from the base line multiplied by the width of the peak at half of its height is equal to 93% of the peak area. The peak height is the distance from the peak maximum to the peak base, line *CH* in Figure 11.8 and the peak width at half-height is represented by a line parallel to the base bisecting the peak height and terminating at the sides of the peak, line *FG* on Figure 11.8.

In comparison of symmetrical peaks, this method is as useful as calculating areas. You can reduce the experimental error of measuring widths of peaks by using a somewhat higher chart speed so as to obtain wider peaks. Figure 11.9 illustrates calculation of relative amounts by this method.

Weight of Peaks

When peaks are not symmetrical or when peak overlapping or tailing has occurred, the best way to obtain quantitative information is to cut out and weigh the peaks. The weights so obtained will be proportional to the areas of the peaks, which in turn will be pro-

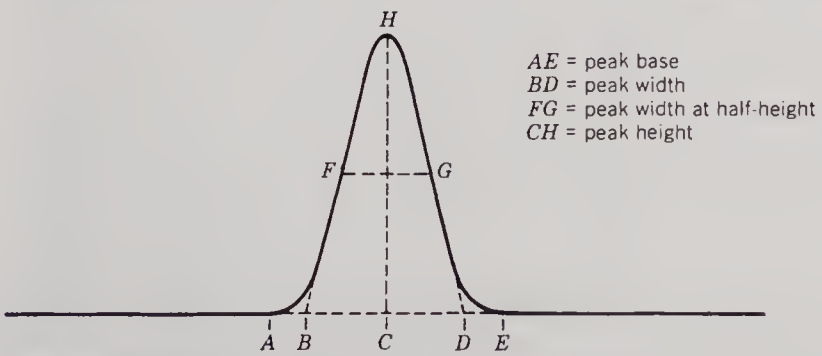


FIGURE 11.8 Parts of a GLC peak.

Area $A = (h)(w_{\frac{1}{2}}) = (54.0\text{ mm})(8.0\text{ mm}) = 432\text{ mm}^2 = 430$ (2 significant figures)

Area $B = (h)(w_{\frac{1}{2}}) = (92.0\text{ mm})(14.0\text{ mm}) = 1288\text{ mm}^2 = 1290$ (3 significant figures)

Area ratio $\frac{B}{A} = \frac{1290\text{ mm}^2}{430\text{ mm}^2} = \frac{3.0}{1.0}$

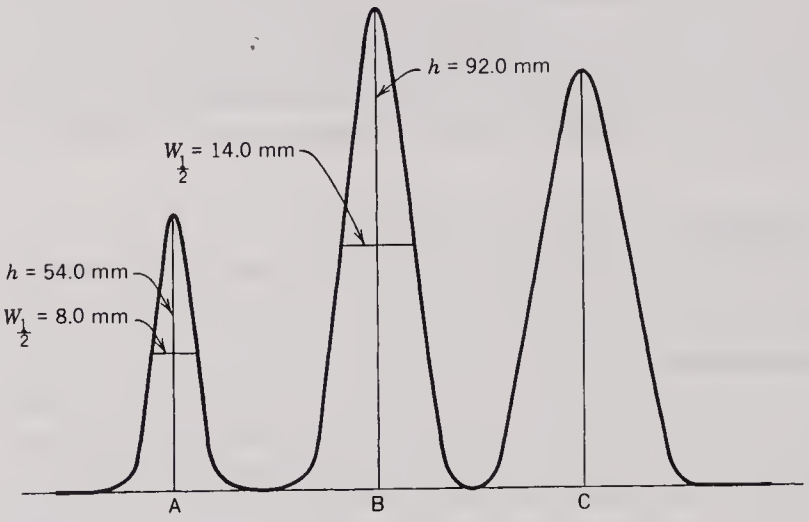


FIGURE 11.9 Composition ratio determination by triangulation.

portional to the compounds' weights or moles, depending on how standards are prepared.

Let us suppose that we have a mixture of ethanol and water to be analyzed. We shall first prepare a set of standards. Into five labeled vials we shall measure and mix thoroughly ethanol and water in several mole fraction ratios: 0 ethanol/1 water, 0.25 ethanol/0.75 water, 0.50 ethanol/0.50 water, 0.75 ethanol/0.25 water, 0.05 ethanol/0.95 water. Next we shall inject at least four samples of each standard into the gas chromatograph, taking care to inject as nearly as possible exactly the same amount each time. We shall obtain four sets of peaks for each standard sample, one set for a permanent notebook record and three to analyze. Next we shall cut out carefully with a scissors each peak of the three sets, trying to make the cuts along the center of the pen tracings. We shall then simultaneously weigh the three peaks of each component in each standard on an analytical balance and, dividing the total weight by 3, obtain an average weight. Next, for each standard we shall calculate the ethanol/water ratios of the peak weights and construct the plot shown in Figure 11.10. We shall treat the unknown ethanol/water sample in the same manner to obtain an ethanol/water peak weight ratio. Suppose we found this ratio to be 1.8. From the plot of Figure 11.10, we find the unknown sample to be 0.50 mole fraction ethanol.

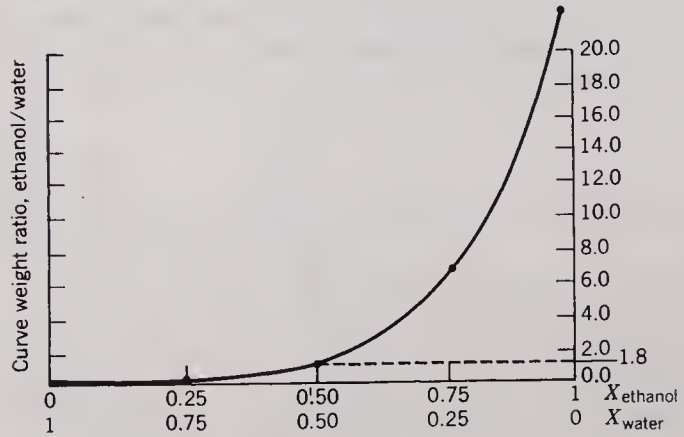


FIGURE 11.10 GLC cut-and-weigh standard curve.

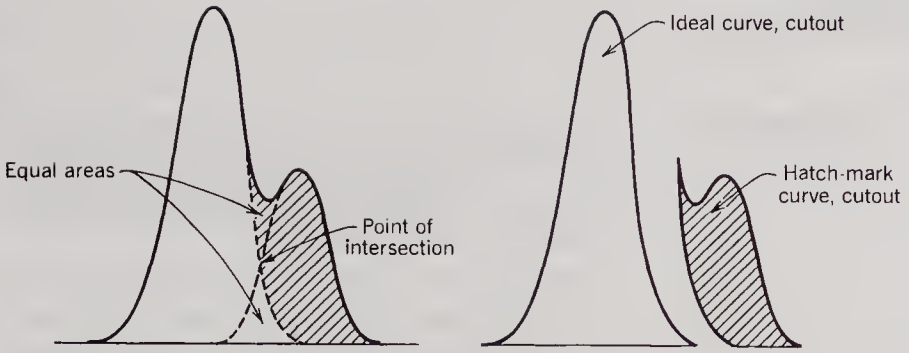


FIGURE 11.11 Analysis of poorly resolved peaks.

In order to conserve class time on the gas chromatograph your instructor might prepare a single set of standards and peak weights for the entire class to use.

It is usually important to make the standard and unknown curves with little delay in time (at least on the same day) so that GLC conditions are as invariant as possible.

When peaks overlap, an estimate of their complete shapes must be made. In such a case you draw imaginary lines indicating the shapes of the ideal peaks, as shown in Figure 11.11. The point at which the imaginary lines cross should give equal areas within the crossed line region above and below the point of intersection. Next, cut out one peak as its ideal peak; then cut out the other, with the shape shown in the hatch-marked area of Figure 11.11. This peculiarly shaped, hatch-marked curve, however, has the same area as the ideally shaped smaller original peak.

11.6 EXPERIMENTAL PART
GLC Analysis of an Unknown Binary Mixture

Time Required: Around 20 min/student/sample at the instrument

Review Techniques and Principles:

Storing samples	(0.12)
Labeling	(0.13)
Lab notebook	(1)

You will be given a mixture which will be binary combinations of pentane, hexane, heptane, octane, and nonane. You must determine (1) the identity of the components, and (2) the molar and weight ratios of the components.

Method. Use a nonpolar stationary phase like Apiezon or DC-200 and a column length of at least 6 ft. Choose GLC methods of qualitative and quantitative analysis which seem to be most applicable to your situation, or as directed by your instructor. Be sure to keep samples of unknowns tightly closed so that evaporation will not change concentrations. Use column and injection port temperatures of about 100 °C. Make a table in your notebook which has columns for identity, retention time, resolution, mole ratio, and weight ratio. In the identity column list the names of all standards involved, and list the peaks from the unknown sample as peak No. 1 and peak No. 2. Entitle your table, "Table (number). GLC Data for Unknown (number)." To determine the resolution of the unknowns, identify them; then, using the two standards identical to those in your sample, put five drops of each in a test tube, mix them well, and inject a sample into the gas chromatograph.

Writing the discussion. Discuss what results led you to the conclusion regarding identity of the components of the mixture; which component was eluted first and why; and why the resolution was or was not good and how you might improve it if necessary.

11.7 EXERCISES

Prelaboratory

1. If you were given a choice of dinonyl phthalate or carbowax as a stationary phase for separating water and methanol, which would you choose?
2. What are the differences and similarities between a separation in a separatory funnel and in a gas chromatograph?
3. Make and label a schematic drawing of a gas chromatograph.
4. List eight items that you will record on the chart paper before injection is made.
5. Make a flow diagram of the technique of filling a syringe, removing bubbles therefrom, injecting the sample into the gas chromatograph, and cleaning the syringe.
6. What is required flow rate for a $\frac{3}{16}$-in.-i.d. column?

Postlaboratory

1. Explain why the wrong choice of stationary phase results in poor resolution.
2. Analyze by triangulation peak *C* in Figure 11.9 and report the ratio *C*/*A*.
3. Select from Table 11.1 stationary phases to separate (a) ethyl ethanoate (acetate) and butyl ethanoate (acetate), (b) *n*-pentane and ethoxyethane (ethyl ether), (c) the components of a sample of gasoline, and (d) ethanal and propanone (acetaldehyde and acetone).
4. A student needed to make a GLC quantitative analysis of a mixture of butanol and water. To obtain a high degree of accuracy, he prepared six sets of GLC cutout curves for his unknown. He then obtained fractions by use of a standard curve carefully prepared by a friend a few days earlier. Critique the method used.
5. In Figure 11.12:

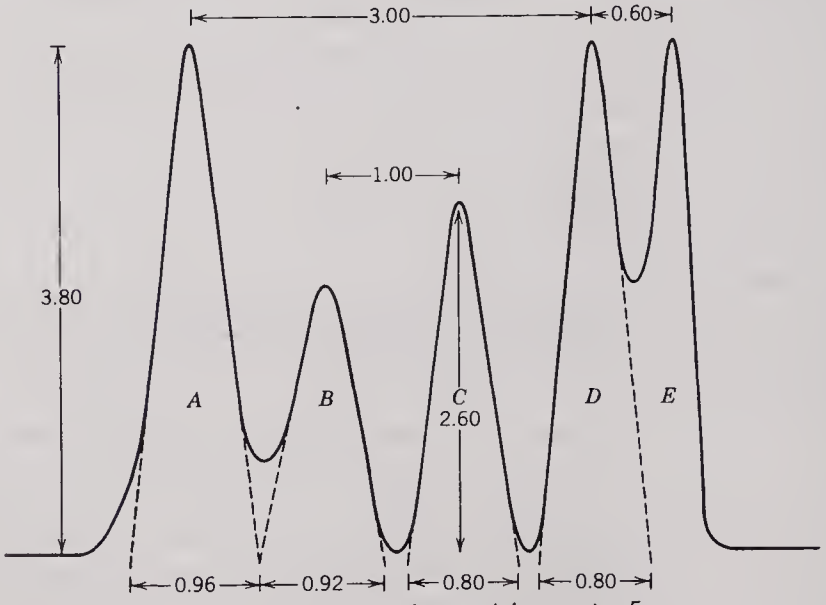


FIGURE 11.12 GLC chromatogram for postlab exercise 5.

(a) What is the resolution between peaks *A* and *D*?
(b) What is the resolution between peaks *D* and *E*?
(c) What is the resolution between peaks *B* and *C*?
(d) What is the mole ratio between peaks *A* and *C*?

Distances given are in centimeters.

REFERENCE

1. Schupp, D. E. "Gas Chromatography." In *Technique of Organic Chemistry*, E. S.; Weisberger, A., Eds.; Interscience: New York, 1968.

TECHNIQUE 12

POLARIMETRY

An important physical property in synthesis, identification, and characterization of many organic substances is **optical rotation,** the property of rotating plane-polarized light in a clockwise (+, *d*, or dextro) or counterclockwise (−, *l*, or levo) direction. Modern usage prefers + and −. The instrument used to measure the rotation of plane-polarized light is called a **polarimeter,** and the process of making the measurements, calculations, and interpretations is known as **polarimetry.**

In this technique, we shall briefly explore plane-polarized light and the rotation of plane-polarized light by optically active molecules.

12.1 DISCUSSION OF OPTICAL ROTATION

Plane-Polarized Light

One way of thinking about light is in terms of its wave nature. We can describe the wave characteristics of light in the same way as we describe waves of water. Imagine water waves moving at a velocity v past an anchor post as shown in Figure 12.1. Because the crests and troughs of the waves are perpendicular to the direction of propagation (direction in which they are moving), they are said to be **transverse waves.** The wavelength, λ (lambda), is the distance between adjoining crests (or between any other two similar adjoining points); the **wave velocity,** or frequency v is the rate at which crests pass the post.

Light waves are similar to water waves, but consist of two *simultaneous* transverse waves. One wave is electric in nature; the other, at right angles to the first, is magnetic in nature. We therefore refer to light as electromagnetic (em) radiation. Figure 12.2 illustrates the wave character of light. E represents the plane of the electric vector and H is the plane of the magnetic vector. (Recall from physics that a vector is a quantity

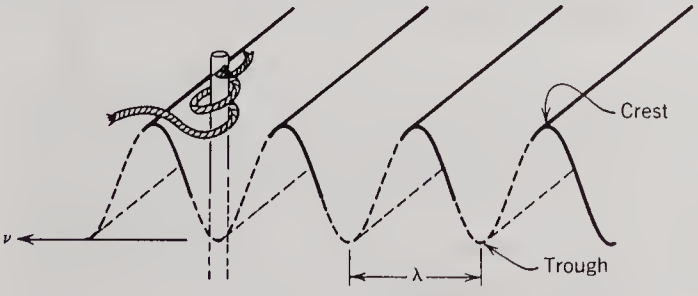


FIGURE 12.1 Water waves passing a post.

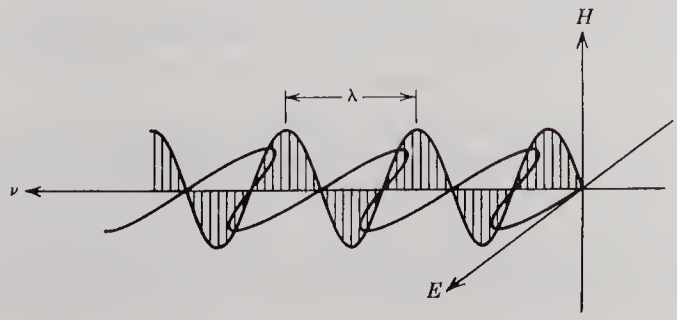


FIGURE 12.2 Electromagnetic waves.

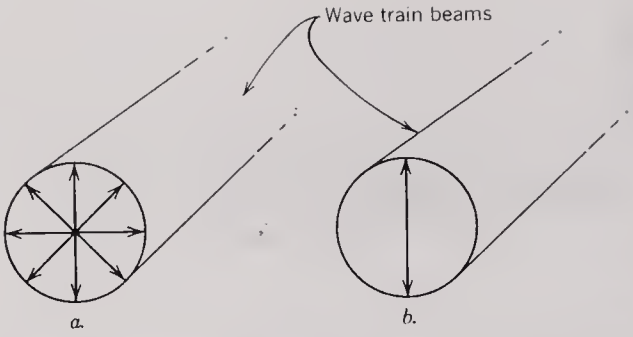


FIGURE 12.3 Representation of ordinary and plane-polarized light.

with both magnitude and direction.) The wave velocity of em radiation is about 3×10^8 m/s. Electromagnetic energy comes to us in short bursts of energy waves called **wave trains.**

Each wave train of ordinary light has its vector planes randomly oriented with respect to other em trains. Figure 12.3*a* depicts the randomly oriented electric vector planes of a beam of wave trains moving toward us. Actually there would be an infinite variety of planes rather than just the four shown. Figure 12.3*b* shows only wave trains in one plane and therefore represents plane-polarized light. Polarization in this sense means nonrandom orientation. **Plane-polarized light,** then, is light in which the electric vectors are all in the same plane, the plane of polarization. Ordinary light can be polarized by passing it through a Nicol prism or a sheet of Polaroid®. A Nicol prism is made from a crystal of Iceland spar (calcite); Polaroid® consists of tiny crystals of a quinine compound all oriented with their axes parallel.

Rotation of Plane-Polarized Light

You probably recall from your studies of stereoisomerism that chiral molecules (enantiomers and diastereomers, except *meso*) rotate plane-polarized light.

When plane-polarized wave trains pass through a molecule, their electric and magnetic fields interact with electrons in the molecule. The interaction changes the planes of the electric and magnetic vectors of the wave train. In achiral molecules, rotations in one direction are canceled by those in the other direction. But in chiral molecules, in which the electron distribution is not symmetrical, rotation in one direction is greater than that in the other. Although a single molecule changes the plane of rotation only slightly, the effect of millions of molecules is to make an observable change called optical rotation. It is given the symbol α (alpha) and is always reported along with its sign of rotation (*d* or *l*, + or −).

More particularly, we usually report the optical rotation as **specific rotation,** defined by equations 12-1 and 12-2:

$$[\alpha]_\lambda^t = \frac{\alpha}{ld} \tag{12-1}$$

for neat (pure) liquids, and

$$[\alpha]_\lambda^t = \frac{\alpha}{lc} \tag{12-2}$$

for solutions, wherein

$[\alpha]_\lambda^t$ = specific rotation at the specified temperature and wavelength of light

α = the observed rotation

l = path length of the sample in decimeters

d = density of the neat (by itself) liquid in g/ml at the specified temperature

c = concentration of solution in g/ml of solution

The observed rotation depends on the number of molecules through which the plane-polarized light passes because each molecule rotates the light a tiny amount. The

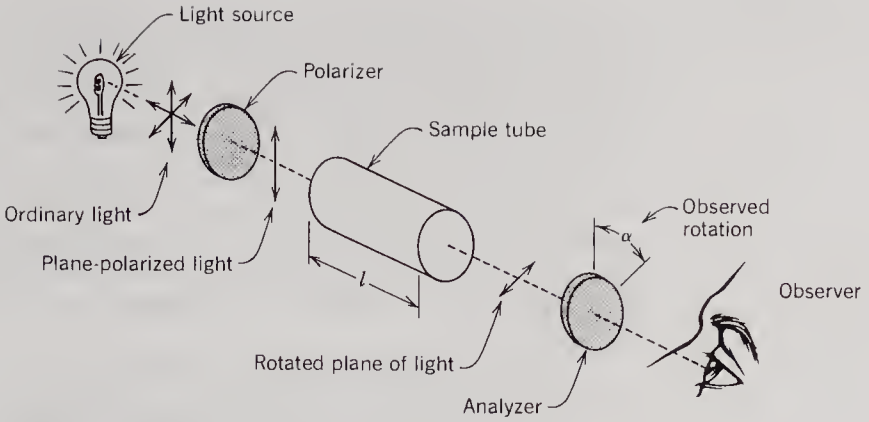


FIGURE 12.4 Schematic diagram of a polarimeter.

number of molecules in turn depends on density or on concentration. Observed rotation also depends on the **path length,** that is, how long is the path of molecules through which the light travels. It should be obvious to us that if density or concentration increases we find molecules closer together; therefore a given beam of plane-polarized light passes through more of them. We might expect that observed rotation is directly proportional to concentration. However, in many instances, the proportionality is not exact, probably because solute-solute interactions, which occur to a greater extent in highly concentrated solutions, affect rotation to a different degree than solute-solvent interactions. For the same reason, different solvents have an effect on observed rotation which can be so severe as to even change the sign of rotation!

Temperature is important because it changes density of neat liquids. For example, at the lower density due to higher temperature there are fewer molecules in a given path length. Temperature also changes concentrations of solutions because of the expansion or contraction that a solution undergoes as temperature changes. In addition, temperature changes relative numbers of conformers present at any one time. For example, at higher temperatures, the populations of less energetically favorable conformers increase. This changes optical rotation because the various conformations of an optically active molecule have different capabilities to rotate plane-polarized light. One further change in rotation with temperature results from changes in solvation characteristics (solute-solvent interactions).

The wavelength of light determines the magnitude and in many cases even the direction of rotation. In general, shorter wavelength leads to greater rotation. The yellow D line of sodium (actually two closely spaced lines at average position 5893 Å) is most commonly used. At such wavelength and at 20 °C, the specific rotation would be reported as $[\alpha]_D^{20}$.

The instrument that determines the degree and direction of rotation is called a **polarimeter.** There are many varieties of polarimeter, but they all employ the same basic schematic makeup shown in Figure 12.4. The light source provides monochromatic light (all one wavelength). The function of the polarizer is to plane polarize ordinary light emitted by the source. The light that is not allowed through the polarizer is reflected or absorbed within the unit. The plane-polarized light next passes through the sample, and if the sample is optically active, the plane of polarization is changed. The **analyzer,** actually a second polarizer, is rotated until the Nicol prism axis or the Polaroid crystal axes line up with the plane of light emerging from the sample cell. The degree of rotation of the analyzer gives α.

12.2 THE TECHNIQUES

Sample Preparation The sample may be colored but must be clear, containing no dust or filter paper fiber; so filter the sample carefully by gravity or distill it from a clean still.

If the sample is a liquid that is not highly viscous and you have an ample amount to use in the polarimeter, you might choose to examine its optical rotation as a neat liquid. Such an examination would be appropriate if the optical rotation is less than 360° for the neat liquid. Measurement of a liquid neat is often the method of choice because there is no error incurred during preparation of a solution, there are no solvent effects on rotation, and the observed rotation will be greater and easier to observe, an important factor if the compound rotates plane-polarized light only slightly. If the sample is neat, put it directly into the sample tube to the depth prescribed by the manufacturer. If no information about optical rotation is known for the sample, you will have to test it first as a solution at two different concentrations to be sure that the optical rotation is less than 360°.

If you are going to analyze a solution, prepare it in a tared volumetric flask, using up to 2 g of solute per 100 ml of solvent. Weigh to the number of significant figures made feasible by your polarimeter and/or volumetric flask. The actual concentration depends on solubility and on the degree of rotation anticipated. If the rotation is slight, higher concentrations are desirable. The most commonly used polarimetry solvents are water, ethanol, methanol, and trichloromethane (chloroform). Be sure to report what solvent has been used.

If a prepared solution is not clear, carefully filter it by gravity. To prevent excessive evaporative concentration changes, chill the solution in an ice bath and then filter it rapidly into a flask set in an ice bath.

Using the Polarimeter

Put the sample in the sample tube and place the tube in the polarimeter. Analyze the sample by looking through the eyepiece at what is referred to as a double field (or triple field in some instruments). You will probably observe a split image, wherein half of the circular field is of greater light intensity than the other half. Figures 12.5 and 12.6 illustrate split field images. Rotate the analyzer until the image sections appear to be of the same intensity. Make and record three to six replicate readings on the same sample by readjusting the split images several times; then average the readings. Record the temperature.

First, calibrate the instrument by obtaining a zero reading when the sample tube contains only the solvent that will be used to dissolve the solute. If a neat liquid is to be analyzed, read the zero with the tube empty. The "zero" point might actually be some number near zero. Whatever the number is, record it as your zero reading.

To obtain the rotation of the neat liquid or solution, follow the same procedure as for zeroing the instrument. The observed rotation is the difference between the average value for the substance of interest and the average value for the zero reading.

Actually, it is not possible to say whether a rotation is + or − from a single determination. For example, we would not know whether a reading of 40° was +40° or −320° (if we disregard the + and − signs and add the numbers, the sum is always 360°). We must determine the optical rotation using two different concentrations. For example, if a 1.0*M* sample gives a reading of +40° or −320°, and a 1.2*M* sample gives

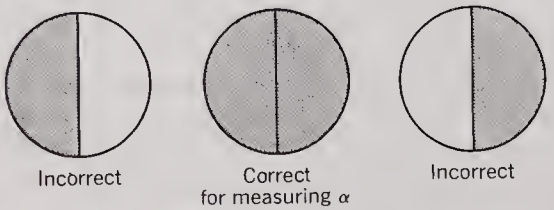


FIGURE 12.5 Double field images.

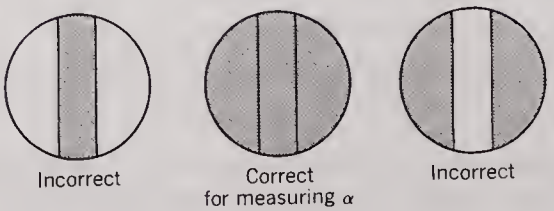


FIGURE 12.6 Triple field images.

a reading of $+48°$ or $-312°$, the correct readings must be $+40°$ and $+48°$ because an increase in concentration *must* produce an increase in rotation, and in this case the negative rotation decreased at the higher concentration.

If toxic solvents are being used, put the polarimeter in a hood.

12.3 EXPERIMENTAL PART
Identification of a Sugar

Time Required: 10 min/student at polarimeter

Review Techniques and Principles:

Lab notebook (1)

You will be given as an unknown a 10-ml sample of aqueous dextrose or levulose at 10.0 g/100 ml concentration. The names of the compounds are directly related to the direction of rotation. Your task is to identify the substance and calculate the specific rotation.

In your laboratory notebook, construct a table that allows for recording temperature, wavelength, path length, three observed rotations, an average rotation, and the actual rotation for water and for your unknown at two concentrations.

Obtaining optical rotations. Your laboratory instructor will show you how to use the polarimeter in your laboratory. First, calibrate the instrument with water: Put water in a clean analyzer tube, rotate the analyzer until the field image is the same intensity throughout the entire field, and record the reading. Repeat the analyzer rotation and recording twice more. Take an average of the three recorded readings as the zero point. Pour the water from the tube.

Using a dry, clean analyzer tube (or one that you have rinsed twice with small amounts of your unknown solution), pour your solution into the tube, again rotate the analyzer, read the observed rotation, and record it. Repeat the analyzer rotation and recording twice more. Record the average.

Dilute your unknown with enough water to make the concentration 5.0 g/100 ml (double the volume). Obtain the observed rotations and the average.

To get the actual rotations of your unknown solutions, subtract the average observed rotation of water (the zero point) from the average observed rotations of the unknown solutions. Calculate the specific rotation of your unknown from those of your two solutions and identify the unknown. Obtain its literature value and calculate the percent error. Record the make and model of polarimeter.

Writing the discussion. Report the identity and explain how you arrived at that conclusion. Discuss your percent error in terms of the polarimeter, your technique, purity of sample, and so on.

12.4 EXERCISES

Prelaboratory

1. What is a split field image? How should the field appear when you read optical rotation?
2. How many readings of optical rotation should you take?
3. What variables should you record in your notebook with respect to using the polarimeter?

4. A student noted that the observed rotation of a solution appeared to be +8.5°. On dilution of the sample with more solvent, the observed rotation was found to be 205.0°. Explain why the more dilute sample appeared to give a higher observed rotation.
5. A student prepared for polarimetry a 10.00% solution of a relatively high-boiling liquid in methanol. The solution was somewhat cloudy, so she distilled it slowly and carefully until only about one-twentieth of the volume remained in the distilling flask. The distillate was clear enough for polarimetry; so she obtained and reported the specific rotation. Comment on her procedure.

Postlaboratory

1. Is the optical rotation levo, or dextro, if an 80.0% solution of a substance gives a reading of +15.0° (−345.0°) and an 81.0% solution gives a reading of +13.3° (−346.7°)?
2. What is the specific rotation measured at 431 nm and 25 °C in a 1.00-dm tube of a liquid with density 0.843 g/ml if readings are +32.4, +32.6, +32.3, +32.5, +32.4, and +32.1?
3. A 0.232-g sample of cholesterol is dissolved in 10.0 ml of chloroform and analyzed at 20 °C using the sodium D line and a path length of 5.00 cm. The observed rotation is −146.0° at this concentration and −36.5° when 0.0580 g is dissolved in 10.0 ml. What is the specific rotation?
4. A student noticed many small insoluble particles in a solution that had been prepared for polarimetry. Because the remaining laboratory time was quite short he hastened the filtration process by using vacuum filtration. Was this, or was it not, a good idea? Explain.

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1. Shriner, R. L.; Fuson, R. C.; Curtin, D. Y. *The Systematic Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1956.

TECHNIQUE 13

REFRACTOMETRY

Refractive index, or index of refraction, symbolized by η (eta), is a physical property useful for identifying liquids or indicating their purity. Refractive index is especially useful for helping to identify hydrocarbons because we cannot make solid *derivatives* of them (Part III). Refractive index is very accurate, sometimes being measured up to eight places right of the decimal.

13.1 DISCUSSION OF REFRACTIVE INDEX

Refractive index is the ratio of the velocity of light in vacuum to its velocity in a given substance:

$$\eta_\lambda^t = \frac{v_{\text{vacuum}}}{v_{\text{substance}}} = \frac{\sin a}{\sin \beta} \tag{13-1}$$

wherein

η_λ^t = the refractive index at a specified centigrade temperature and wavelength of light

a = the angle of incidence for beam of light striking the surface of the liquid

β = the angle of refraction of the beam of light in the medium (see Figure 13.1)

When we pass an angled beam of light, $h\nu$, into a liquid, the velocity of the light is reduced and its direction changes, that is, the light is **refracted.** Its velocities in the two media are related to the angles of incidence and refraction. Actually, because it is difficult to determine refractive index using vacuum, air is used instead, and the slight difference is compensated for by the instrument.

We can see by examining the symbol for refractive index that its measurement depends on two variables, temperature and wavelength. Temperature is important because the density of the liquid is a function of temperature; if the density of a liquid changes, the velocity of light through it changes. The wavelength must be specified because light of different wavelengths is refracted to different degrees. The wavelength that is ordinarily used is that of the sodium D line, in which case we report the wavelength as D or may omit it, as, for example, for ethanol

$$\eta_D^{25} = 1.359 \quad \text{or} \quad \eta^{25} = 1.359$$

If we use other wavelengths, we must report their values in nanometers.

Refractive index is usually reported to four places to the right of the decimal. However, it will change even for small amounts of impurity, and without considerable purification, the last two decimal places will not be reproducible.

13.2 THE REFRACTOMETER

The instrument on which refractive index is measured is called a **refractometer.** There are a number of refractometers, but the one most widely used is the Abbe refractometer. Its popularity is due to several factors: (1) the refractive index can be directly read in the same place as the adjustment image; (2) only a few drops of sample are needed; (3) white light can be used, since a compensator makes the refractive index that value that would be observed for the sodium D line; (4) temperature control of the sample is

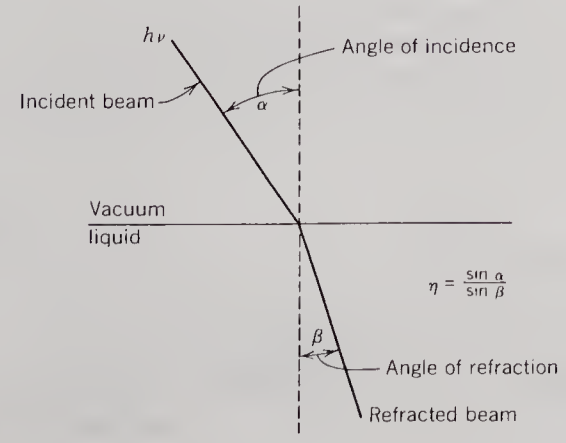

FIGURE 13.1 Refraction and refractive index.

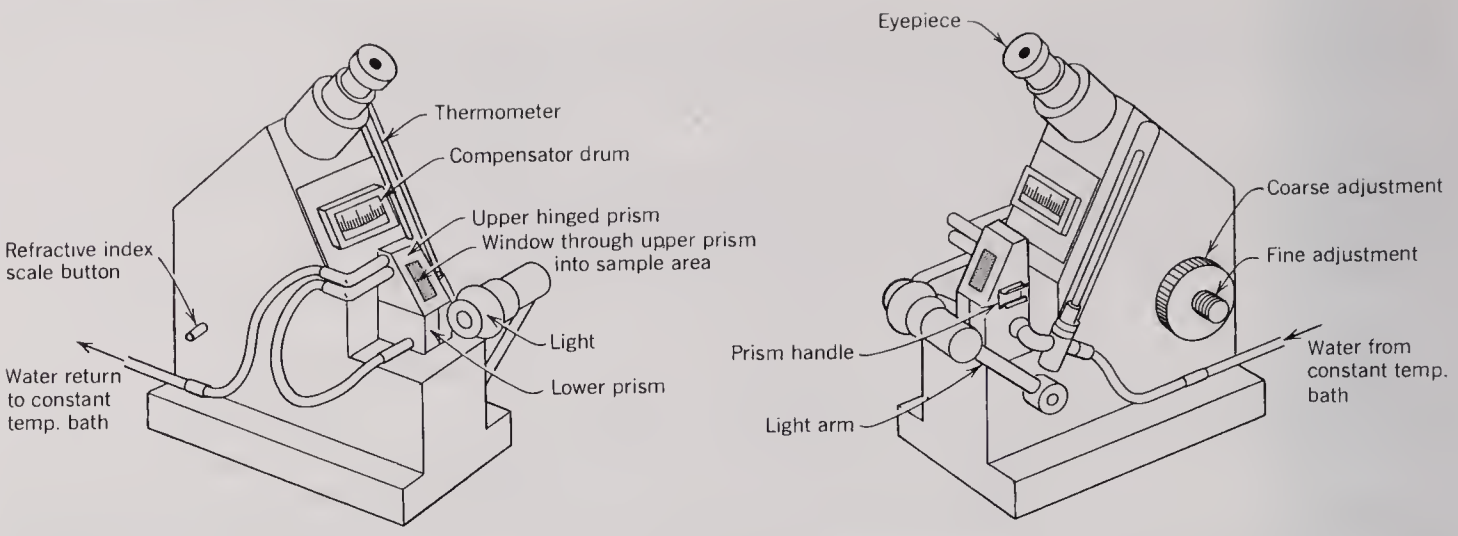

FIGURE 13.2 Abbe refractometer.

possible; (5) accuracy is very high: ± one in the ten-thousandths place. Figure 13.2 illustrates two views of an Abbe refractometer.

13.3 THE TECHNIQUES

The sample must be very pure and free of all extraneous matter. It is customary to take a sample while obtaining the distillation boiling point with a scrupulously clean receiver.

Using the Refractometer

Begin circulation of water from the constant-temperature bath well in advance of using the instrument.

Place the sample between the two prisms. For nonviscous, volatile liquids that flow freely, introduce the sample from an eyedropper into the channel alongside the closed prisms. For more viscous liquids, squeeze gently the prism handles and swing open the upper prism. Drop two or three drops of the liquid onto the lower prism without touching its surface. *Extra special care must be taken not to scratch the surfaces of the prisms.* Lower the upper prism and lock it into position. The liquid will spread out between the prisms, making a thin, even film. You will be able to tell when the liquid is adequately spread on the faces of the prisms because the window into the sample area will appear darker and clear.

Turn on the light and look into the eyepiece. Move the lamp arm up and rotate the light so it shines through the window into the sample area. Now adjust the light and the coarse adjustment knob until the field seen in the eyepieces is illuminated so that the light and dark regions are separated by as sharp a boundary as possible. Figure 13.3 illustrates fields with dark and light portions. If the boundary has colors associated with it and/or appears somewhat diffuse, rotate the compensator drum on the face of the instrument until the boundary becomes noncolored and sharp. Readjust the position of

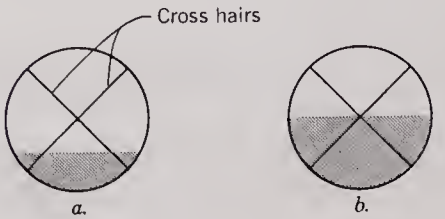

FIGURE 13.3 Views of field in refractometer. (*a*) Incorrect. (*b*) Correct.

the lamp if necessary to get the sharpest possible boundary. Next, rotate the coarse and fine adjustment knobs until the boundary is centered in the cross hairs of the field as shown in Figure 13.3. Press the refractive index scale button and read the value that appears on the field. Now move the boundary out from the cross hairs and recenter it to get a second reading. Take several replicate readings and report the average value. Record the temperature, and the make and model of the instrument.

Taking care not to scratch the surfaces, clean the refractometer prism faces immediately after use. Gently wipe (not rub) the prism faces with a soft tissue paper moistened with acetone (IUPAC propanone), ethanol, or ligroine. Repeat wiping with a piece of clean, soft, moistened tissue until the prism faces are clean. The surface of the upper prism will appear frosted when clean. After cleaning, put the upper hinged prism into the closed position.

When you determine refractive index on toxic substances, work in a hood or well-ventilated area.

Temperature Corrections

Refractive index decreases as temperature increases. We customarily report refractive indices at 20 °C. If the measurement is made at other than 20 °C as indicated on the thermometer of the instrument, correct the measurement by either using a correction factor or a reference liquid.

Correction Factor

Variations due to changes in temperature are somewhat dependent on the class of compound observed, but are usually somewhere between 0.00035 and 0.00055 per C°. Taking the average value of 0.00045 serves as a fair approximation for most liquids. The corrected refractive index is given by

$$\eta_{\text{corrected}} = \eta_{\text{observed}} + 0.00045 \times (t - 20.0) \qquad (13\text{-}2)$$

in which t is the thermometer temperature. If, for example, the refractive index of acetic acid at 16.0 °C is found to be 1.37317, the refractive index at 20.0 °C would be $1.37317 + 0.00045\,(16.0 - 20.0) = 1.37137$ (this is really too many significant figures considering that an approximation is being used).

Reference Liquid

Choose as a reference a liquid that is similar in composition, structure, and properties to the liquid of interest. Measure the refractive index of the reference at the same temperature as for the liquid of interest. The corrected value for refractive index is given by

$$\eta_{\text{corrected}} = \eta_{\text{observed}} + \eta_{\text{ref}}^{20} - \eta_{\text{ref}}^{t} \qquad (13\text{-}3)$$

wherein η_{ref}^{20} is the literature value at 20 °C for the reference liquid and η_{ref}^{t} is the measured value of the reference liquid.

13.4 EXPERIMENTAL PART
Identification of Unknown

Time Required: About 10 min/student at the refractometer

Review Technique and Principles:

Lab notebook (1)

You will be given as an unknown about 0.5 ml of *n*-butyl acetate (IUPAC butyl ethanoate, η_D^{20} 1.3940), glycerine (IUPAC 1,2,3-trihydroxypropane, η_D^{20} 1.4716), methyl benzoate (IUPAC methyl benzenecarboxylate, η_D^{20} 1.5165), or benzaldehyde (IUPAC benzenecarbonal, η_D^{20} 1.5454). Your task is to identify the substance by refractometry.

Using the refractometer. Raise the hinged prism on the Abbe refractometer and, using an eyedropper, place two drops of your unknown on the middle of the fixed prism and close the prisms. Switch on the lamp and move it into position to light the field viewed through the eyepiece. Using the handwheel and compensating drum adjust the split field to give a sharp line. Center the line on the cross hairs and then depress the display switch. Read and record the refractive index and the temperature. Make two repetitive measurements. Apply a method of temperature correction if necessary. Average the three refractive index values. Clean the prisms of the refractometer using methanol as a solvent. After the prisms are dry, lower the hinged prism and turn off the lamp.

Writing the discussion. Report the identity of the unknown and justify your conclusion.

13.5 EXERCISES

Prelaboratory

1. What precaution must be taken when introducing the sample onto the prisms or when cleaning up?
2. What is the function of the coarse and fine adjustment knobs?
3. Under what circumstances would the compensator drum be rotated?
4. What solvents are usually used for cleaning the prisms after use?
5. What is the standard temperature at which η should be determined?
6. Write a stepwise summary of using an Abbe refractometer.

Postlaboratory

1. Which temperature correction method for refractive index should be more reliable? Explain.
2. Does refractive index have units? Explain.
3. If the refractive index of a substance was found to be 1.4877 at 25.0 °C, what would the value be corrected to 20.0 °C?
4. What is the refractive index of a substance for which α is 40.0° and β is 35.0°? The temperature of measurement was 20.0 °C and the sodium D line was used.
5. Explain on the basis of substance densities why refractive index is lower at higher temperatures.
6. Stu Dent obtained the refractive index of a liquid in the following manner. He put 10 drops on the lower prism, spreading the liquid with the eyedropper, closed the prisms, and obtained a reading of 1.51724. Noting the temperature to be at 26 °C, he added 0.00045 C° to the observed value. Critique his procedure.

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TECHNIQUE 14

ULTRAVIOLET-VISIBLE SPECTROSCOPY

Ultraviolet-visible (UV–VIS) spectroscopy is the oldest of the spectroscopic techniques and was once widely used for structure determination. However, newer instrumental techniques are more structure revealing and easier to interpret. Although not much used for structural analysis anymore, UV–VIS spectroscopy is commonly used for quantitative analysis because it is not unusual for small concentrations of compounds to strongly absorb ultraviolet and/or visible energy. Therefore considerable precision and accuracy is possible in measuring concentrations.

14.1 SPECTRA AND LIGHT

The word "spectrum" as used in the context of spectroscopy has two meanings: First, it might refer to the distribution of energy emitted by a radiant source like the sun or artificial lighting; second, it might refer to a graphic representation of energy absorbed by a chemical compound. The meaning is usually clear from the manner in which the word is used.

The Nature of UV and VIS Radiation

To make the following discussion more meaningful you should review Section 12.1. What we term "light" is a very small portion of a spectrum of electromagnetic energy. Electromagnetic (em) energy is radiant energy, the sort of energy that radiates from a hot surface like the sun or a light bulb. Quantum mechanics teaches that this kind of energy has a dual nature, possessing not only properties of a wave with electric and magnetic components but also properties of a particle. But for our discussion of UV–VIS spectra we are more interested in its wave character and shall think in terms of **photons,** which are concentrated bundles of energy that we describe in terms of frequency and wavelength. A photon constitutes one wave of a wave train, a succession of similar wave pulses. The longer the wavelength, the smaller is a photon's energy and frequency. The wavelength unit we usually employ is the nanometer (nm), sometimes referred to as a millimicron (mμ). One nm is equal to one-thousandth of a millionth of a meter (nm = 10^{-9} m). Sometimes we use angstroms (Å) rather than nanometers, 1 Å being equal to 10^{-1} nm or 10^{-10} m.

All imaginable wavelengths of this kind of energy, from the most energetic to the least, comprise the system known as the electromagnetic spectrum, shown in Figure 14.1. Notice that parts of the electromagnetic spectrum are more or less familiar to you. The X-rays used by physicians, ultraviolet rays that can cause sunburn, the visible light we see, microwaves used for cooking, radio waves, television waves, and radar waves are all from different parts of the em spectrum.

Note from Figure 14.1 that UV lies in a higher energy region of the em spectrum than visible. Visible and UV radiation can be separated by a prism, and although our eyes can not observe spectral results of photon separations in the UV as they do for the visible, we have instruments that can.

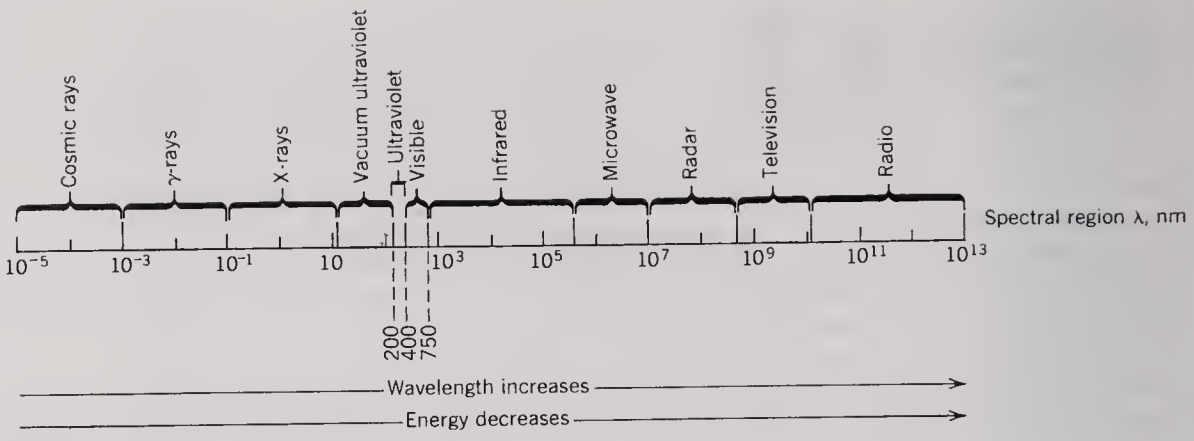

FIGURE 14.1 The electromagnetic spectrum.

Photon Absorption Absorption of energy in the visible and UV region of the em spectrum depends on the electronic structure of the molecule. Absorption of energy occurs when an electron in an orbital is excited by a photon and moves up to an unoccupied, higher energy orbital. The amount of energy to excite the electron is **quantized.** That is, the energy must be just the right amount, a quantum, of energy. The quantum of energy depends on the kind of orbital the electron is in and the kind of orbital to which it is excited, usually an antibonding orbital. In the transition from its ground state molecular orbital to the antibonding orbital, *all* of the energy of a photon is absorbed, not just part of it. Furthermore, the electron cannot absorb more than enough energy to make the transition to the higher energy level. It is an all or nothing process.

The more tightly that electrons are held in their orbitals, the more energy it takes to excite them from the orbitals. Therefore it takes more energy to excite an electron from a sigma (σ) orbital than from a pi (π) orbital. And it takes more energy to excite an electron from a pi orbital than a nonbonding (n) orbital such as is found for the nonbonded electron pairs of oxygen, nitrogen, sulfur, and so on. The electrons in sigma orbitals require photons in the high-energy, short-wavelength UV region; nonbonded and many pi electrons are excited in the lower energy, longer wavelength UV region; and some electrons are excited by photons of the visible region. The antibonding orbitals are indicated by superscript asterisks, σ^* and π^*. The transition from a σ to antibonding σ orbital is indicated by the notation $\sigma \rightarrow \sigma^*$; a π orbital to antibonding π orbital by $\pi \rightarrow \pi^*$. A transition from a nonbonding orbital to an antibonding π orbital is given by $n \rightarrow \pi^*$. A simple summary of electronic levels and transitions is shown in Figure 14.2.

If we direct at a compound a beam of photons with a specified wavelength, the compound will absorb the photons only if it has the correct structural characteristics. Customarily in an analysis of a compound, we start with a beam of photons at one end of the UV or visible (VIS) spectrum and regularly change the beam to photons of increasingly higher or lower energy, a process we refer to as a **scan.** As a scan is made,

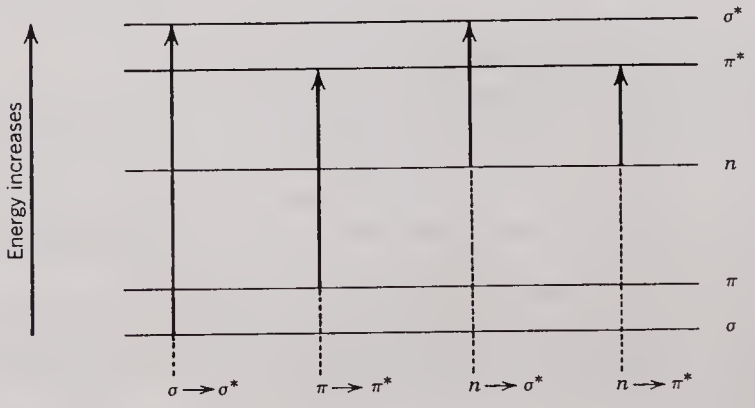

FIGURE 14.2 Electron transitions.

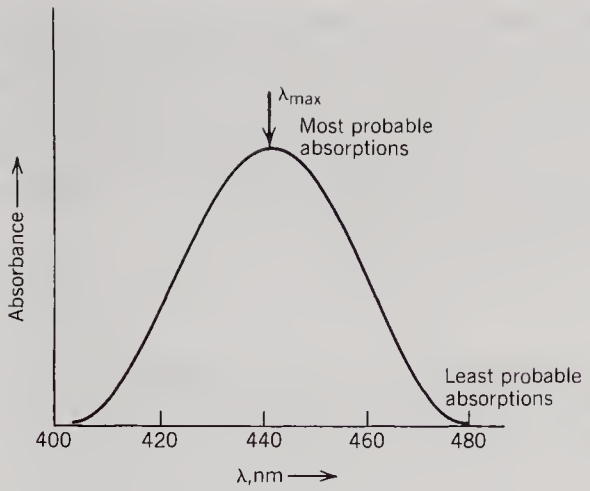

FIGURE 14.3 Electronic absorption spectrum.

a compound absorbs energy in accord with its ability to have an electron excited by a particular wavelength. The curve that the instrument records is the compound's spectrum (plural is spectra), a plot of wavelength, frequency, or related units versus percent transmission or absorbance. We define percent transmission and absorbance (A) as follows:

$$\%T = \frac{\text{radiation intensity transmitted or reflected (100)}}{\text{incident radiation intensity}} \tag{14-1}$$

$$A = \log \frac{\text{incident radiation intensity}}{\text{radiation intensity transmitted or reflected}} \tag{14-2}$$

Notice in Figure 14.3 that an electronic spectrum of a compound is not a single, sharp peak but is a more or less smooth curve representing absorptions over a rather wide range of wavelengths. The reason for this wide range is that atoms of molecules are arranged in an almost infinite number of positions with respect to each other because of vibrations of the atoms as their bonds stretch, bend, and twist. The electrons between atoms that are somewhat stretched apart require excitation by a different quantum of energy than electrons between atoms with a more contracted bond; electrons in bonds that are twisted or bent are excited by photons that are different from those in straighter bonds. Therefore, the spectrum is a composite of thousands of absorptions over a range of wavelengths. The most probable absorptions, that is, the ones that occur most often, give the highest peaks on the recorded spectrum; the least probable absorptions will produce the portions of the recorded spectrum which are near the bottom.

The visible spectrum for a given compound is a smooth curve with one or more maxima (depending on how many types of electronic transitions are taking place) and with the base of the curve at the bottom of the chart paper. The wavelengths at the maxima are indicated as λ_{max}.

14.2 QUANTITATIVE UV–VIS SPECTROSCOPY

Absorption of photons is proportional to concentration of the sample and to path length:

$$A \propto lc \tag{14-3}$$

A is the **absorbance,** l is the pathlength in centimeters, and c is the concentration in moles per liter. We should expect A to depend on l and c because both l and c are related to the numbers of molecules that can absorb light. The introduction of a constant, **epsilon** (ε), changes the proportionality into an equation known as **Beer's law:**

$$A = \varepsilon lc \tag{14-4}$$

Epsilon has units of 1/cm × mole because absorbance is unitless, being a logarithmic function of the ratio of incident to transmitted light (equation 14-2). Epsilon is called the

molar absorptivity or **molar extinction coefficient,** and is related to the probability that light of given wavelength incident on the sample will actually be absorbed by the electrons in the molecule. Absorptivity is a property of a given compound but depends on wavelength and solvent. Ordinarily absorptivity is reported for each maximum in the curve, and can be determined by measuring the absorption for a known concentration over a known path length. The values are plugged into equation 14-5, a rearranged form of equation 14-4:

$$\varepsilon = \frac{A}{lc} \tag{14-5}$$

when ε is measured at λ_{max}, it is often referred to as ε_{max}. Once epsilon is known for a given compound, it can be used to determine concentrations.

14.3 INSTRUMENTATION

The UV–VIS spectrophotometer is an instrument that emits an em ray of continually changing wavelength, beginning at one end of the spectrum and progressing to the other end. The beam passes through the sample and the instrument measures the amount of radiation that is absorbed. Most modern spectrophotometers have two chambers through which beams are passed: one for sample and one for the pure solvent in which the sample is dissolved. When both chambers are used, the instrument is said to be in *double-beam mode.* The double-beam mode results in automatic subtraction of absorptions due to solvent.

Figure 14.4 is a simplified schematic diagram of a UV–VIS spectrophotometer. The radiation source for the visible region of the spectrum is a tungsten incandescent bulb, and the UV radiation source is a hydrogen or deuterium discharge tube. A deuterium

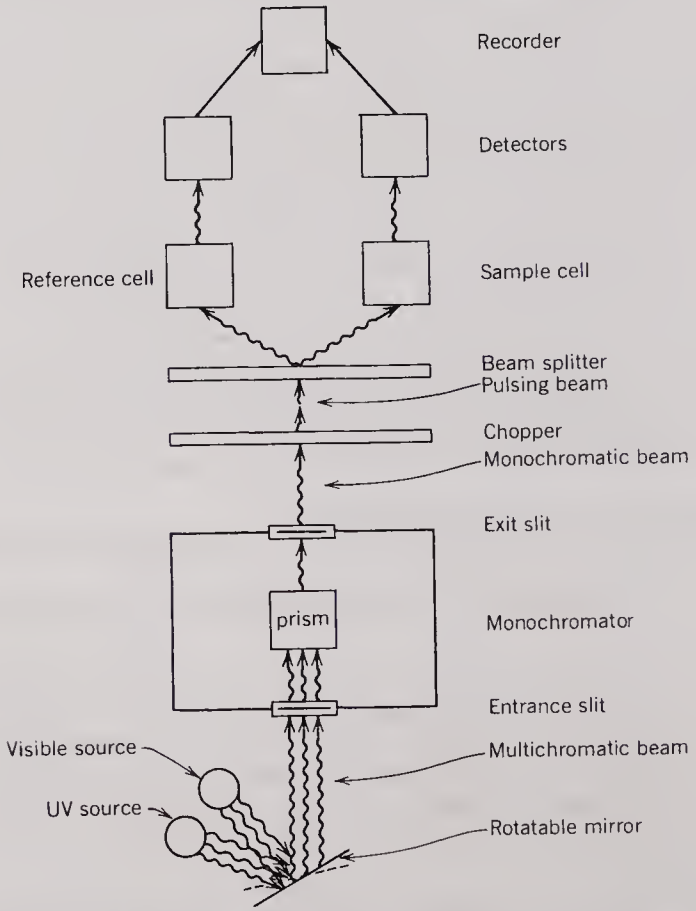

FIGURE 14.4 Schematic diagram of UV–VIS spectrophotometer.

source is more expensive but more durable. The manually rotatable mirror allows the operator to change from one source to the other. A multichromatic beam (a beam of all wavelengths) is produced by the source and enters the monochromator through a beam-narrowing slit.

Prisms in the monochromator split the multichromatic beam of photons into groups of photons within a very narrow wavelength range. The wavelength of the near-monochromatic beam that is allowed through the exit slit is determined by the angles of the prisms. By continuously changing the prism angles, a sequence of wavelengths can be permitted to exit, thereby producing a scan from one end of the UV or visible spectrum to the other.

The chopper divides the monochromatic light into short bursts which are alternately directed by the beam splitter into the reference and sample cells.

The detectors measure and compare the radiation arriving at them. The difference in intensity of the reference and sample beams is converted into an electrical impulse and sent to the recorder, where it is traced on chart paper as a spectrum.

14.4 THE TECHNIQUES

Sample Preparation

UV–VIS samples generally consist of solutions. The concentration of the solution to be used should be such that an absorbance of about 1 is produced at the maximum of the curve. This is more important for quantitative work, but relative heights of the curves are better measured for qualitative work as well. If ε is known, the concentration to give an absorbance of 1.00 can be calculated from Beer's law. If the substance is an unknown, trial and error dilution will have to be made to get the absorbance to be about 1.

For samples which have more than one λ_{max}, for which the molar adsorptivities differ considerably, you can obtain accurate information only by running the sample at more than one concentration. Sometimes it can appear that there is only one maximum, whereas another maximum can be observed at higher concentration.

To prepare a solution, weigh the solid or liquid to be analyzed in a tared volumetric flask, then add solvent up to the volume mark on the flask neck. If dilution is required, remove aliquots from the flask with a pipet and transfer them to another volumetric flask.

The Solvent

Ideally, a solvent for UV and visible spectroscopy should be transparent (nonabsorbing) over the entire spectral region to be examined. A number of such solvents exist because they possess only sigma bonds, which do not adsorb in the visible and near UV ranges. Good solvents include cyclohexane, ethanol, methanol, and water.

You should use solvents that are of spectral grade or very pure, and handle them so they do not become contaminated. Because some impurities absorb very intensely, tiny amounts of such an impurity introduced into the solvent along with the sample could produce a spectrum that would alter the appearance of, or even obscure, the spectrum of the compound of interest.

Sample Cells

Cylindrical or rectangular cells are available in varying sizes. The rectangular cell with a 1.00-cm path length is most common and requires about 3 ml of solution. For visible spectra, Pyrex cells are appropriate, but for UV work, expensive quartz cells are required because ordinary glass has a considerable absorption in the UV region.

The cells *must* be clean. Rinse them several times with solvent before use, between successive determinations, and after use. They should be handled *only* on the frosted sides. When filling a cell, you should not let solution run down the outside of the clean cell. Put cell caps on immediately after filling to prevent evaporation that would change the concentration. When you insert the cells into the cell holder of the instrument take

care that the frosted sides are parallel to the beam. Cell holder springs or clamps must *never come in contact with the window sides* because they might scratch the windows.

Obtaining the Spectrum

There are many kinds of UV–VIS instruments available. However, the controls you might have to adjust are similar for all instruments. The following is an outline of the procedure to follow in obtaining a spectrum.

1. Put source selector switch in UV or visible mode as required.
2. Turn instrument switch to "on"; turn recorder switch to "on."
3. Turn on UV source if necessary.
4. Rotate wavelength dial to the approximate position of the compound's maximum absorption.
5. Adjust the instrument for 0% transmission (infinite absorbance).
   a. Place the reference cell, filled with solvent, in the reference compartment; put an opaque block in the sample compartment.
   b. Close the cell compartment cover.
   c. With the zero adjust knob, bring the needle on the percent transmission scale to 0% transmission.
   d. Adjust the recorder pen so that it rests on the 0% transmission line on the chart paper.
6. Adjust the instrument for 100% transmission (0 absorbance).
   a. Remove the opaque block from the sample beam and replace it with the sample cell filled with solvent only.
   b. Close the cell compartment cover.
   c. With the 100% adjust knob, bring the needle on the % transmission scale to 100% transmission (0 absorbance).
   d. Adjust the recorder pen so that it rests on the 100% transmission (0 absorbance) line.
7. If you are scanning from high to low wavelength, set the wavelength slightly higher than that at which you want to start. Turn the instrument on "scan" until the wavelength is at the desired starting point; then stop the scan. Align the recorder pen and the desired starting position of the chart paper. Mark the paper and record the wavelength of the starting position.
8. Scan through the region of the spectrum you are interested in. Mark the paper with the wavelength of the final pen positions. This scan gives you a base line and indicates any deviation from the zero absorbance line.
9. Replace solvent in the sample cell with the solution of interest.
10. Repeat step 7.
11. Scan through the region of interest. Mark the chart paper.
12. Remove the chart paper from the recorder. Be sure to record the sample, date, operating conditions, and make and model of spectrophotometer and recorder.
13. If others will be using the instrument, leave spectrophotometer and recorder at "standby" or "on." If you are the last to use the instruments, turn them off. If the recorder pen has a sheath, put it on.
14. Remove the cells and clean them immediately.

Cleaning up

Clean the cells immediately after use. Rinse them several times with the solvent used during the spectral runs. Clean especially dirty cells with detergent or hot nitric acid. You must not scrub cells with abrasive cleaners or with any implement that could scratch them.

Work in a hood might be required during preparation of solutions and cleanup.

Cleaning cells with hot nitric acid requires caution to prevent chemical burns.

TABLE 14.1 List of Unknowns

Compound	λ_{max}	ε_{max}	λ_{max}	ε_{max}	Solvent
Benzoic acid	230	10,000	270	800	Water
Methyl salicylate	237	11,200	305	5,300	Methanol
Cylcohexene	207	447			Ethanol
Cyclohexanone	276	26	280	27	Methanol
Chlorobenzene	210	7,600	265	240	Ethanol
Phenol	210.5	6,200	270	1,450	Water
2-Nitrophenol	272	6,600	345	3,200	Methanol
4-Nitrophenol	228	7,510	311	11,000	Methanol
Aniline	230	8,600	280	1,430	Water

14.5 EXPERIMENTAL PART
Identification of an Unknown

Time Required: 1–2 hr; 20 min/student at the instrument

Review Techniques and Principles:

Glassware (0.2, 0.3)
Lab notebook (1)

You will be given 10 ml of an unknown selected from Table 14.1. Its solvent and molarity will be made known to you.

Analysis. Run a spectrum of the base line for your solvent. Then run a spectrum of your unknown to determine molar absorptivity and wavelength at point of maximum absorption. Make dilutions if required by your instructor. Subtract solvent absorptions from solution absorptions at positions of maximum absorptions to get the net absorption due to the compound. Do not discard your unknown solution until you are satisfied with your experimental work; then pour it into its assigned recovery container. Tape or glue your recorded spectrum into your notebook.

Writing the discussion. Report your unknown's identity and discuss what evidence led you to it. Determine the percent error for all molar absorptivities and wavelengths at maximum absorption, and try to rationalize if necessary.

14.6 EXERCISES

Prelaboratory

1. Why must a solvent used for spectrophotometry be pure?
2. What absorbance value is most ideal for interpreting visible spectra?
3. Describe how you dilute a sample solution in order to conserve solvent.
4. What property of the compound might require obtaining a spectrum at more than one concentration?
5. What parts of sample cells should not be touched?
6. What precaution must be taken when inserting cells into the cell compartment?

Postlaboratory

1. If epsilon is $2\overline{0},\overline{0}00$ and a 1.00-cm cell is being used, what molar concentration would be necessary to obtain an absorbance of 1.00?

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1. Dyer, J. R. *Applications of Absorption Spectroscopy of Organic Compounds*; Prentice-Hall: Engelwood Cliffs, NJ, 1965.
2. Silverstein, R. M.; Bassler, G. C.; Morrell, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974.
3. *Atlas of Spectral Data and Physical Constants for Organic Compounds*; Grasselli, J. G., Ed.; CRC: Cleveland, OH, 1973.

TECHNIQUE 15

INFRARED SPECTROSCOPY

At the beginning of the twentieth century, Sir William Herschel discovered invisible radiation just beyond the red, low-energy end of the visible spectrum. Because this radiation is energetically inferior to red photons, the word, "red" was attached to the prefix "infra," which means, "inferior to," or "lower" (in energy). Infrared (IR) spectroscopy, developed during the 1940s, is today the most widely used spectroscopic technique in organic chemistry. The infrared spectrum of a compound is useful for determining structure, identifying compounds, and for quantitative analyses.

The following discussion is a much simplified treatment of IR spectroscopy, its goal being to acquaint you with basic principles and with the more readily distinguished IR energy absorptions.

15.1 THE IR VIBRATIONAL PHENOMENON

To best comprehend the following discussion, you should first review Sections 11.1, 13.1, and 14.1.

The IR region of the em spectrum extends from wavelengths of 0.8 to 200 microns ($\mu = 10^{-6}$ m). But the region of most interest to the IR spectroscopist is from 2.5 to 15 μ because it is these wavelengths that give rise to molecular vibrations.

Rather than being a rigid grouping of atoms, a molecule is internally in constant motion. We can imagine that a molecule is similar to a group of balls attached to each other by coiled springs that stretch and bend. It is the same with bonds between atoms. If the atoms of a bond move back and forth linearly as in Figure 15.1*a*, we call this mode of vibration a **stretching mode.** If a bond angle changes, we refer to the motion as a **bending mode.** We call stretching and bending the fundamental modes of vibration. Stretching is either **symmetric** or **asymmetric** (Figure 15.1), and bending occurs as **scissoring, rocking, wagging,** or **twisting** (Figure 15.1*c*). We refer to scissoring and rocking as in-plane vibrations, and wagging and twisting as out-of-plane vibrations. vibrations.

Stretching and bending normally occur as frequently as 10^{15} (100 trillion) times per second, the exact frequency depending on the kinds of atoms bonded together, on their bond strengths, on how fast they are rotating, and to a small extent on their environment inside and outside of the molecule. The frequency of a given type of vibration is always within a narrow range for a specific bond. Vibration is caused by quantized absorption of energy: a bond can absorb em energy only of a frequency that matches the frequency

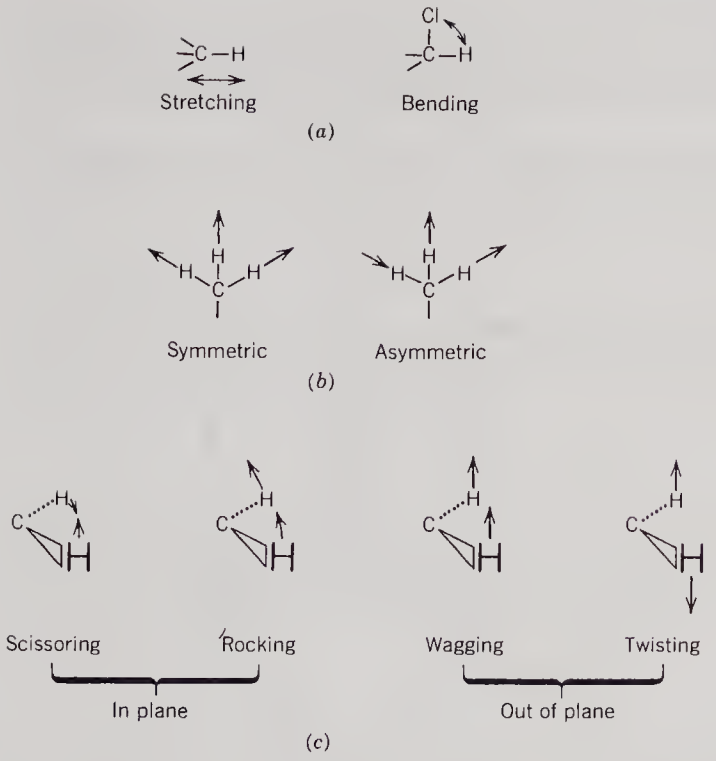

FIGURE 15.1 Modes of vibration.

of its own vibration; it is this correspondence that makes IR analysis possible. That is, if a molecule absorbs IR energy within a certain narrow frequency range, the presence of a particular kind of bond is indicated.

15.2 INSTRUMENTATION

The absorption by molecules of IR energy at various frequencies is detected by a spectrophotometer.

Figure 15.2 is a schematic diagram of a double-beam spectrophotometer, in which one beam of IR radiation acts as a reference, and the other passes through the sample being analyzed. The actual instrument is quite a complicated system of a dozen or more focusing mirrors which direct the beams to the right places at the right times.

The **source** of IR energy is a Globar (silicon carbide rod) or Nernst filament (a combination of zirconium, thorium, and cerium oxides or zirconium, erbium, and yttrium oxides) electrically heated to about 1500 °C. Mirrors separate the IR radiation into two beams and direct them through the sample and reference cells.

The **chopper** is a semicircular mirror that rotates about 10 times per second, alternately permitting either the sample or reference beam to pass through the beam-narrowing slit into the monochromator.

The **monochromator** separates the beam into groups of photons within a very narrow frequency range. There are two basic kinds of monochromators: prisms and gratings. As IR energy passes *through* a **prism,** the prism separates photons of different frequencies (or wavelengths) in the same way that a glass prism separates white light into its rainbow colors. But because glass prisms absorb IR radiation, an IR prism is made of a crystalline salt like sodium chloride. To prevent disintegration of the crystal by moisture in the air, the prism must be kept above room temperature. A **grating,** consisting of series of parallel straight grooves in a planar surface, diffracts IR radiation from its *surface* at an angle in accord with frequency. Rotation of the monochromator determines the frequency of photons allowed to pass through the exit slit, and makes possible a scan of the IR spectrum from one end to the other.

The **detector,** a thermistor or thermocouple, measures the IR radiation intensity

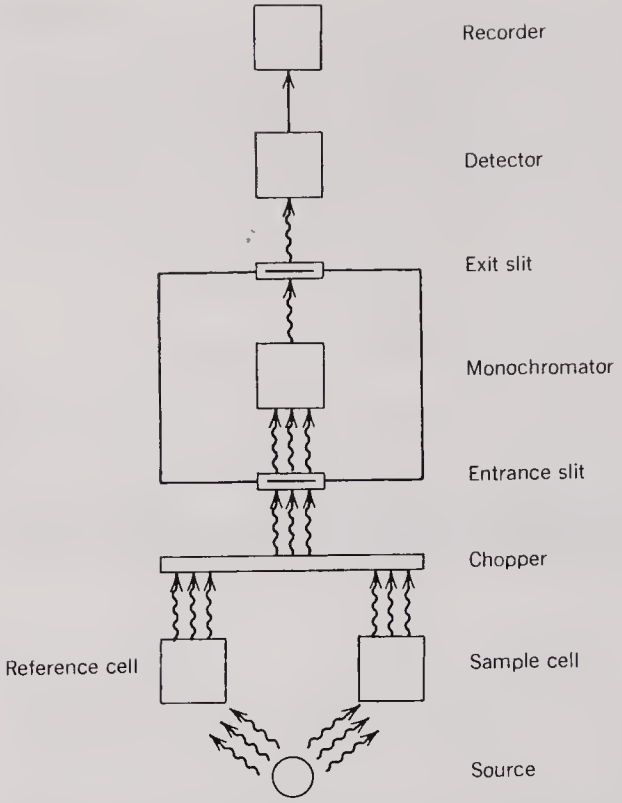

FIGURE 15.2 Schematic diagram of infrared spectrophotometer.

that falls on it. It converts the difference in intensity of the reference and sample beams to an electrical impulse and sends it to the recorder.

When sample dispersions scatter the IR radiation, the base line of the spectrum is too low on the chart paper. Putting an attenuator in the reference beam is helpful. The **attenuator** is a screen that can be positioned at various angles in the beam so as to attenuate (reduce) the beam. The more oblique the screen position, the more attenuated the beam will be. Some instruments have a built-in attenuator or an attenuator attachment. If there is none, you can use a square of ordinary wire gauze or window screen.

15.3 IR SPECTRA

When the recorder plots an IR spectrum like that in Figure 15.3 it makes a tracing of absorption or percent transmission versus wavelength and/or wavenumber. Please refer

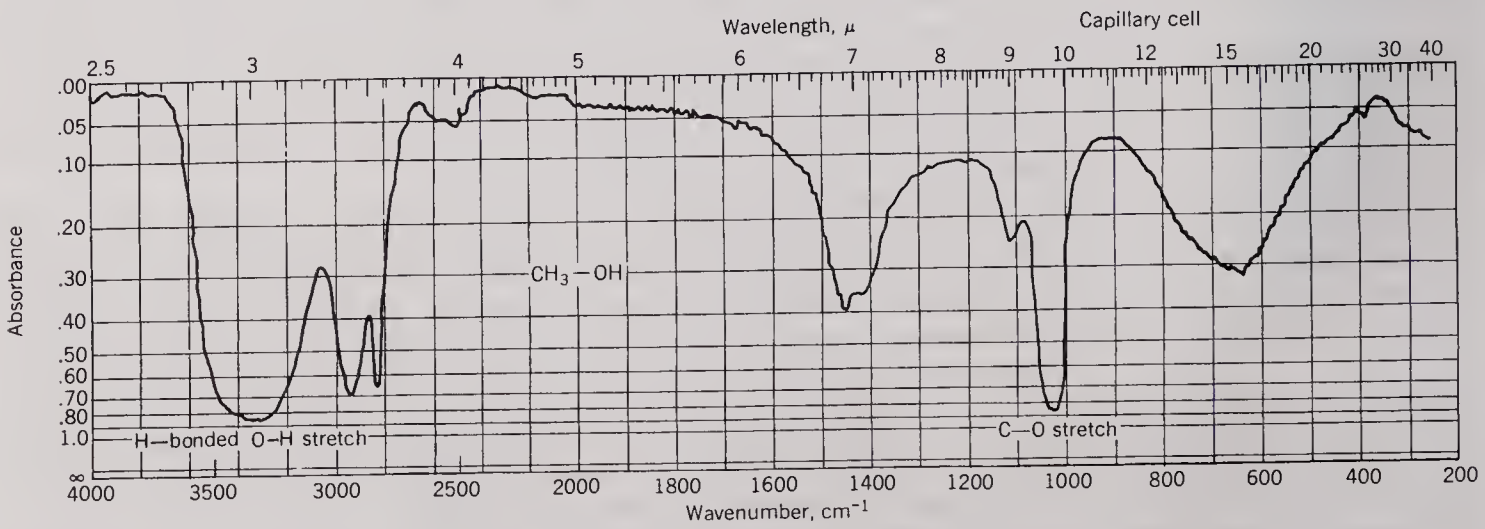

FIGURE 15.3 IR spectrum of methanol (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

to Section 14.1 for a discussion of absorption and percent transmission. Notice that IR chart paper has zero absorption at the top of the paper, whereas UV–VIS chart paper has it at the bottom. Consequently, IR absorptions have their maxima pointing downward.

IR Bands We refer to the plotted absorptions as **bands.** IR bands are characterized by their intensities, by their shapes, and by their positions of absorption on the spectrum.

Band Position

On Figure 15.3 there are numbers at the top and bottom of the spectrum that are related to the energies of the absorbed IR photons and therefore to the frequencies of bond vibrations. The energy of the vibration is

$$E = h\nu = \frac{hc}{\lambda} \tag{15-1}$$

wherein h is Planck's constant (6.35×10^{-27} erg-s), ν is the frequency (s^{-1}), c is the speed of light (3.00×10^{10} cm/s), and λ is wavelength (cm). By rearranging equation 15-1, we see that wavelength is related to frequency by

$$\lambda = \frac{c}{\nu} \tag{15-2}$$

Equations 15-1 and 15-2 show us that wavelength is inversely proportional to energy and to frequency. Therefore, at the bottom of the IR chart paper the wavelength number gets smaller toward the left, high-energy end of the spectrum.

Notice that at the top of the chart paper the numbers get larger toward the left. These are **wavenumbers,** $\bar{\nu}$, and are defined by the relationship

$$\bar{\nu} = \frac{\nu}{c} = \frac{10^4}{\lambda} \tag{15-3}$$

The units for wavenumbers are cm^{-1}, referred to as reciprocal centimeters. Wavenumber is commonly but incorrectly called frequency, an obvious error since the unit for wavenumber is cm^{-1}, whereas the unit for frequency is always a reciprocal unit of time, such as sec^{-1}. However, this erroneous use of the word is so common that you will have to get used to it!

To convert from wavelength in microns to wavenumber in cm^{-1} and vice versa, substitute the known value in equation 15-4 and solve for the other:

$$\bar{\nu}\lambda = 10{,}000 \tag{15-4}$$

IR spectra can be plotted linear in either λ or $\bar{\nu}$, but not both at once. For example, Figure 15.5 is linear in wavenumber; Figure 15.6 is linear in wavelength. The same spectra can *appear* quite different when linear λ is compared with linear $\bar{\nu}$!

Bandwidth

From what you have read about vibrational absorptions, you might expect all IR bands to be very sharp lines. However, vibrational energy absorptions are usually accompanied by changes in rotational energy levels, resulting in absorption of IR photons over a range of energies. Furthermore, the monochromator and slit do not make perfect separations of radiation into only one frequency. IR bands are qualitatively referred to as sharp, narrow, or broad. On Figure 15.4, the bands at 920 cm^{-1} and 1145 cm^{-1} are sharp, at 1600 cm^{-1} is medium, and at 3350 cm^{-1} is broad.

Band Intensity

Band intensity relates to the amount of energy absorbed by the sample. If the absorbance of energy is high, the amount transmitted to the detector is correspondingly low. The

vertical coordinate on IR chart paper is either *absorbance* (A) as in Figure 15.3, or *percent transmittance* ($\%T$) as in Figure 15.4. (The $\%T$ is shown at about 1660 cm^{-1} in this spectrum.) Notice that as A increases, $\%T$ decreases.

Intensity is qualitatively described as weak, medium, and strong (intense). When the base line is set at 100%T (0.00A), a weak band exhibits more than about 80%T (less than about 0.10A), and a strong band involves less than about 20%T (more than about 0.70A). If the baseline is not at 100%T, use proportional values to get a qualitative idea of intensity. On Figure 15.4 (baseline at 94%T), the band at 3350 cm^{-1} is strong, at 840 cm^{-1} is medium, and at 2700 cm^{-1} is weak.

Regions of the IR Spectrum

We can divide the IR spectrum into two segments: The first is the region from 1400 cm^{-1} (7.14 μ) to 4000 cm^{-1} (2.50 μ), which is where the more energetic stretching occurs. It is sometimes referred to as the **functional group region.** The second is the part from 650 cm^{-1} (15.4 μ) to 1400 cm^{-4} (7.14 μ), which contains the bending vibrations and weaker stretches. This segment of the spectrum usually contains many absorptions and is often difficult to interpret, but is so characteristic of a compound that we refer to it as the **fingerprint region.** Comparison of a compound's IR fingerprint with that of a known sample serves as almost certain identification.

One way to approach identification of spectra is to use functional group correlation tables, which can be found in the references cited at the end of Technique 15. As a start, you will probably need only the following samples of spectra and the information that accompanies them.

Analysis of Spectra

The following information is arranged alphabetically according to compound class.

Alcohols and Phenols

Please refer to Figures 15.3 and 15.4. The *O—H stretch* is the most characteristic absorption. It is strong and sharp at 3650–3600 cm^{-1} (2.74–2.78 μ) if the sample is vapor phase or dilute solution in nonpolar solvent. As concentration increases, intermolecular hydrogen bonding increases and a strong, broad band at 3550–3200 cm^{-1} (2.82–3.13 μ) appears at the expense of the sharp band. Sometimes both non-hydrogen-bonded and hydrogen-bonded stretches are present. The *C—H stretch* appears as a strong band at 1260–1000 cm^{-1} (7.93–10.00 μ), and its position helps to classify the compound as phenol (1260–1180 cm^{-1}), 3° alcohol (1200–1125 cm^{-1}), 2° alcohol

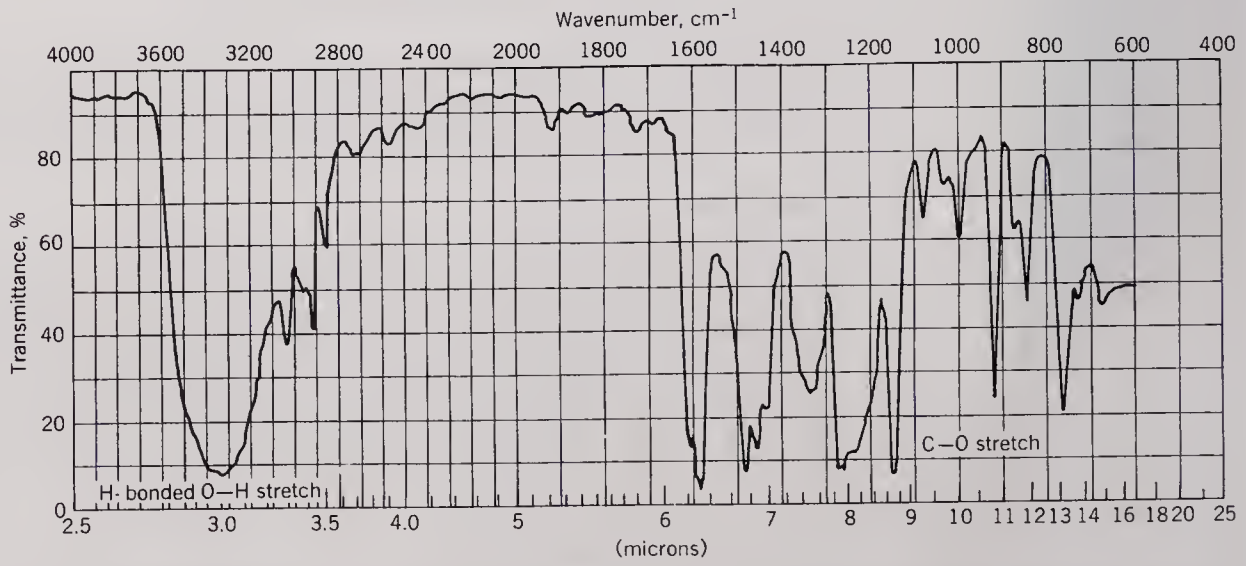

FIGURE 15.4 IR spectrum of *m*-cresol (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 143. Reprinted by permission.

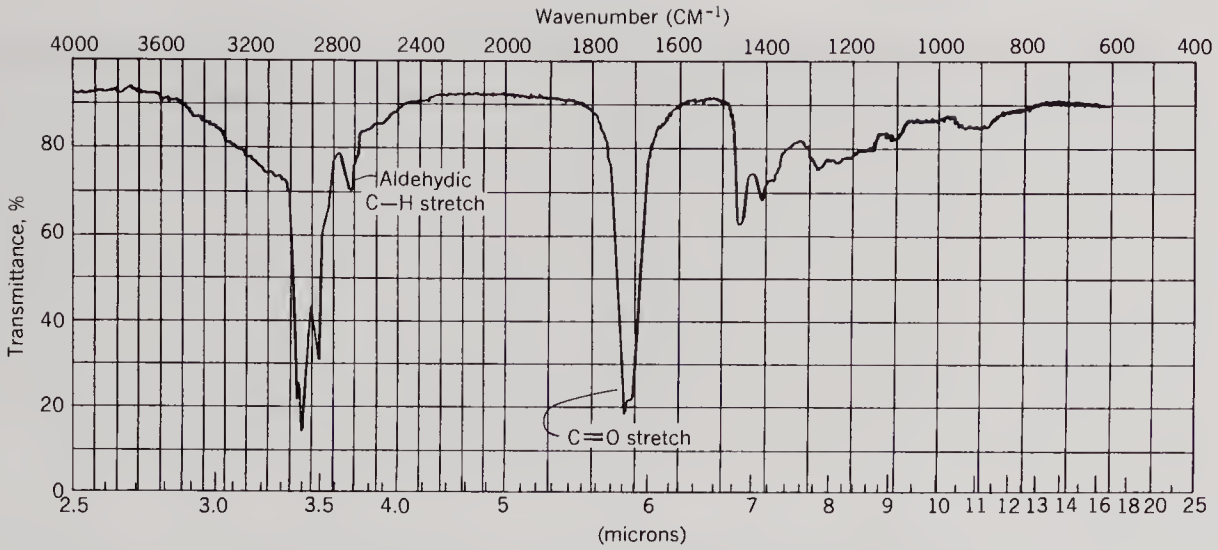

FIGURE 15.5 IR spectrum of heptaldehyde (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 145. Reprinted by permission.

(1125–1090 cm^{-1}), or 1° alcohol (1086–1050 cm^{-1}). Phenols also produce characteristic *aromatic* absorptions (see below).

Aldehydes

Please see Figure 15.5. The *C=O stretch* for an aliphatic aldehyde is a strong, narrow band near 1730 cm^{-1} (5.78 μ). Conjugation shifts the absorption to around 1710–1685 cm^{-1} (5.85–5.94 μ). The *aldehydic C—H stretch* at 2830–2695 cm^{-1} (3.53–3.71 μ) is generally weak and might appear as two bands.

Alkanes

The spectrum of hexane in Figure 15.6 is typical of alkanes. Alkane spectra generally have few bands. The *C—H stretch* usually has a few strong, sharp bands at around 3000 cm^{-1} (3.33 μ). The *C—H bends* appear as quite sharp bands of medium intensity at 1465–1150 cm^{-1} (6.83–8.70 μ) for methylene and at about 1375 cm^{-1} (7.28 μ) for methyl.

The spectra of *cyclic alkanes* are similar, but increasing ring strain moves the C—H stretch to increasingly higher wavenumber; cyclopropane absorbs at up to 3100 cm^{-1} (3.23 μ).

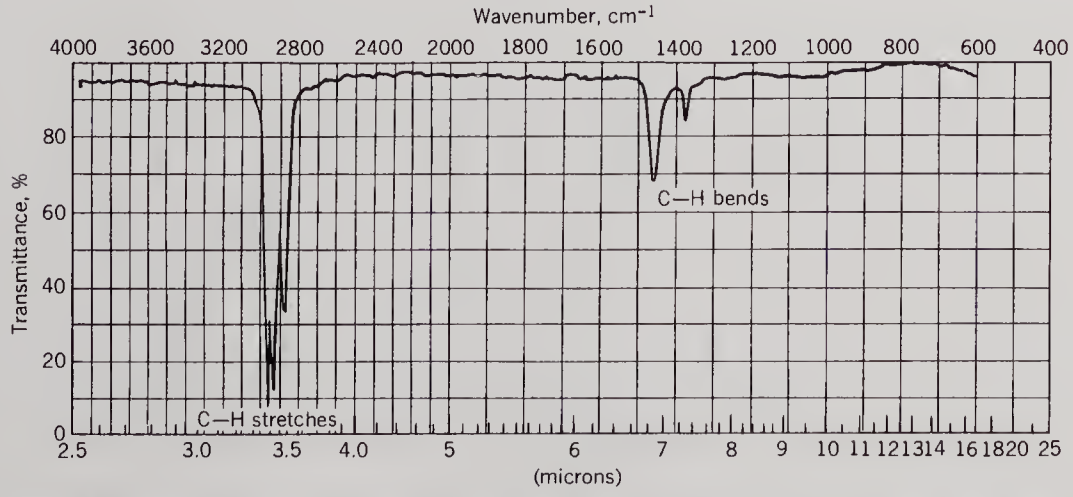

FIGURE 15.6 IR spectrum of hexane (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 139. Reprinted by permission.

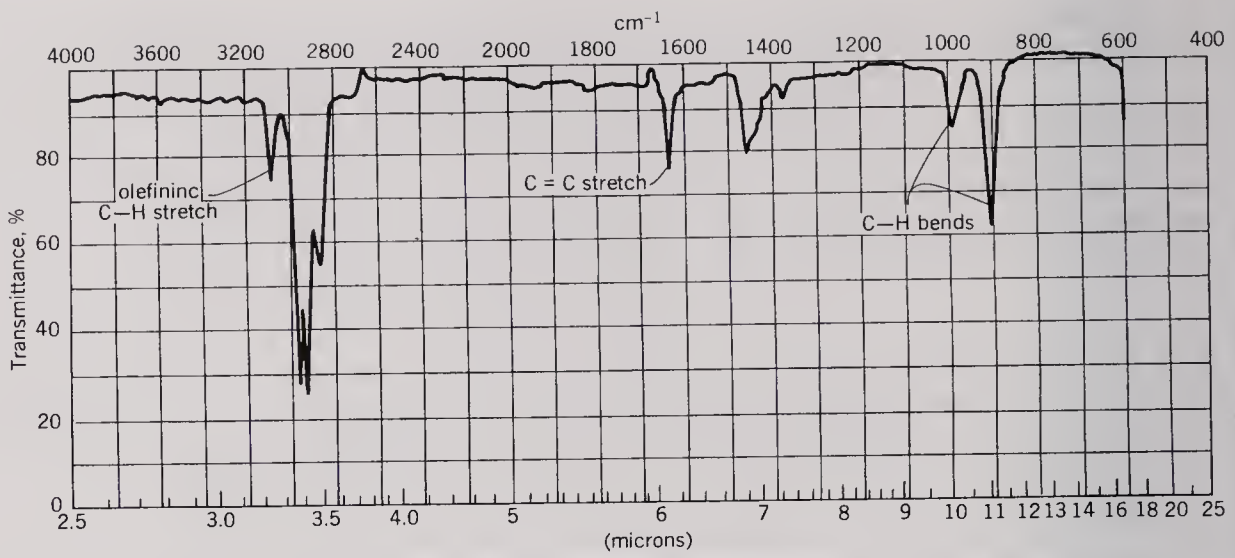

FIGURE 15.7 IR spectrum of 1-hexene (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 140. Reprinted by permission.

Alkenes

Please refer to Figure 15.7. The *C=C stretch* produces a generally sharp, weak, band at about 1675–1600 cm^{-1} (5.95–6.25 μ). Conjugation shifts the band to lower energy. If the C=C bond is symetrically substituted (same groups on each side of C=C) there will be *no absorption*. The olefinic *C—H stretch* usually produces sharp bands around 3100–3000 cm^{-1} (3.22–3.33 μ); *C—H bending* modes absorb between 1000 and 650 cm^{-1} (10.00–15.40 μ), producing sharp bands of medium to strong intensity. These bands are often diagnostic for substitution around the double bond: $RCH{=}CH_2$, 995–985 cm^{-1} (10.05–10.15 μ); $R_2C{=}CH_2$, 895–885 cm^{-1} (11.17–11.30 μ); *cis* RHC=CRH, 730–665 cm^{-1} (13.70–15.04 μ); *trans* RHC=CRH, 980–960 cm^{-1} (10.20–10.42 μ); $R_2C{=}CHR$, 840–790 cm^{-1} (11.91–12.66 μ).

Alkynes

Please see Figure 15.8. The *C≡C stretch* produces a sharp band of weak to medium intensity if the C≡C bond is *not* symmetrically substituted, that is, if different groups are on either side of C≡C. The band appears at 2140–2100 cm^{-1} (4.67–4.76 μ) for monosubstituted alkynes, and at 2260 to 2190 cm^{-1} (4.43–4.57 μ) for disubstituted alkynes. Conjugation shifts the band to lower energy. The acetylenic *C—H stretch* is a strong, sharp band at 3333–3267 cm^{-1} (3.00–3.06 μ).

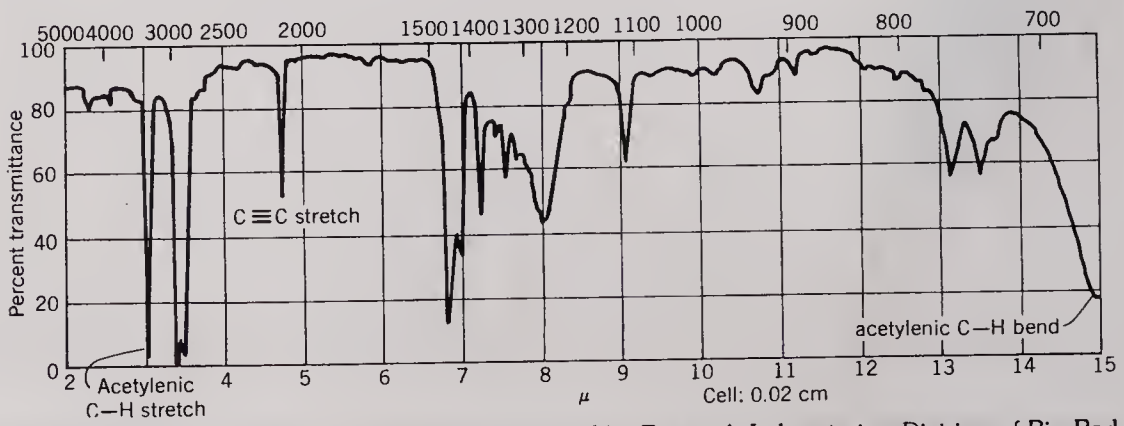

FIGURE 15.8 IR spectrum of 1-hexyne (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

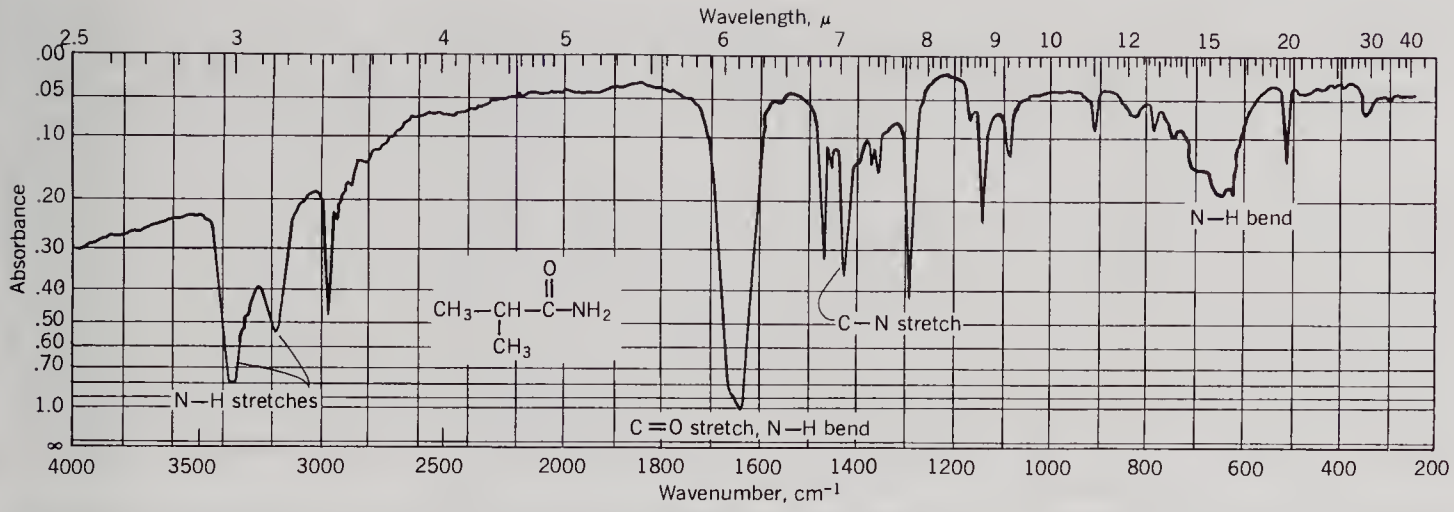

FIGURE 15.9 IR spectrum of isobutyramide (KBr). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

Amides

Please refer to Figure 15.9. A moderate to strong broad *N—H stretch* occurs at 3500–3100 cm^{-1} (2.85–3.25 μ). In dilute solution, unsubstituted amides display two moderately intense bands near 3520 cm^{-1} (2.84 μ) and 3400 cm^{-1} (2.94 μ) due to the symmetric and asymmetric stretches, respectively. In solid, concentrated, or neat samples, the absorbance is shifted to lower energy. The *C=O stretch* gives a strong, narrow absorption at about 1670–1640 cm^{-1} (5.99–6.10 μ). A medium, narrow N—H in-plane bend can sometimes be seen around 1655–1590 cm^{-1} (6.04–6.29 μ); and a weaker broad out-of-plane N—H bend is found around 700–600 cm^{-1} (14.28–16.67 μ).

Amines

Please see Figure 15.10. The most distinguishing feature of an amine spectrum is the *N—H stretch* of variable strength and width. Dilute solutions of 1° amines produce two weak bands near 3500 cm^{-1} (2.86 μ) and 3400 cm^{-1} (2.94 μ); those of 2° amines yield a weak band around 3350–3310 cm^{-1} (2.98–3.02 μ). The neat N—H stretches of primary amines are around 3400–3330 cm^{-1} (2.94–3.00 μ) and 3330–3250 cm^{-1}

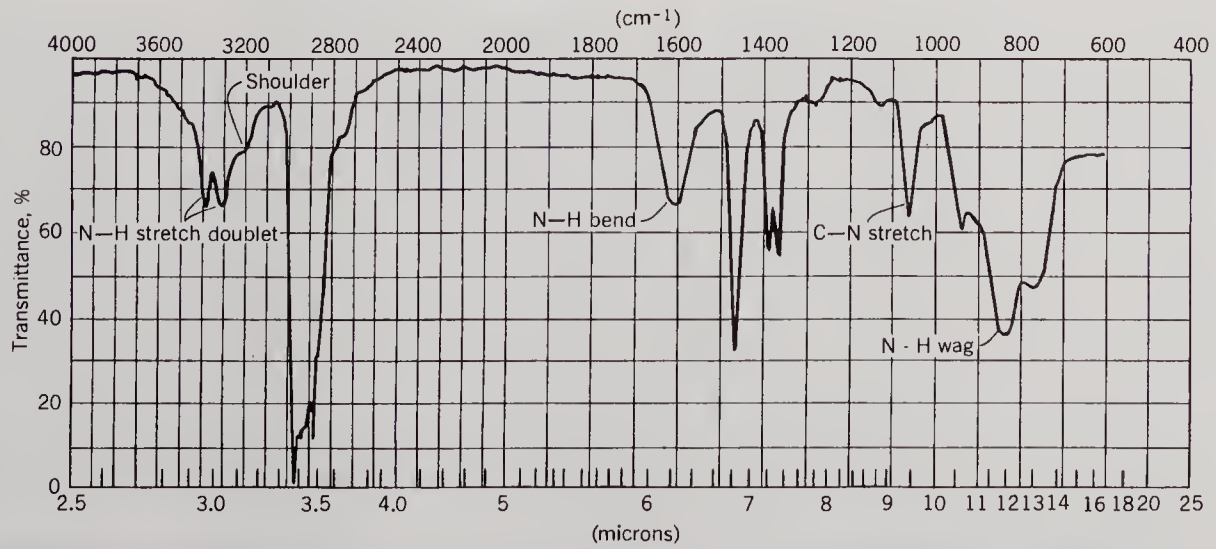

FIGURE 15.10 IR spectrum of isobutylamine (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 144. Reprinted by permission.

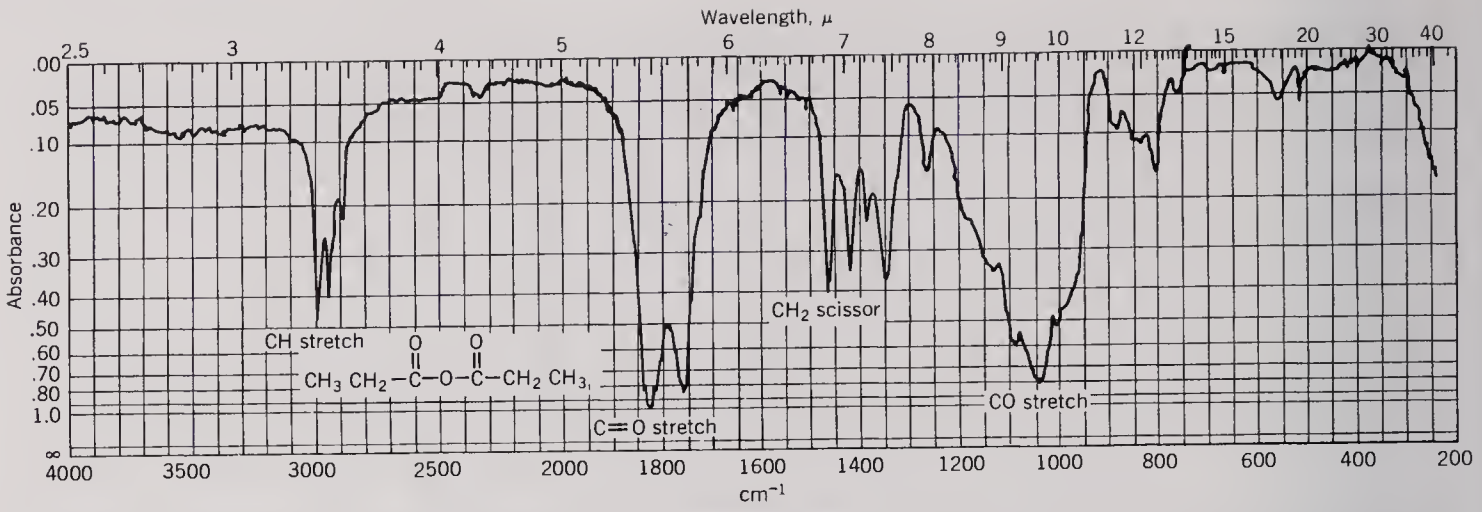

FIGURE 15.11 IR spectrum of propionic anhydride (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

(3.00–3.08 μ). Hydrogen-bonded N—H stretching occurs at lower energy, and is weaker and often narrower than a hydrogen-bonded O—H stretch. Another feature that helps to distinguish N—H from O—H is that in liquid primary and secondary amines, a shoulder usually is found on the low energy side of the N—H stretching band. The *C—N stretch* is weak to medium for aliphatic amines and is found at about 1250–1020 cm^{-1} (8.00–9.80 μ). The C—N stretch of aromatic amines is found at 1342–1266 cm^{-1} (7.45–7.90 μ) and is strong.

Amine salt spectra display a strong, broad N—H absorption at 3000–2700 cm^{-1} (3.33–3.57 μ). In addition, 1° amine salts absorb at 2800–2000 cm^{-1} (3.57–5.00 μ) with multiple bands of medium intensity; 2° salts absorb with strong multiple bands all the way down to 2273 cm^{-1} (4.00 μ) and perhaps with a medium band near 2000 cm^{-1} (5.00 μ); 3° salts absorb from 2700–2250 cm^{-1} (3.70–4.44 μ).

Anhydrides

Please see Figure 15.11. The *C=O stretch* exhibits two strong narrow bands near 1818 cm^{-1} (5.50 μ) and 1750 cm^{-1} (5.71 μ). Conjugation shifts absorption to lower energy,

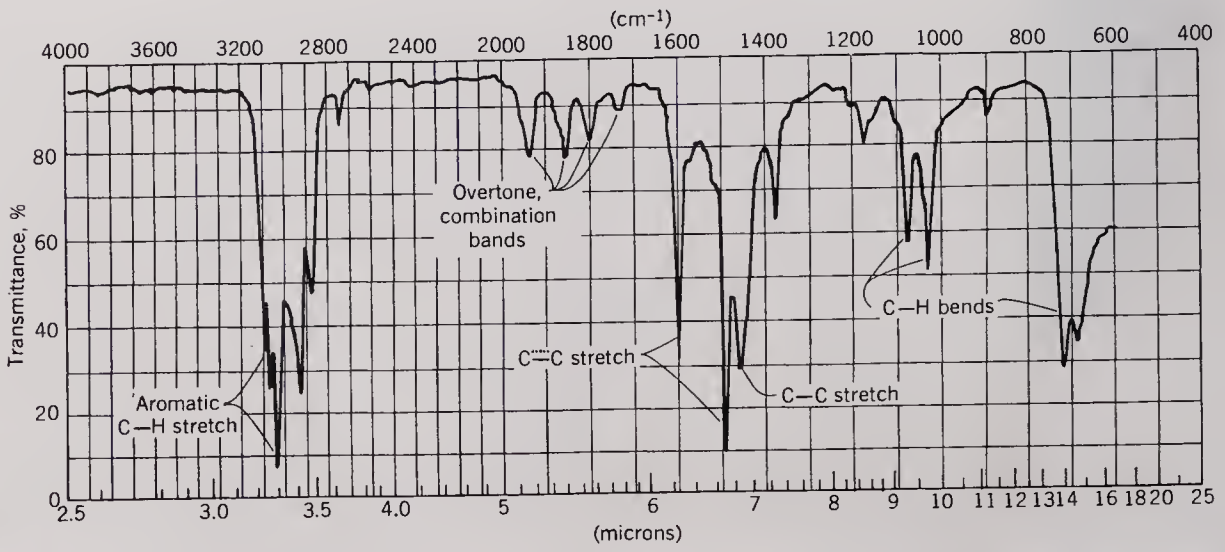

FIGURE 15.12 IR spectrum of toluene (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 141. Reprinted by permission.

whereas ring strain in cyclic anhydrides shifts absorption to higher energy. The lower energy absorption is characteristically of a bit less intensity. The *C—O stretch* is strong and broad between 1300 and 1900 cm^{-1} (7.69–11.11 μ).

Aromatics

As we see in Figure 15.12, spectra of aromatic compounds exhibit characteristic bands in three spectral regions. The *C—H stretch* is a sharp band of weak to medium intensity around 3100 to 3000 cm^{-1} (3.23–3.33 μ). The *C=C stretch* vibrations occurring at 1600–1585 cm^{-1} (6.25–6.31 μ) and 1500–1400 cm^{-1} (6.67–7.14 μ) are sharp and of varying intensity. Often appearing in pairs in both of these regions, these bands are diagnostic of aromatic structure. The most prominent bands are those of the *C—H bends,* the medium to strong, narrow to sharp absorptions at 1300–1000 cm^{-1} (7.70–10.00 μ) being in-plane bends, and those at 900–675 cm^{-1} (11.11–14.82 μ) being out-of-plane bends. The weak *combination and overtone* absorptions (Figure 15.13) observed in the region 2000–1650 cm^{-1} (5.00–6.06 μ) are characteristic of the substitution pattern on the ring.

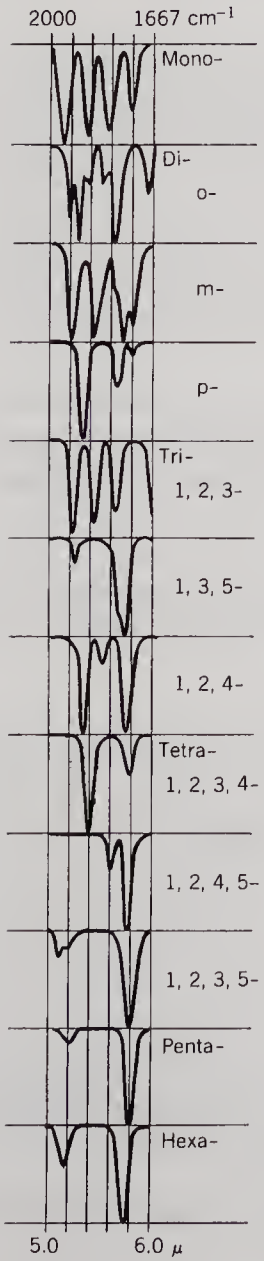

FIGURE 15.13 Substitution patterns for benzenoid compounds. John R. Dyer, *Applications of Absorption Spectroscopy of Organic Compounds,* © 1965, p 52. Reprinted by permission of Prentice-Hall, Englewood Cliffs, NJ.

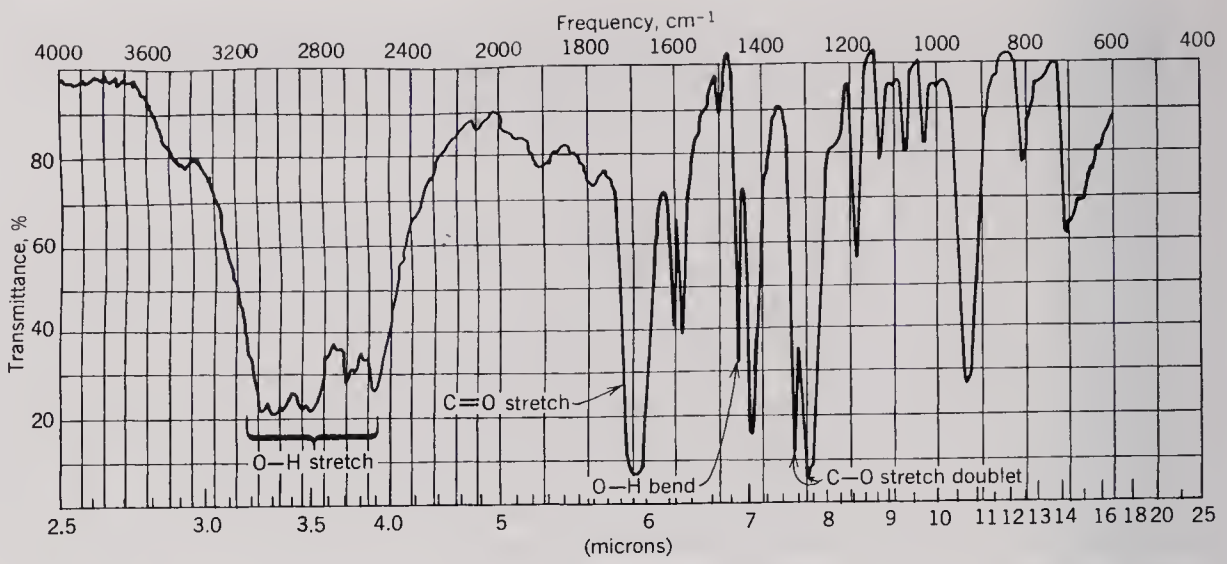

FIGURE 15.14 IR spectrum for benzoic acid (KBr). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 145. Reprinted by permission.

Carboxylic Acids

Please see Figure 15.14. The strong, narrow *C=O stretch* at 1720–1680 cm^{-1} (5.81–5.86 μ) is more intense than that of aldehydes and ketones. The *C—O stretch* at 1320–1210 cm^{-1} (7.58–8.26 μ) is medium to strong and narrow, sometimes appearing as two bands. The hydrogen bonded O—H stretch is a strong, very broad absorption at 3300–2500 cm^{-1} (3.03–4.00 μ) and often overlaps C—H stretching bands. A weak, sharp non-hydrogen-bonded stretch might or might not be present. A medium intensity *O—H in-plane bend* appears at 1440–1395 cm^{-1} (6.94–7.17 μ) and a moderately intense, broad *out-of-plane O—H* bend often occurs near 920 cm^{-1} (10.87 μ).

Carboxylic Acid Halides

Acyl halides show a strong, narrow *C=O stretching* band at 1815–1785 cm^{-1} (5.51–5.60 μ). Conjugation shifts the absorption to lower energy.

Esters

Please see Figure 15.15. The strong, narrow absorption band of the *C=O stretch* occurs at 1750–1735 cm^{-1} (5.71–5.76 μ) for aliphatic esters. Conjugation with double bonds

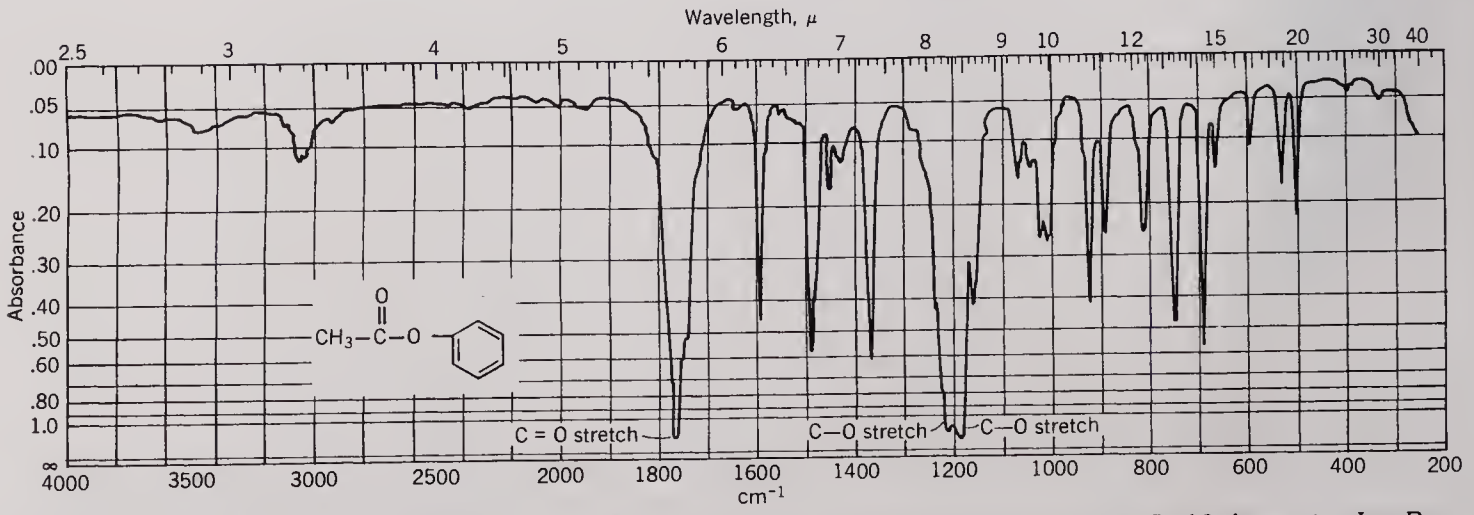

FIGURE 15.15 IR spectrum for phenyl acetate (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

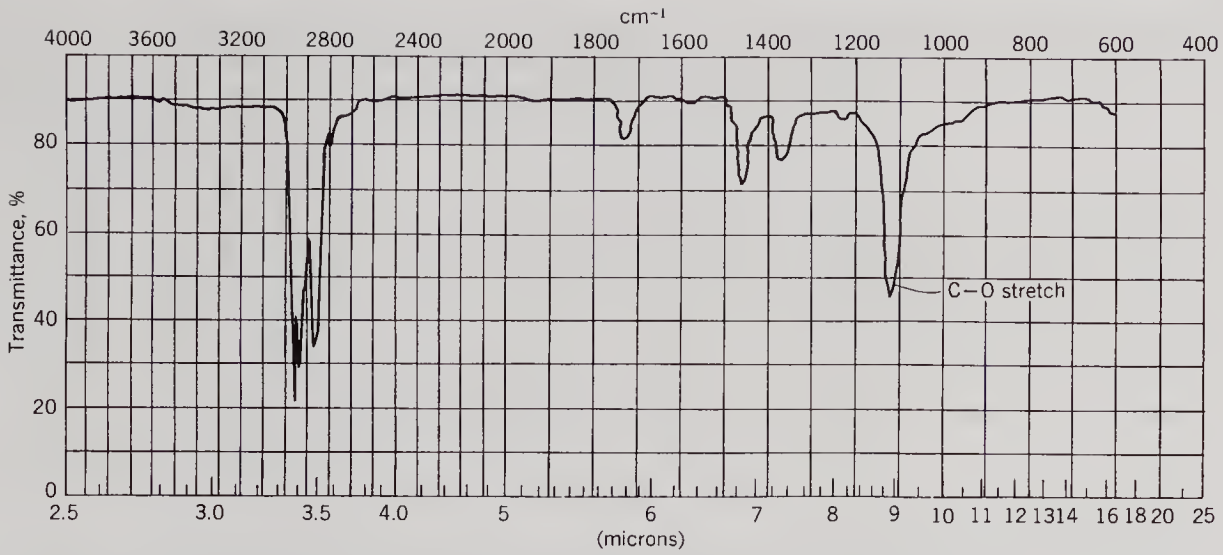

FIGURE 15.16 IR spectrum of *n*-butyl ether (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 142. Reprinted by permission.

or aromatic ring in the acid part shifts absorption to lower energy; conjugation with double bonds or aromatic ring in the alcohol portion or ring strain in lactones shifts absorption to higher energy. Strong, sharp to narrow *C—O stretching* occurs in two bands at 1300–1000 cm^{-1} (7.70–10.00 μ).

Ethers

Please see Figure 15.16. The most characteristic band for ethers is the medium to strong, narrow *C—O stretch* around 1150–1085 cm^{-1} (8.70–9.23 μ). Phenyl and vinyl ethers might give two bands at the higher energy end of the range.

Halogenated Compounds (other than Acyl Halides)

Figure 15.17 is the spectrum of carbon tetrachloride. The C—X absorption position depends on the type of halogen: For C—F, 1400–730 cm^{-1} (7.14–13.70 μ); for C—Cl, 850–550 cm^{-1} (11.76–18.18 μ); for C—Br, 690–515 cm^{-1} (14.49–19.42 μ); for C—I, 600–500 cm^{-1} (16.67–20.00 μ). The greater the number of halogens, the more intense and complicated the absorptions are likely to be.

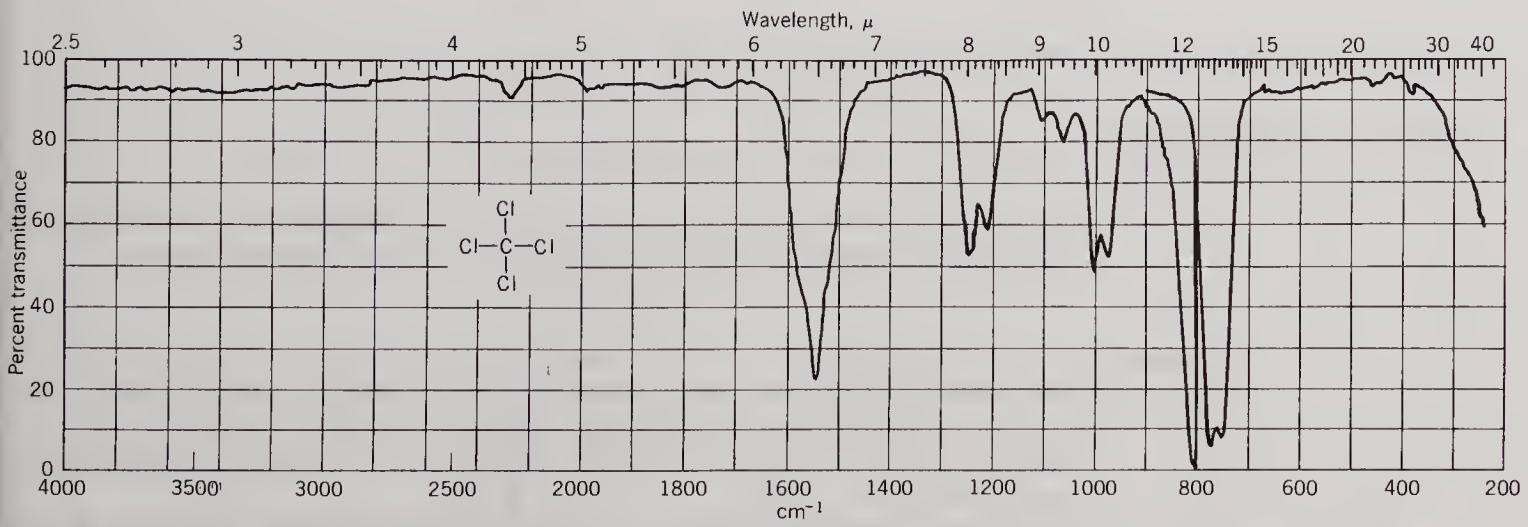

FIGURE 15.17 IR spectrum of carbon tetrachloride (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

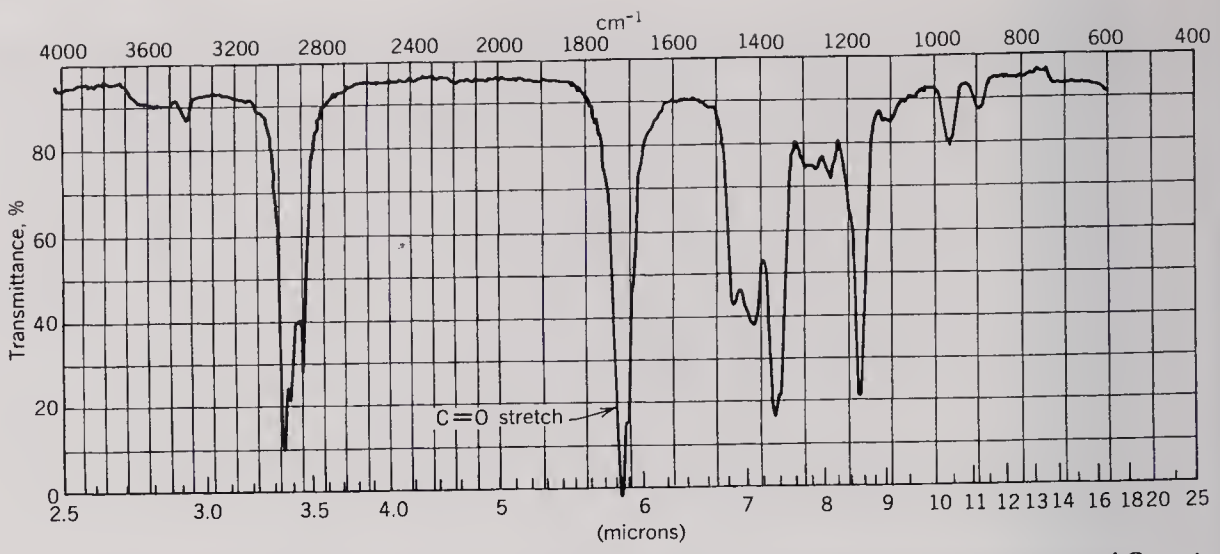

FIGURE 15.18 IR spectrum of 2-pentanone (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 134. Reprinted by permission.

Ketones

Figure 15.18 shows that the most characteristic feature of an open chain or cyclic six-member ring ketone is the strong, narrow *C=O stretch* at about 1715 cm^{-1} (5.83 μ). Conjugation with double bonds or aromatic ring or in enols moves the absorption to lower energy. In cyclic ketones, ring strain shifts the band to higher energy, about 0.10 μ each time a carbon is removed from the ring.

Nitriles

The most characteristic absorption of a nitrile is the strong, sharp absorption of the *C≡N stretch* at 2260–2240 cm^{-1} (4.42–4.46 μ). Conjugation with C=C or aromatic rings slightly shifts the absorption to lower energy.

Nitro Compounds

The *N=O stretch* yields two strong, narrow bands near 1550 cm^{-1} (6.45 μ) and 1372 cm^{-1} (7.29 μ). Conjugation with C=C or aromatic rings shifts the absorption to lower energy.

Phenols

Please see the section on alcohols.

15.4 THE TECHNIQUES

Briefly stated, the techniques involve preparation of the sample in an appropriate sampling method, recording the spectrum, cleaning up, and analyzing the spectrum.

Sampling

The most ideal situation for sampling would be to determine the IR spectrum in the vapor phase because interactions between molecules would be minimal. Gas phase spectra are possible for many compounds, but most laboratories do not have the necessary equipment. Anyway, quite satisfactory spectra can be obtained in liquid or solid form in most cases.

All preparations of samples involve salt plates or cells, which are relatively fragile and must be handled gently. Because glass absorbs IR radiation in the region of interest,

sampling equipment usually is made from an inorganic salt like NaCl. Since such salts are water soluble they must be stored in a desiccator, handled only by their edges, and never exposed to compounds containing water.

Neat Sampling

Obtaining a spectrum of a neat liquid is convenient because of the ease of preparing the sample. Another advantage is that only bands belonging to the liquid itself appear in the spectrum. However, because there is no fixed path length when this method is used, viscous liquids might absorb too strongly because they do not squeeze out well from between the plates. By contrast, nonviscous liquids might have a too short path length and produce all weak bands. You can sample resins, plastics, and other noncrystalline solids neat, but crystalline solids tend to deposit as a powder which scatters the IR beam.

With an eyedropper or stirring rod, put one or two drops of a water-free, neat liquid on a salt plate like that shown in Figure 15.19. Place a second plate over the first and press it down. Next, put the plates in the sample holder and *gently* tighten the screws just enough to hold the plates in place. If rubber gaskets are available, use them to cushion the plates. If the liquid is moderately volatile, put a strip of masking tape all the way around the edges to prevent evaporation. Very volatile liquids require special cells or must be put in solution. To prepare a neat sample of a noncrystalline solid, first make a concentrated solution of the solid in a solvent of moderate volatility. Put a drop or two on the salt plate, and allow the solvent to completely evaporate. Put the single plate in the sample holder. After recording the spectrum, wipe the salt plates clean with a soft cloth or paper saturated with an appropriate solvent.

Solution Sampling

We often prepare samples of liquids and solids in solution, using concentrations of from about 0.1 to 10% in salt cells from 0.1 to 1 mm thickness, the volume required being less than 1 ml.

The solvent to be used must be water free and should not absorb IR radiation strongly in the IR region of most interest. Tetrachloromethane (carbon tetrachloride) and carbon disulfide (IUPAC dithioxomethane) are most often used. The former has few

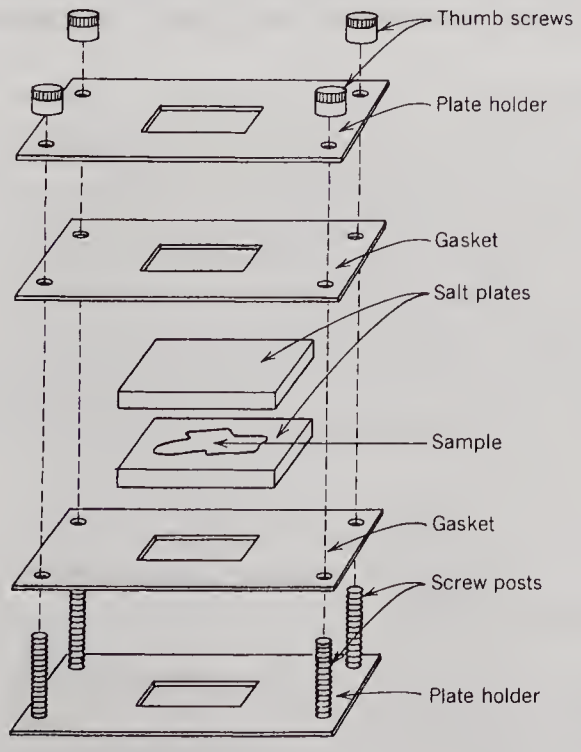

FIGURE 15.19 The mounting of salt plates.

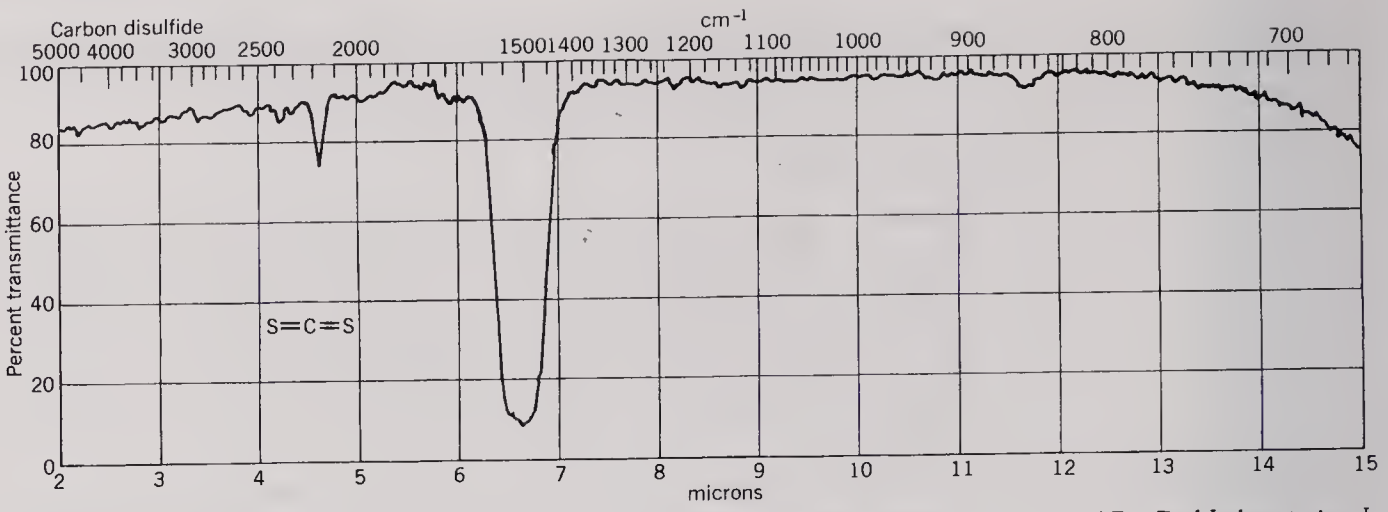

FIGURE 15.20 IR spectrum of carbon disulfide (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

absorptions at wavenumbers greater than 1330 cm^{-1}, and the latter has very little absorption at less than 1330 cm^{-1}. See Figures 15.17 and 15.20. Because of their absorption ranges the two solvents are complementary. When it is desirable to observe the entire spectrum of a compound, you can prepare two samples, one in each solvent. We sometimes use chloroform (IUPAC trichloromethane) because it is a bit more polar and dissolves substances insoluble in CCl_4 and CS_2. Use 10% solutions. You can prepare an approximate 10% sample of a liquid by mixing one drop of the liquid with nine drops of solvent. For solids, use a matchhead size of packed solid with nine drops of solvent. The usual solution cell, shown in Figure 15.21, has at both top and bottom an opening that fits a hypodermic syringe. Fill the cell by drawing solution into the syringe and injecting it into the lower opening. During injection you can see the solution rise in the cell. When the solution is filled to the top of the window and no air bubbles are present, withdraw the syringe and insert Teflon plugs into the opening, first at bottom, then top. Using a clean syringe, fill a reference cell in the same manner as the sample cell, but with solvent only. After recording the spectrum, force clean solvent from the syringe through the cell's top part. Then, blow clean dry air through the cell to expel all solvent.

Note that it is important to report the solvent used because the presence of the solvent causes intermolecular interactions which can affect spectral band positions.

Mull Sampling

When solids need to be analyzed, a neat sample is often unsatisfactory, and a suitable solvent may not be available. In such cases they can be prepared in a mull.

The word "mull" comes from an Old English word "mullen," meaning to grind, or pulverize. As we use the word, a mull is a dispersion of a finely ground substance in a semiviscous liquid, usually Nujol, a pure white mineral oil. Because Nujol is a hydrocarbon, it absorbs IR energy in the C—H stretching and bending regions of the spectrum, as you can see in Figure 15.22. Therefore, Nujol absorptions will be recorded along with those of the compound being analyzed and must be ignored when interpreting a nujol mull spectrum. Another dispersing agent is Fluorolube®, a totally halogenated polymer.

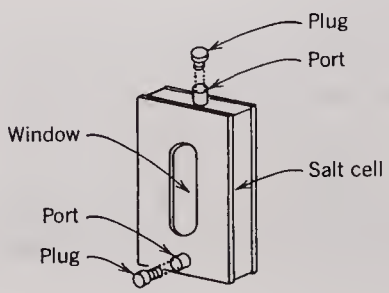

FIGURE 15.21 Solution cell.

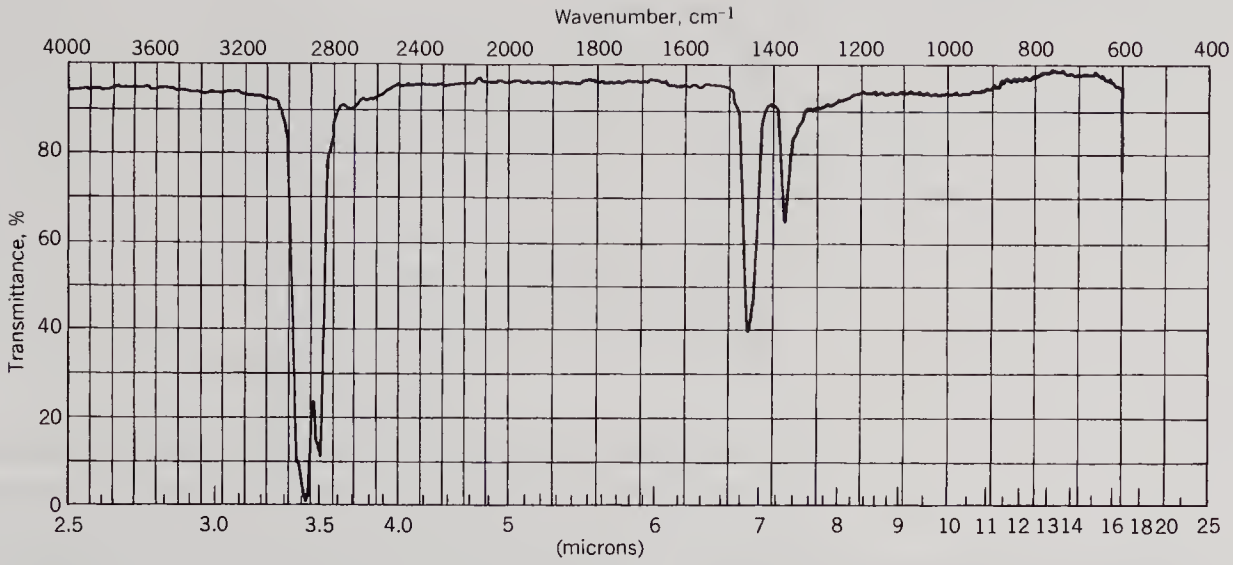

FIGURE 15.22 IR spectrum of nujol (neat). From Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry*; Wiley: New York, 1980, p 149. Reprinted by permission.

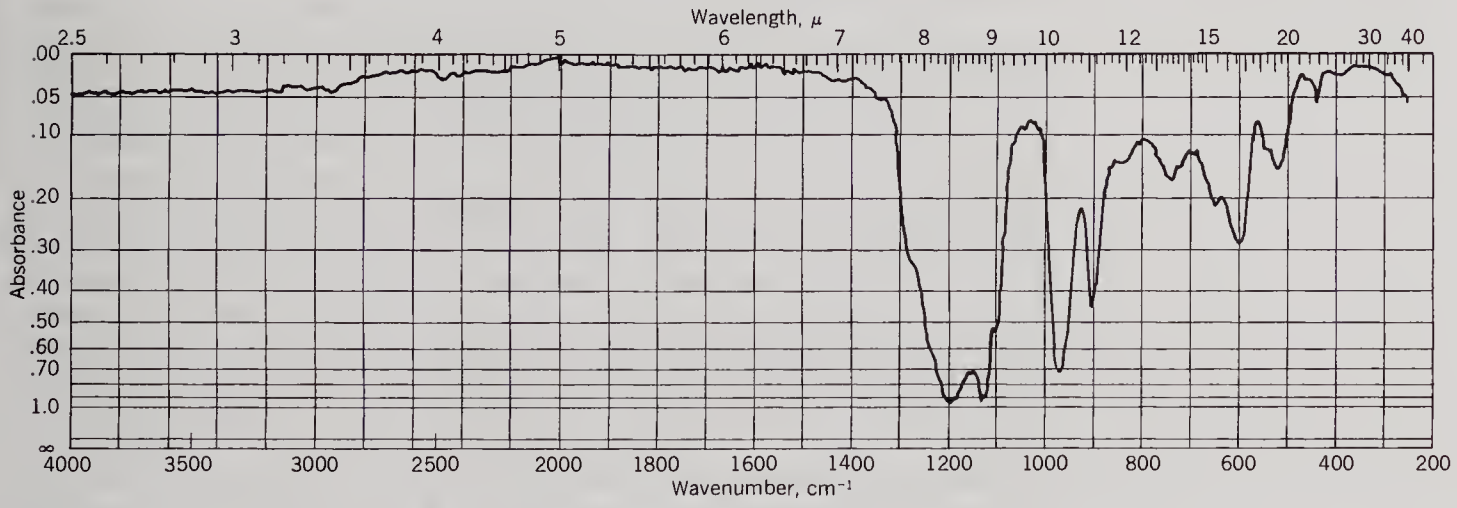

FIGURE 15.23 IR spectrum of fluorolube (neat). © Sadtler Research Laboratories, Division of Bio-Rad Laboratories, Inc. Reprinted by permission.

Comparison of Figures 15.22 and 15.23 teaches that Nujol® and Fluorolube® are complementary in the same way as CCl_4 and CS_2.

To prepare a mull, grind about 20 mg of water-free compound in an agate mortar with an agate pestle for 5 or 10 min until it appears caked and glassy. Then add one or two drops of mulling agent. Grind the sample again for a few more minutes. To avoid scattering of the IR beam, you must grind the sample to a size less than the shortest wavelength of the IR radiation used. With a rubber policeman, transfer the mull to a salt plate. Next, gently press a second plate onto the first, twisting a little to evenly distribute the sample and eliminate air pockets. Put the plates in the sample holder as for a neat liquid sample.

Because the mull film is usually not as transparent as a neat film, the spectrum might not be recorded as high on the chart paper as usual. This greater absorption of energy is the result of diminished sample beam due to IR radiation scattering by the dispersion. You can compensate to some extent by also cutting down the intensity of the reference IR beam with an attenuator.

Clean the plates with hexane in the same way you clean them after neat sampling.

Pellet Sampling

We often get the best spectra of solids when the solid is incorporated into a pellet, a thin disc consisting of the compound finely ground together with potassium bromide. Under

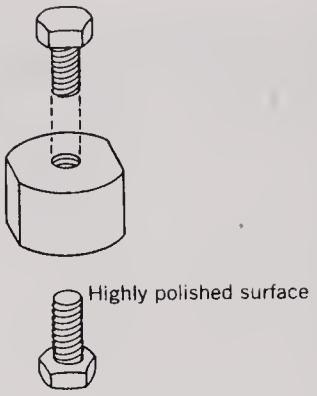

FIGURE 15.24 Mini pellet press.

pressure of about 10,000 lb/in.^{2}, the salt fuses, forming a transparent disc. The quality of the spectrum depends on the fineness of the dispersed compound and its intimate admixture with the powdered KBr. The size of the dispersed particles should be no greater than the wavelength of the IR radiation. If either the compound of interest or the KBr is not completely free of moisture, bands due to water at 3450 and 1640 cm^{-1} will be seen in the spectrum.

To prepare a pellet, grind about 20 mg of dry compound as for mull preparation. Remove all but about 1 mg from the mortar. Now, add about 200 mg of dry, powdered, spectral grade KBr which has been previously ground, heated in an oven at 150 °C for an hour, and stored in a desiccator. Intimately grind the salt and powdered compound in the mortar, then with a microspatula quickly transfer the mixture to a pellet press. The simple, inexpensive press, shown in Figure 15.24, consists of just three parts. To assemble the press, put one bolt in the barrel and screw it in until it is all the way in. Then back it out one full turn. Now, hold the barrel vertical and put the sample into the press in small enough increments so that it is distributed evenly over the polished face of the bolt. Tapping the barrel gently from time to time will help to distribute the sample. Insert the second bolt and hand tighten it. Then using two six-inch wrenches or a wrench and a bench vise, gradually tighten each bolt until you can no longer easily tighten them. Leave the sample under pressure for two or three minutes and then carefully remove both bolts.

Immediately wash the bolts with water as soon as they are removed from the press. Rinse them with acetone, and dry them with a soft cloth or paper, taking care not to scratch the polished faces. The pellet should be left in the barrel, which you mount in front of the sample beam of the IR instrument. To obtain sharper spectra with better resolution, you should dry the pellet for at least 2 hr in a vacuum oven at 1.0 torr and 50 °C. The oven should contain a small dish of P_2O_5 and have a $CaCl_2$ tube on its air vent. After drying, store the sample in a desiccator until you record the spectrum.

After recording the spectrum, gently push the pellet out of the barrel and wash the barrel thoroughly with water, then rinse with acetone and allow it to dry.

Recording the Spectrum

Even on simple instruments there are some adjustments that you will need to make. Your laboratory instructor will show you how to use the instrument available to your laboratory.

Carefully position the chart paper so that the calibration mark on the paper lines up with an indicator on the instrument. Set the transmittance control knob so that the pen rests between 90 and 100% transmittance.

The attenuator in the reference beam might have to be adjusted so that transmittance is near 100%. Low transmittance is most likely for mull and pellet samples.

The scan rate control allows you to change the time it takes to make the scan. The faster the scanning rate, the lower the resolution is likely to be. A scan of about 3 min is generally satisfactory.

The following procedural summary will be basically the same for any IR spectrum.

1. Turn on the instrument.
2. Prepare the sample, and reference cell if necessary.
3. Put the sample in the holder.
4. Position the sample and reference in the appropriate beams.
5. Put the chart paper in place.
6. Adjust the transmission to between 90 and 100%.
7. Adjust the attenuator if necessary.
8. Release the pen onto the chart paper.
9. Set the scan rate.
10. Press the button that starts the scan.
11. After scan is complete, raise the pen.
12. Remove the chart paper.
13. Record all control settings, name of sample, sampling method and solvent, and make and model of instrument.
14. Turn off the instrument if you will be the last person to use it. Otherwise leave it on.
15. Clean up.
16. Return plates and cells to the desiccator.

Spectrum Analysis To analyze your spectrum, concentrate on looking for major functional groups as outlined in Section 15.3. You might find the following outline helpful.

1. Look for a C=O stretch.
2. If a C=O stretch is present, look for the O—H of acids, the N—H of amides, the two C=O stretches of anydrides, and the aldehyde C—H.
3. If C=O is not present, look for O—H of alcohols and phenols, N—H of amines, and C—O of ethers.
4. Look for alkene, alkyne, and aromatic characteristics.
5. Look for nitrile, nitro, and halogen absorptions.
6. Look to see if only alkane absorptions are present.

Finally, when you think you have identified the compound, compare its spectrum with that of a known sample.

15.5 EXPERIMENTAL PART
Identification of an Unknown Liquid

Time Required: 10 min/student at the instrument

You will be given about $\frac{1}{2}$ ml of an unknown liquid. Your task is to identify the sample as one of the following compounds: benzenecarbonal (benzaldehyde), phenylmethanol (benzyl alcohol), 1-phenylethanone (acetophenone), methyl benezenecarboxylate (methyl benzoate), 1-pentanol (*n*-amyl alcohol), or mineral oil.

Procedure. Using salt plates, obtain a neat IR spectrum of the sample. You should be able to quickly narrow the possibilities to a couple of compounds by analyzing the stretching bands at wavenumbers greater than 1600 cm^{-1}. When you think you know what the compound is, confirm its identity by comparing its IR spectrum to that of a known sample obtained from the stockroom or by comparing the IR spectrum with one found in the chemical literature.

Writing the discussion. Identify the unknown and explain how you arrived at the conclusion, noting specific absorptions and what they mean.

Treat any unknown as if it were the most toxic one to be distributed.

15.6 EXERCISES

Prelaboratory

1. Why must IR plates and cells be kept in a desiccator?
2. What is a common problem when viscous liquids are examined neat?
3. What parts of IR plates or cells is it appropriate to touch?
4. What solids can be examined neat?
5. Why must solvents for solution sampling be dry?
6. What the most noteworthy hazards of tetrachloromethane, trichloromethane, and carbon disulfide?
7. How many milliliters of solution should be prepared for a spectrum?
8. Under what circumstances is a reference cell used?
9. Why are CCl_4 and CS_2 considered complementary?
10. Why should screws be tightened gently when putting a sample in a holder?
11. What piece of equipment is used for putting a solution into a salt cell?
12. Describe how a cell is cleaned after use.
13. What particle size in microns is satisfactory for a mull or pellet? How is this size attained? What equipment is used?
14. How should salt plates be cleaned?
15. How should KBr be prepared prior to its use in a pellet?
16. How should pelletizing equipment be cleaned after use?

Postlaboratory

1. In 2-hydroxycyclohexanone, intramolecular hydrogen bonding occurs. The OH stretching band is sharp and is found at a lower energy position in the IR spectrum than when the carbonyl is absent. Explain the position and sharpness in spite of hydrogen bonding.
2. For 2, 6-di-*t*-butylphenol, only one strong, sharp O—H stretch is observed, even in a neat sample. Explain.
3. Explain why the 1,3-hexadiene spectrum shows two bands, whereas the 2,4-hexadiene spectrum has only one band.
4. Explain on the basis of hyperconjugation why propanone has a C=O stretching absorption at lower wavenumber than ethanal.
5. Draw a resonance structure to show why the propenal carbonyl stretch should be at lower wavenumber than that of propanal.

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Acknowledgment
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TECHNIQUE **16**

NUCLEAR MAGNETIC RESONANCE

Nuclear magnetic resonance (NMR) was first successfully demonstrated in 1945. By the 1960s nuclear magnetic resonance spectrometry became generally available for identification and analysis of organic compounds. NMR is currently becoming important for diagnosing brain tumors and may soon replace the commonly used, but more hazardous, X-ray techniques.

Although many atomic nuclei possess magnetic properties, the most commonly studied, most easily understood, and most important atom for NMR analysis of organic compounds is hydrogen. Therefore, we shall confine our attention primarily to the hydrogen nucleus. If you want to study NMR of other atoms, you should consult references at the end of this chapter.

Because most organic chemistry lecture textbooks include a section on introductory NMR theory, we shall discuss only those theoretical topics which are not included therein and which are necessary in order for you to understand NMR laboratory procedures and analyses. Use your lecture text along with the following discussion. For more complete information, refer to the references at the end of this chapter.

16.1 THE NMR PHENOMENON

Because the nucleus of hydrogen-1 is a proton, NMR discussions most often refer to protons rather than hydrogen atoms, and indeed NMR of protons is often called **proton magnetic resonance,** or **PMR.**

Because of its magnetic dipole, the spinning proton behaves in much the same way as a compass needle that points north. However, there are two important differences in its behavior: first, it can align either *with* the external field (low-energy spin state) or *opposite* to it (high-energy spin state); and second, the axis of its magnetic dipole precesses about the axis of the external magnetic field in the same way that a toy top precesses when its rate of spinning slows. **Precession** is a relatively slow gyration of the rotation axis of a spinning body about another line intersecting it so as to produce a cone. Figure 16.1 illustrates the precession of a proton's magnetic dipole, H_p, about that of the external magnetic field, H_0.

Resonance By matching the proton's precessional frequency with a radio frequency (rf) provided by the NMR instrument, we can cause the proton to "flip its spin" and go from the low-

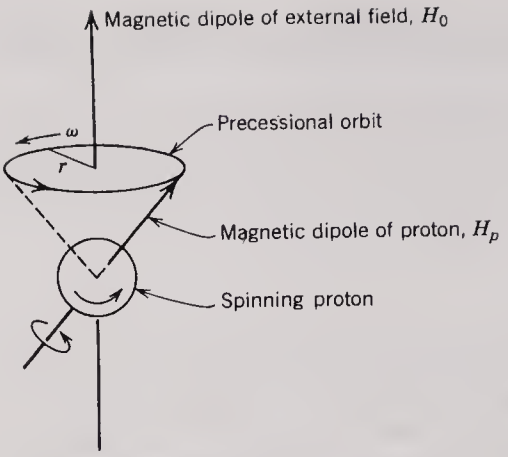


FIGURE 16.1 Precessing proton in external magnetic field.

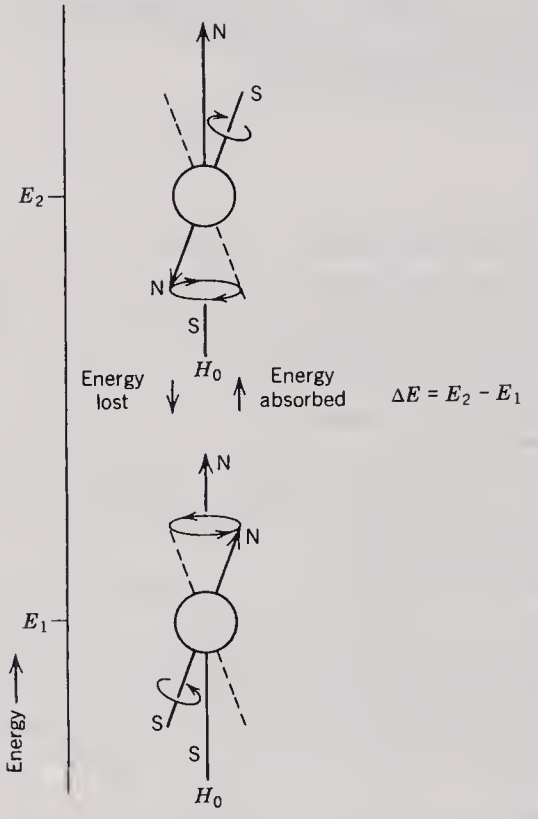


FIGURE 16.2 Flipping the spin.

energy to the high-energy spin state, as shown in Figure 16.2. This frequency matching is called **resonance,** which is a common physical process that can be more generally defined as the phenomenon that results when applied frequency equals that of a natural system. (Note that this is an entirely different use of the word than when it is used to describe electron distribution in π and p orbitals.)

Relaxation Nuclei that have been excited to the higher spin state thermally lose energy to their environment and return to the lower energy state, that is, alignment *with* the external field. You can experimentally observe this phenomenon by feeling the higher temperature of the NMR tube after recording a spectrum. This return to the lower spin state is called **relaxation.**

Saturation Relaxation and excitation occur simultaneously at resonance. That is, some nuclei are relaxing at the same time that others are being excited. In order to observe an NMR spectrum there must be a net absorption of energy. If the population of protons in the

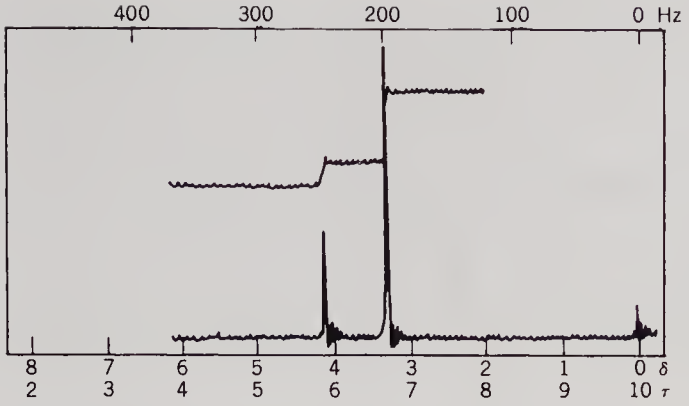


FIGURE 16.3 NMR spectrum of methanol. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

higher spin state becomes equal to that in the lower spin state there can be no further absorption of energy, and **saturation** is said to occur. When saturation prevails, peaks like those in Figure 16.3 will not be recorded.

Relaxation and Peak Width

The relaxation time is important to the appearance of the spectral peaks that you observe, for example, in Figure 16.3. The width of the peak is inversely proportional to the average time that the protons spend in the higher spin state. That is, long times spent in the excited state yield narrow spectral peaks; short-lived high-spin states produce wide peaks. In neat liquids, solutions, and gases, the relaxation time is of the correct duration to produce the reasonably narrow peaks required for good analysis. Relaxation times are shortened by the presence of paramagnetic molecules or ions like O_2 or Fe^{2+}; and also by the presence of certain nuclei, like those of nitrogen, which have magnetic quadrupoles rather than simple dipoles.

16.2 INSTRUMENTATION

Figure 16.4 is a schematic drawing of an NMR spectrometer. The sample is put in a tube placed between the poles of a strong magnet of known strength, H_0, most commonly 14,092 gauss. [A gauss (G) is a cgs unit equal to one line of magnetic flux per centimeter squared.] The rf oscillator uses the applied rf energy, $h\nu$, to generate a secondary oscillating magnetic field that interacts with the protons' angular velocity of precession. The oscillator frequency for 14,092 G magnet is in the neighborhood of 60 MHz (60 million cps). The sweep generator allows the magnetic field, H_0, to be changed slightly in a precise and continuous way. The rf receiver and detector pick up the radiation after it has passed through the sample. The detector notes the difference in rf energy before and after passing through the sample and sends this information to the recorder, which traces out the spectrum on chart paper.

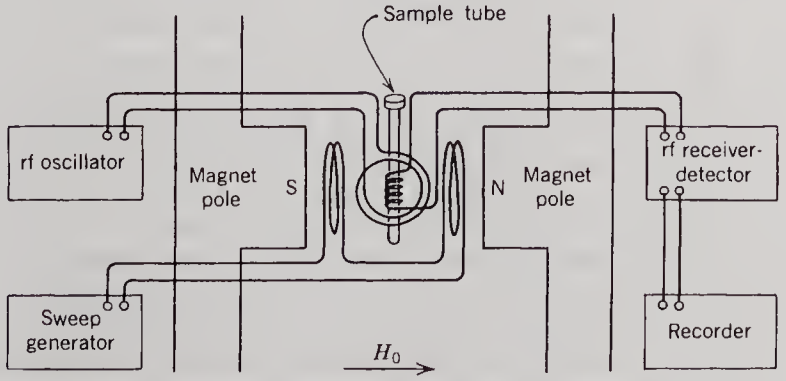


FIGURE 16.4 Schematic drawing of an NMR spectrometer. Varian Associates, Instrument Division.

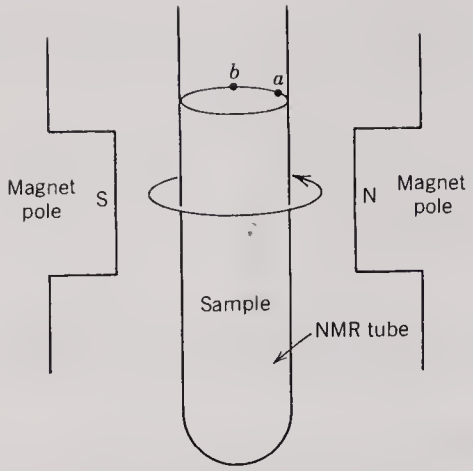


FIGURE 16.5 Sample spinning and homogeneity.

Homogeneity

To obtain good spectra, the magnetic field must be very homogeneous. That is, the field must be equal strength in all regions of the sample. A necessary condition is that of clean, flat, highly polished magnetic poles. But equally important is the location of the various protons. Only in the exact center of the sample tube can all protons experience the same field. Figure 16.5 demonstrates that protons at points *a* and *b* are different distances from the two magnetic poles and therefore do not experience the same field strength. The inhomogeneity due to proton positions can be negated by spinning the sample at a frequency (rps) which is at least equal to the rate of precession of the nuclear magnets. In practice, it is made to spin somewhat faster than that in order to overcome the effects of frictional drag. The spinning averages out the positions of the protons in the sample so that they seem to be in one position.

16.3 NMR SPECTRA

Figure 16.3 is an example of an NMR spectrum along with its integral curve. The spectrum consists of the vertical peaks, and the integral curve is the line with the alternating horizontal and vertical portions. Each group of vertical peaks constitutes a **signal** whose position in the spectrum is characteristic of the kind of proton. The strength of the magnetic field is indicated along the top of the chart paper in cycles per second (Hertz or Hz) and along the bottom in parts per million (ppm) on the **delta scale,** (d). We refer to the left side of the spectrum as **downfield** and the right side as **upfield.**

rf Sweep Versus Field Sweep

There are two ways that spectrometers can bring a proton into resonance: by holding the applied field, H_0, constant and using an rf sweep or by holding the rf energy constant and using a field sweep. **Sweep** in this context means to continually change the rf energy or magnetic field strength in small increments from one end of the spectrum to the other. Figure 16.3 is an NMR spectrum of methanol (methyl alcohol). Using this spectrum as an example, let us first consider an **rf sweep.** In the magnetic field of 14,092 G for a 60-MHz instrument, 60,000,000 Hz causes resonance of the protons used as a standard; and this point is taken as 0. When the rf energy reaches 60,000,200 Hz the methyl protons come into resonance at a point corresponding to 200 Hz on the scale at the top of the NMR paper. As the sweep continues and reaches 60,000,247 Hz the hydroxy proton comes into resonance at a point corresponding to 247 Hz on the upper scale. What you are observing is that higher rf energy is required for downfield protons than for upfield protons. The delta scale at the bottom of the chart paper also reflects this increase in energy from upfield to downfield.

However, from a mechanical and electronic standpoint, it is difficult to generate rf energy which can be changed accurately in very small increments. Magnetic field strengths, however, can be changed very precisely. Therefore it is more appropriate to

hold the rf energy constant and to sweep through magnetic field strengths. So, in a **field sweep** for an instrument with rf energy held constant at 60 MHz, the external magnetic field changes from 14,091.86 to 14,092.00 G, which corresponds to 600 and 0 Hz, respectively. Notice that magnetic field strength increases from left to right even though the numbers increase from right to left. In other words, the chart paper is designed as if an rf sweep were being used. When the applied field is swept, the delta and frequency scales have negative values, although they are never reported that way. Because of this, however, a third scale of numbers was devised: the tau (τ) scale. The **tau scale,** like the delta scale, has ppm for units. Although it is rarely used anymore, you should be aware of it because you will find it in some of the older NMR literature. Tau is related to delta by

$$\tau = 10.0 - \delta \tag{16-1}$$

Many of the spectra in this book have a tau scale at the top of the spectrum.

When analyzing an NMR spectrum there are basically four kinds of information we look for: the number of signals, their spectral positions, the way they are split, and their integration. All of these are discussed in your lecture text.

16.4 ANALYSIS OF SPECTRA

Procedure To analyze an NMR spectrum, you will find the following stepwise sequence helpful.

1. Note how many kinds of protons are present by counting the numbers of signals exclusive of the TMS (tetramethylsilane standard) signal at zero. For example, the spectrum of diethyl ether in Figure 16.6 shows three signals, one of which belongs to TMS. Therefore, there are two kinds of protons in diethyl ether, one centered at 3.4 ppm, and one at 1.1 ppm.
2. Note the spectral positions of the signals and try to deduce the environment of the proton. This is easiest to do if you have additional information available like a molecular formula to tell you what atoms are present or an IR spectrum to suggest what functional groups are in the molecules. If you have no other information, the best you can do is make an educated guess based on study of the compound classes that follow or based on tables of proton chemical shifts. For example, the signal at 3.4

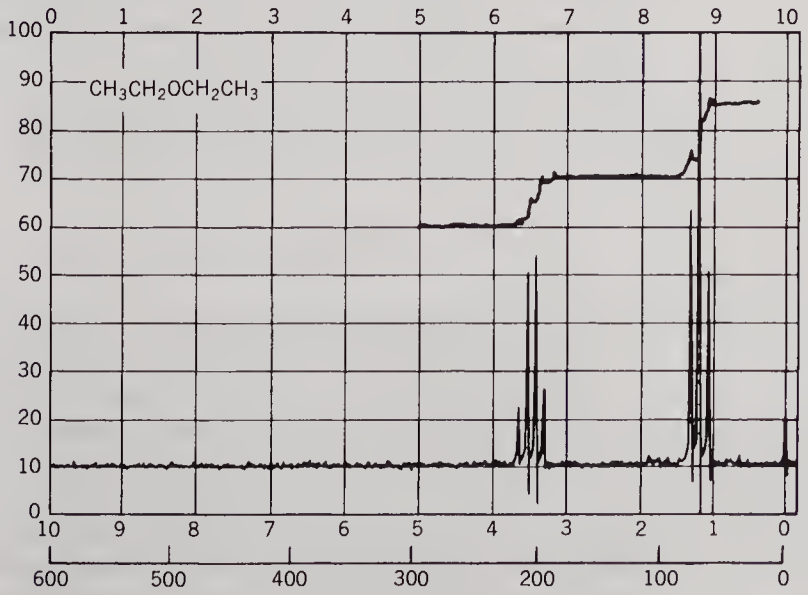


FIGURE 16.6 NMR spectrum of diethyl ether. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

ppm in Figure 16.6 suggests the presence of protons on carbon near halogen or oxygen such as would be found in an alkyl halide, ether, or alcohol.

3. Determine the relative numbers of protons by examination of the integration line. Areas under the curves are measured electronically by an integrator and plotted on the spectrum as a stepped line like that shown in Figure 16.3 or 16.6. The horizontal portion of the integral line between signals is an integral **base line.** The vertical distances between base lines (integrals) gives us a way of finding the *relative* numbers of protons in a compound; so for an integration line to be of value, there must be two or more kinds of protons. In using integral ratios you must be aware that integrals might be as much as 10% in error. Measuring from base line to base line for the integral at 3.4 ppm in Figure 16.6 gives 30.2 mm, and for the integral at 1.1 ppm gives 45.2 mm. Division of 45.2 by 30.2 yields a proton ratio of 1.50/1.00; using the multiplier 2 tells us the proton *ratio* (not the actual number of protons) is 3/2. If at this point you know the molecular formula, you can convert the *relative* ratio to the *actual* ratio. The molecular formula for diethyl ether is $C_4H_{10}O$; so divide the actual number of protons, 10, by the sum of protons in the relative ratio (3 + 2 = 5), obtaining the quotient 2. This quotient tells you there must be an actual ratio of protons twice as great as the relative ratio, that is, the actual ratio of protons must be 6/4.
4. Analyze the first-order splitting to determine how many protons are near the proton whose signal is being split. In Figure 16.6, we see that the signal at 3.4 ppm is split into four peaks; therefore there are 4 − 1 = 3 nearby protons. The signal at 1.1. is split into a triplet; therefore there are 3 − 1 = 2 nearby protons. Notice that the coupling constants are the same and that peak height asymmetries point toward each other.

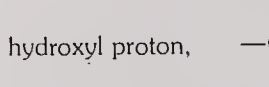
Assign a structure for the unknown compound that is completely in agreement with *all four* points of the analysis. If the structure is not consistent with each point, it is not the correct structure.

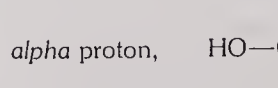
Functional Groups

The following compound classes are arranged alphabetically, and all chemical shifts are given on the *delta* scale.

Alcohols

Please refer to Figure 16.3, which shows the spectrum of methanol (methyl alcohol). The electronegativity of oxygen shifts downfield the signal of both hydroxyl proton and the proton on carbon bound to oxygen:

hydroxyl proton,  0.5–6.0 ppm

alpha proton,  3.3–4.0 ppm

The wide variation in chemical shift for hydroxyl proton depends on the extent of hydrogen bonding, hence on concentration, solvent, and temperature.

Another phenomenon related to hydrogen bonding is the proton exchange that occurs among hydroxyl protons of alcohol molecules:

$$ROH_a + R^1OH_b \rightleftharpoons ROH_b + R^1OH_a \qquad (16\text{-}2)$$

This occurrence is particularly evident when traces of acid are present. The result is that there is no spin-spin splitting involved with a hydroxyl proton either for the signal of the hydroxyl proton itself or with a nearby proton. The reason is that the proton exchange

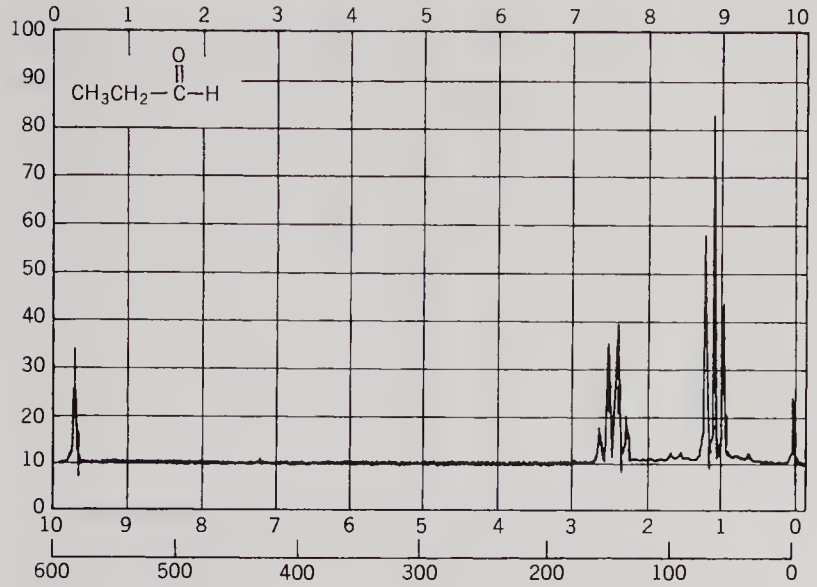


FIGURE 16.7 NMR spectrum of propanal. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

rate is fast relative to the time required to flip a spin. Notice that in the spectrum of ethanol there is no splitting for the hydroxylic proton at 2.6 ppm; also that the splitting of the methylene proton signal at 3.7 ppm into a quartet is due only to the three methyl protons. In absolutely pure, anhydrous alcohols splitting is observed because the rate of proton transfer is relatively slow in absence of acid and water.

It is relatively easy to tell which proton, if any, in an NMR spectrum is hydroxylic. After obtaining the spectrum, put one or two drops of D_2O in the tube and shake it vigorously for a couple of minutes, during which time deuterium will exchange with the alcohol hydroxylic proton:

$$ROH + D_2O \rightleftharpoons ROD + HOD \qquad (16\text{-}3)$$

A second spectrum will then show the absence of the hydroxylic proton because deuterium absorbs rf energy in a different rf region. Another simple procedure that is often effective requires only that the concentration of alcohol be changed five- to tenfold. A second spectrum will show the signal of the hydroxylic proton at a different chemical shift whereas the other signals remain in the same place.

Aldehydes

As the NMR spectrum of propanal (propionaldehyde) in Figure 16.7 indicates, there are two notable chemical shifts to be observed for aldehydes:

alpha proton, **H**—C—C(=O)—H 2.0–2.7 ppm

aldehydic proton, R—C(=O)—**H** 9.5–9.6 ppm

The downfield shift for the *alpha* proton is due to the electronegativity of carbonyl oxygen. Oxygen also causes part of the downfield shift for the aldehydic proton, but the remainder is due to paramagnetic anisotropy in which the aldehydic proton is deshielded. Although it is possible for a carboxylic proton to absorb in this region, it is generally a little farther downfield (10–11 ppm); therefore, a chemical shift around 9.5 is usually indicative of an aldehyde.

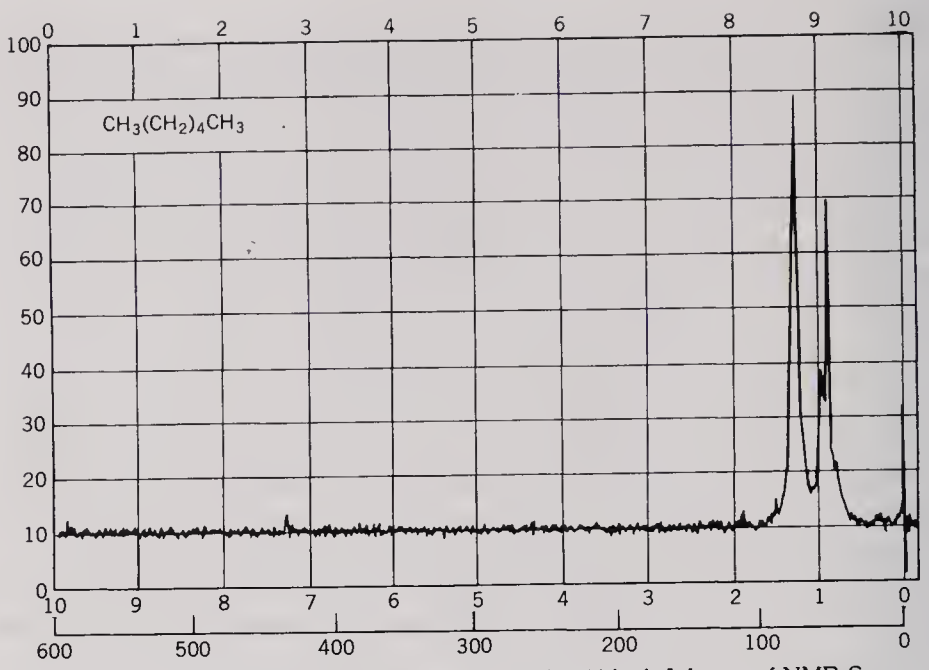


FIGURE 16.8 NMR spectrum of hexane. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Alkanes

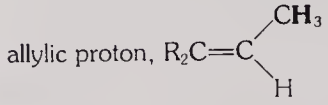
The spectrum of hexane in Figure 16.8 is typical of an alkane. Because the signals of similar kinds of protons are so close they generally overlap and produce complex multiplets that are difficult to interpret. In the absence of nearby functional groups, alkyl protons have chemical shifts as follows:

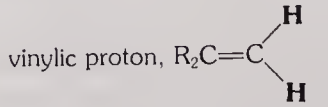
1°, RCH_3	0.8–1.0 ppm
2°, R_2CH_2	1.2–1.4 ppm
3°, R_3CH	1.4–1.7 ppm

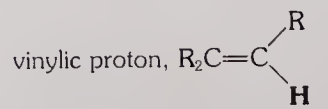
Cyclic alkanes have NMR spectra similar to those of open chain alkanes. The chemical shifts of equatorial protons are about 0.1 to 0.7 ppm downfield from those of axial protons.

Alkenes

Please refer to Figure 16.9, the NMR spectrum of cyclohexene. It contains two absorptions typical of alkenes:







The downfield shifts compared to alkane protons are due to paramagnetic deshielding. The anisotropic effect is similar to that for aldehydes, but the downfield shift is not as large because there is no electronegative atom present. The deshielding is greater for the vinylic protons than for allylic protons because, being closer to the circulating pi

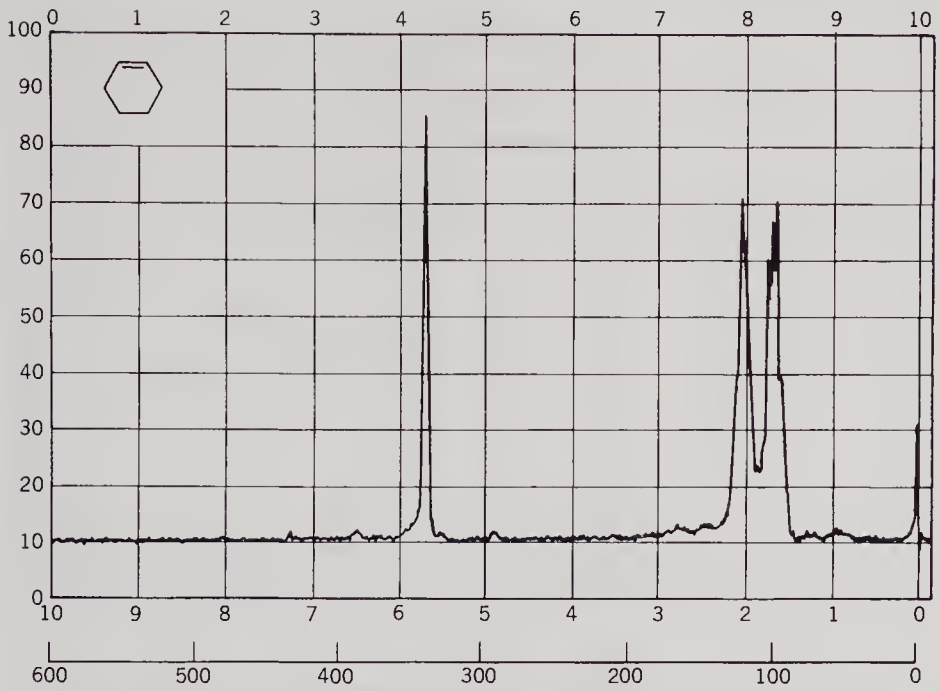


FIGURE 16.9 NMR spectrum of cyclohexene. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

electrons, they are in a stronger part of the induced field. This effect is depicted in Figure 16.10. Vinylic and allylic proton signals are shown in Figure 16.12.

Alkyl Halides

Figure 16.11, the NMR spectrum of 1-bromopropane (*n*-propyl bromide), illustrates the downfield shift characteristic of the presence of halogen. The chemical shifts due to halogens on the same carbon as the proton are

RCH_2—Cl	3.6–3.8 ppm
RCH_2—Br	3.4–3.6 ppm
RCH_2—I	3.1–3.3 ppm

The protons separated from halogen by one or more carbons are less influenced by the electronegativity of halogen and have their chemical shifts only slightly downfield from the corresponding alkane absorptions. So, in the 1-bromopropane spectrum, the triplet

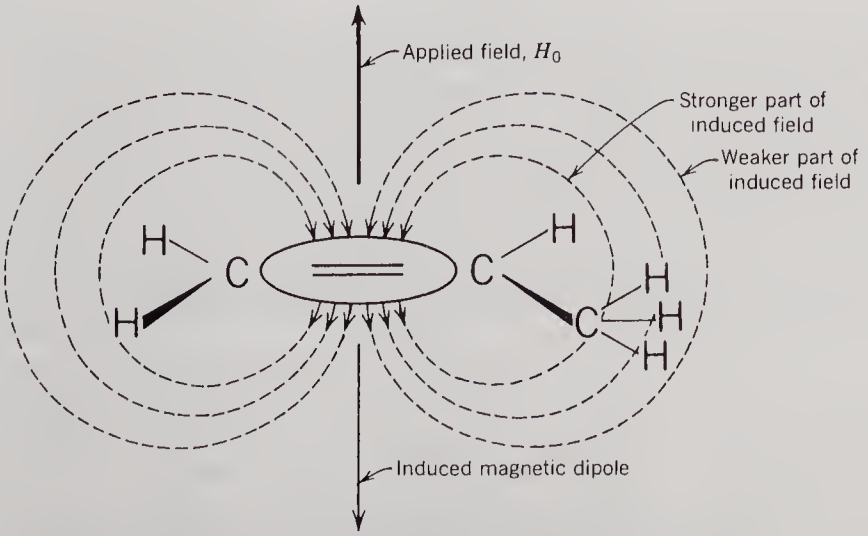


FIGURE 16.10 Paramagnetic deshielding of vinylic and allylic protons.

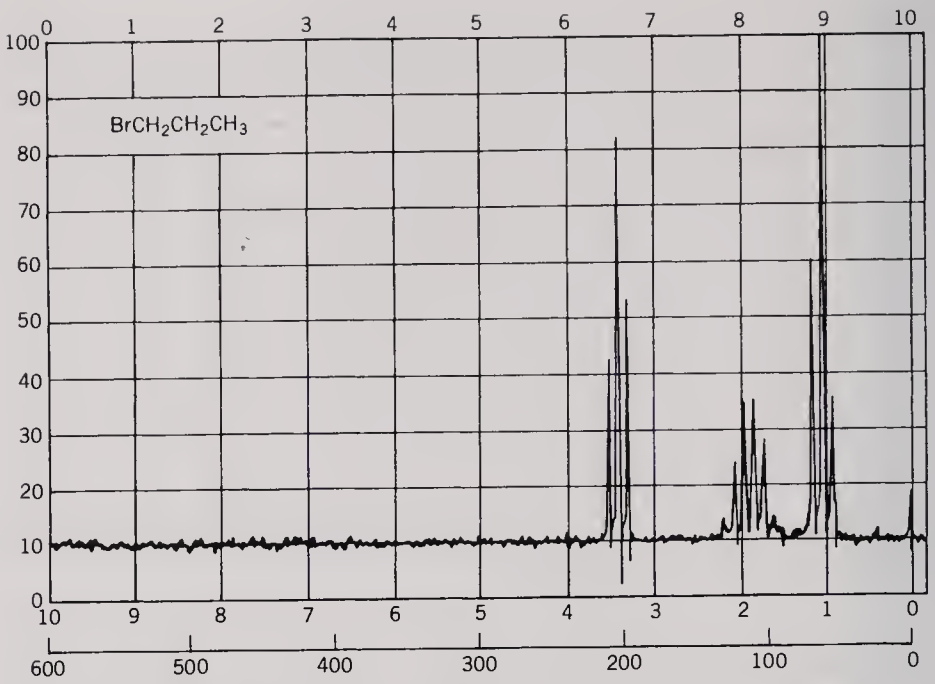


FIGURE 16.11 NMR spectrum of 1-bromopropane. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

farthest downfield must belong to the protons on the halogen-bearing carbon, the triplet farthest upfield must belong to the methyl protons, and the multiplet in between must be that of the methylene protons on carbon once removed from halogen.

Alkynes

Please see Figure 16.12, the NMR spectrum of 2-methyl-1-buten-3-yne. It contains one of the two chemical shifts most characteristic of terminal alkynes:

propargylic proton,	H—C≡C—$\mathbf{CH_3}$	1.8–2.5 ppm
acetylenic proton,	R—C≡C—**H**	2.5–3.1 ppm

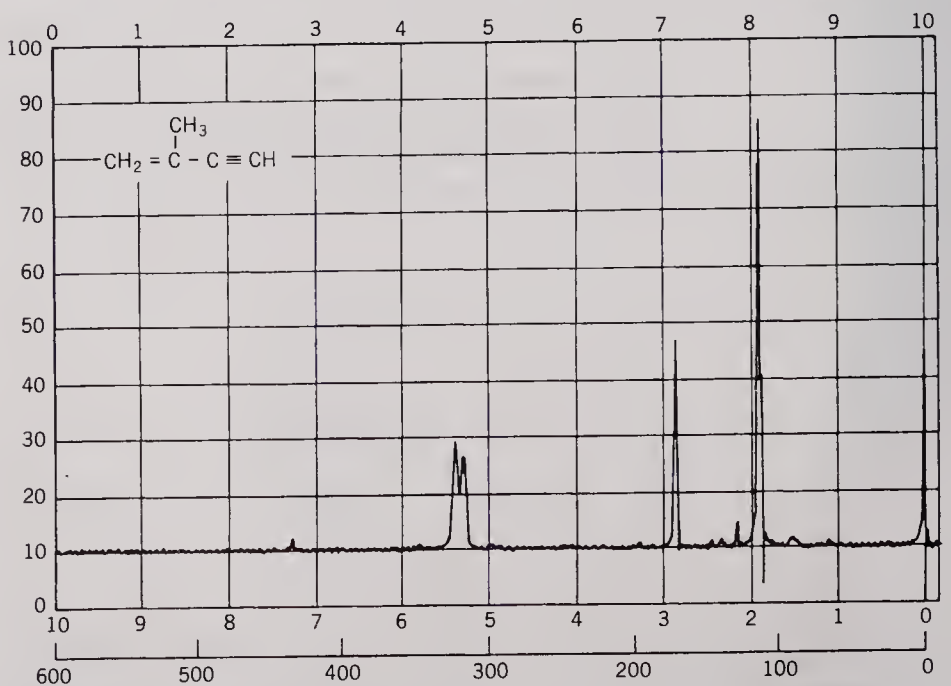


FIGURE 16.12 NMR spectrum of 2-methyl-1-buten-3-yne. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

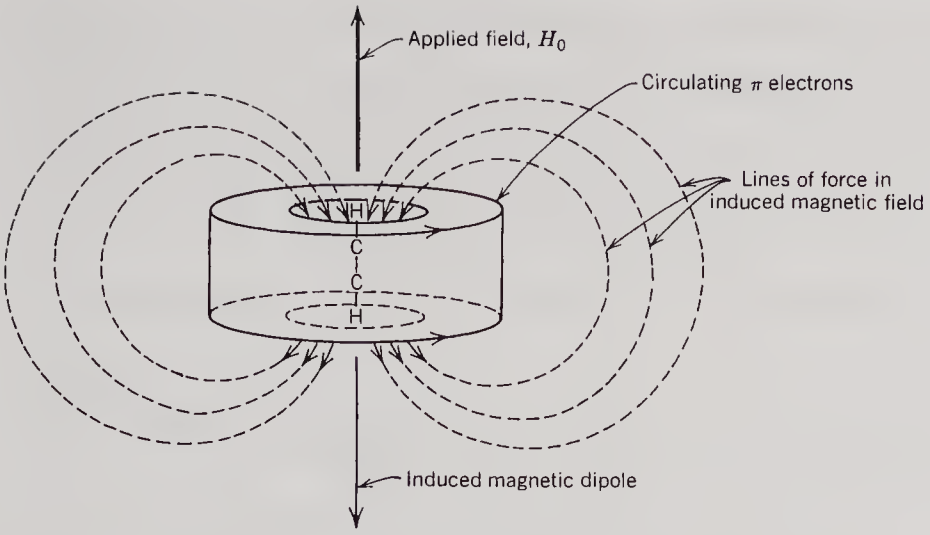
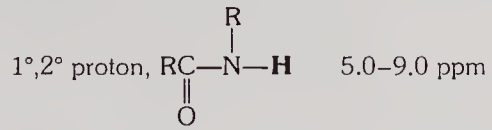


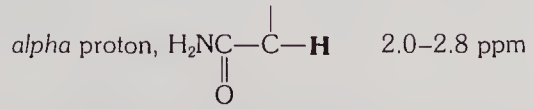
FIGURE 16.13 Magnetic field of ethyne. From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974, p 168. Reprinted by permission.

Propargylic protons, like allylic protons, have their chemical shifts somewhat downfield from those of alkane methyl groups because of *paramagnetic deshielding,* the result of ring currents depicted in Figure 16.13. Acetylenic protons, on the other hand, absorb farther upfield than vinylic protons because of *diamagnetic shielding,* also the result of the same ring currents. The splitting of the acetylenic proton signal into a triplet at 1.9 ppm in the spectrum of Figure 16.12 is the result of longer range coupling through the pi bond to the vinyl proton with its signal at 5.3–5.4 ppm.

Amides

Figure 16.14 is the NMR spectrum of acetanilide (IUPAC *N*-phenylethanamide), which contains the characteristic amide absorptions





The absorption of amido protons is well downfield because of the electronegativities of nitrogen and carbonyl oxygen and paramagnetic deshielding. Their signals are broad and unsplit because of the interaction of the protons with three continually changing spin states of the *nitrogen* nucleus. Sometimes the signal is so broad that it is hardly observable. Thus the spectrum of acetanilide shows a low, broad hump at 8.9 ppm for the amido proton.

The methyl protons *alpha* to carbonyl have a singlet for their signal, because there are no protons on adjacent atoms. The multiplet centered at 7.3 is due to aromatic proton signals.

Amines

The characteristic amino proton absorptions are

alkyl,	RNH_2, R_2NH	0.5–3.5 ppm
aryl,	$ArNH_2$, Ar_2NH	3.0–5.0 ppm

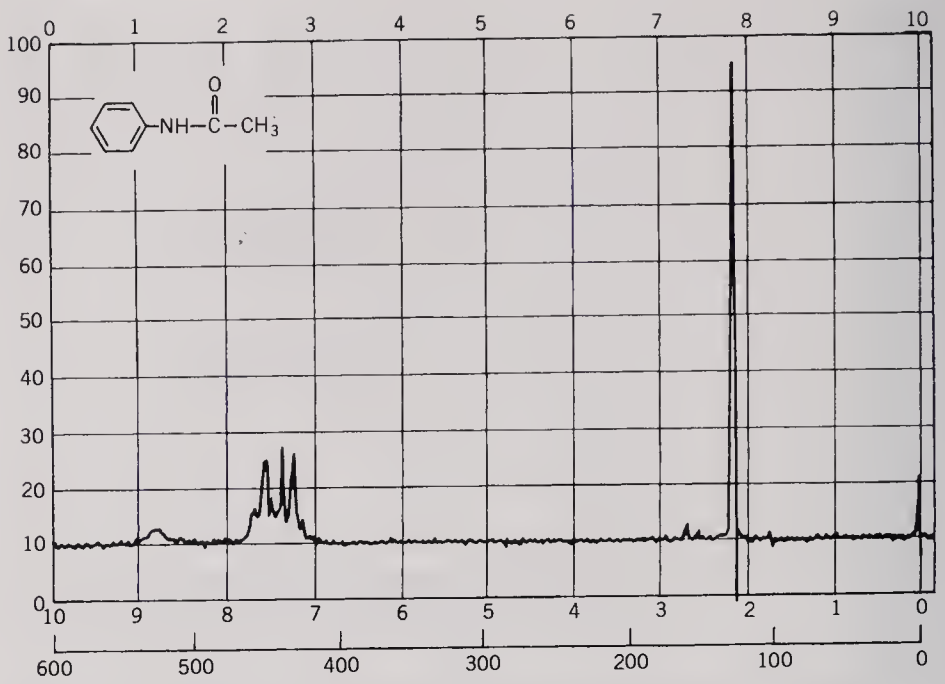


FIGURE 16.14 NMR spectrum of acetanilide. From the Aldrich Library fo NMR Spectra, Edition 2, Charles J. Pouchert.

The proton on a nitrogen, like that on an oxygen, can undergo chemical exchange in presence of trace amounts of acid:

$$R_2\ddot{N}—H + H^1—A \rightleftharpoons R_2\overset{\overset{H^1}{|}}{\overset{\oplus}{N}}H + A^{\ominus} \rightleftharpoons R_2\ddot{N}—H^1 + H—A \qquad (16\text{-}4)$$

The rate at which the proton transfers occur, and solvent characteristics, temperature, and concentration of amine determine the character of the N—H signal. If exchange is rapid, as it is for most *aliphatic amines*, the N—H proton is decoupled from the nitrogen atom and from neighboring protons, and a sharp singlet arises in the spectrum. Figure 16.15 for diethylamine (IUPAC *N*-ethylethanamine) typifies this effect. Notice the small N—H singlet at 0.8 ppm just to the right of the triplet. Notice also that the methylene

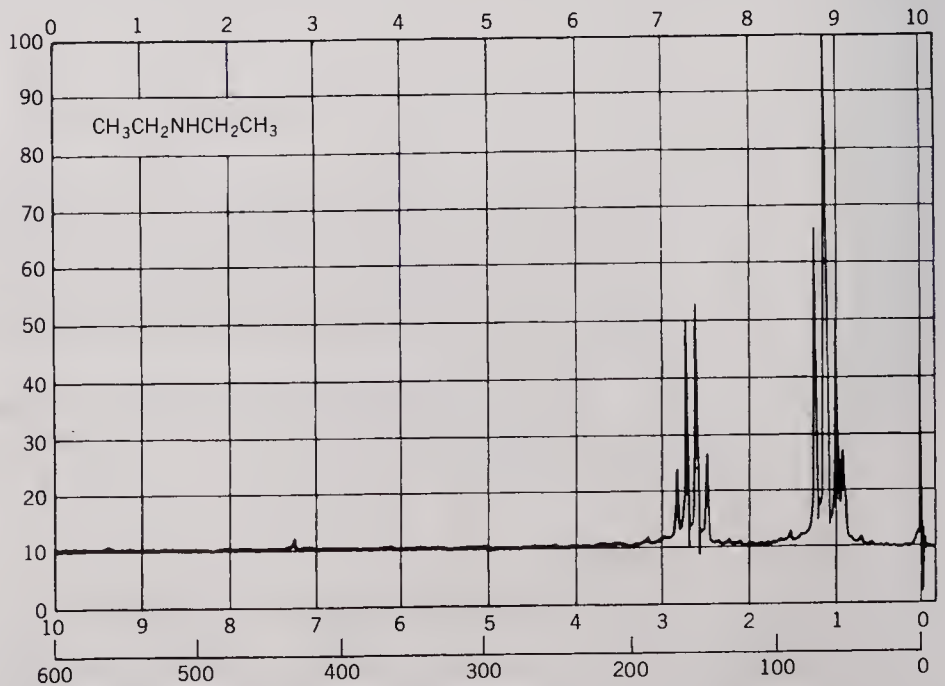


FIGURE 16.15 NMR spectrum of diethylamine. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

proton signal at 2.7 ppm is split into a quartet only by the methyl protons and not by amino proton.

At slower chemical exchange rates, the N—H peak is broader. Pyrroles, indoles, and some aromatic amines fall into this category.

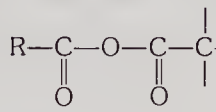
Protons on the nitrogen atom of *amine salts* exchange slowly, and hence absorb as a broad peak downfield from amino hydrogen signals:

ammonium proton	6.0–8.5 ppm

The ammonium protons are coupled to protons on adjacent carbon atoms.

Anhydrides

The typical NMR absorption is like that for other similar carbonyl compounds:

alpha proton,  2.0–2.8 ppm

This chemical shift is the result of the electronegativity of the oxygen atoms and paramagnetic deshielding.

Aromatics

We see in Figure 16.16 that the pi electron ring current in benzene produces a strong paramagnetic deshielding for phenyl protons, and for aromatic protons generally.

Also, to a much lesser extent, it affects the chemical shifts of benzylic protons,

unsubstituted phenyl protons	7.2 ppm
benzylic protons	2.2–2.5 ppm

In general, electron-withdrawing substituents shift aromatic proton absorptions downfield from 7.2 ppm and electron donor groups shift them upfield. Sometimes, protons *ortho, meta,* and *para* to a substituent have chemical shifts similar enough that one peak appears for their absorptions, but this is often not the case.

Figure 16.17 is the NMR spectrum of toluene. The signal at 2.35 ppm is due to the benzylic protons, and that at 7.2 belongs to phenyl protons. See also the other aromatic spectra: benzoic acid (Figure 16.18), methyl benzoate (Figure 16.19), and *p*-methoxyacetophenone (Figure 16.20).

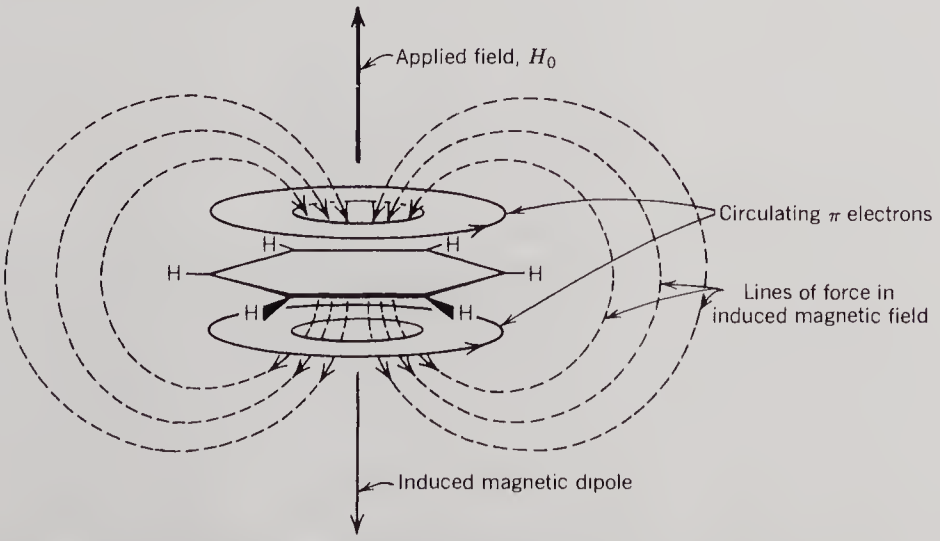


FIGURE 16.16 Magnetic field of benzene. From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds,* 3rd ed.; Wiley: New York, 1974, p 168. Reprinted by permission.

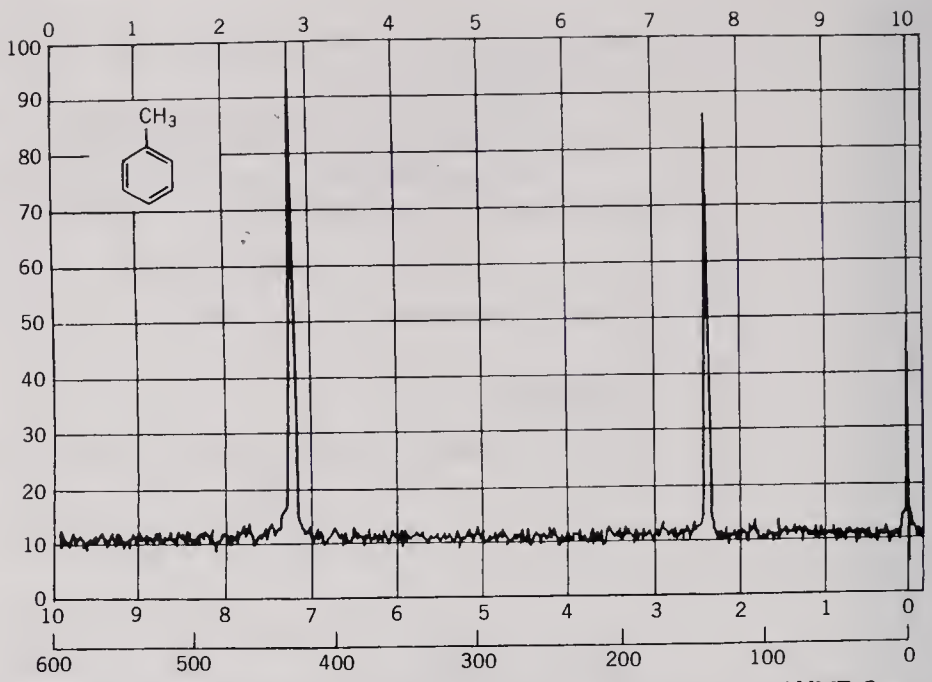


FIGURE 16.17 NMR spectrum of toluene. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

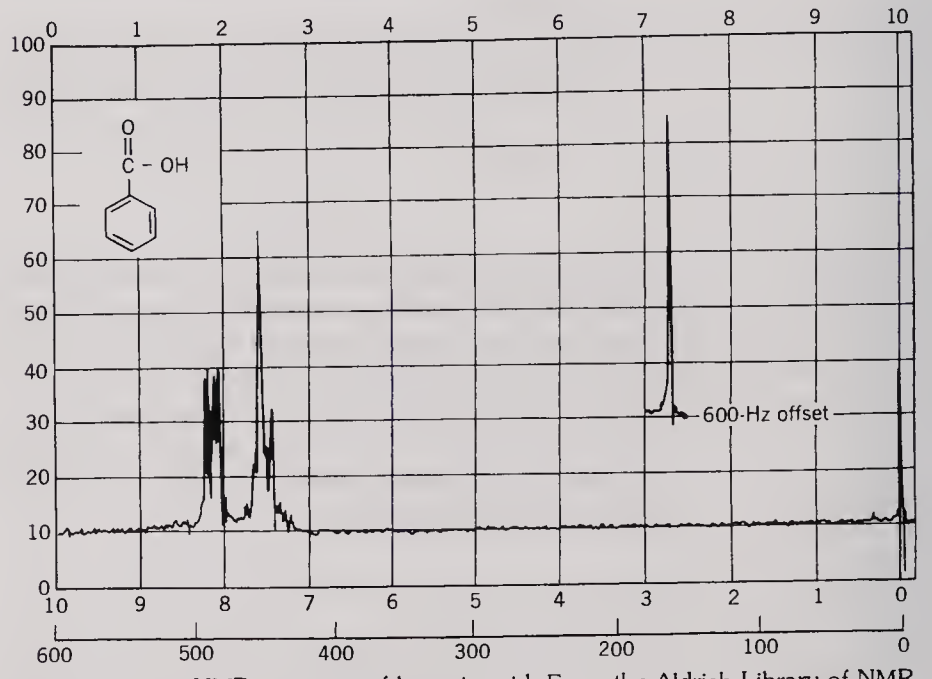


FIGURE 16.18 NMR spectrum of benzoic acid. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Carboxylic Acids

Please refer to Figure 16.18, the NMR spectrum of benzoic acid. This spectrum exhibits one of the two typical features of carboxylic acid spectra:

carboxyl proton, R—C(=O)—O—**H** 10.0–13.2 ppm

alpha proton, HOC(=O)—C(—**H**)— 2.0–2.8 ppm

The carboxyl proton behaves in the same way as does the hydroxyl proton of

alcohols, but its shift is farther downfield because of resonance withdrawal of electron density into the carbonyl and to a lesser extent because of paramagnetic deshielding. This chemical shift is variable, depending on solvent and temperature, but depends only slightly on concentration. This proton undergoes exchange readily with other acidic protons like those of water and alcohols. The width of the carboxyl singlet ranges from sharp to broad, depending on the rate of exchange.

If it is necessary to determine which absorption belongs to the carboxyl proton, the same procedure can be used as was described for the hydroxyl proton of alcohols.

The *alpha* proton chemical shift is typical of that for other carbonyl compounds.

Carboxylic Acid Halides

The NMR absorption of *alpha* protons is like that for other similar carbonyl compounds because of proximity of electronegative atoms and paramagnetic deshielding.

alpha proton, $X-\underset{\underset{O}{\|}}{C}-\underset{|}{C}-\mathbf{H}$ 2.0–2.8 ppm

Esters

The characteristic chemical shifts for esters are those resulting from *alpha* protons on both acid and alcohol portions of the ester:

alcohol *alpha* proton, $RC(=O)-O-\underset{|}{C}-\mathbf{H}$ 3.3–4.0 ppm

acid *alpha* proton, $ROC(=O)-\underset{|}{C}-\mathbf{H}$ 2.0–2.8 ppm

Figure 16.19 is the NMR spectrum for methyl benzoate. The singlet at 3.9 ppm is due to the methoxy protons; the multiplet at 7.2–7.6 ppm is due to *meta* and *para* protons; and that at 7.9–8.1 ppm is due to *ortho* protons, shifted downfield because of resonance and inductive withdrawal of electrons by the carbonyl. Notice how the mul-

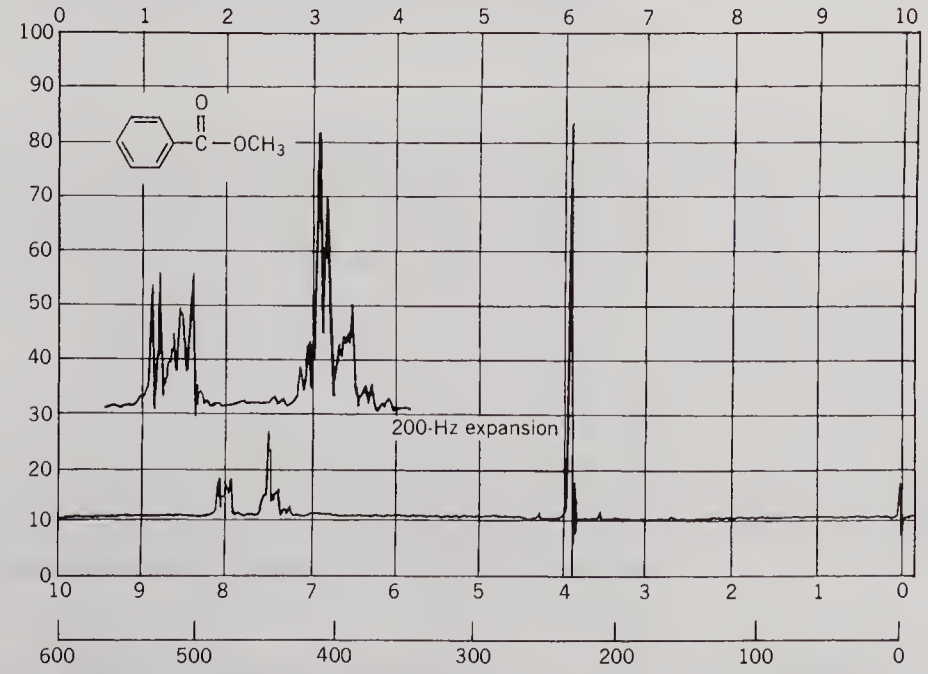


FIGURE 16.19 NMR spectrum of methyl benzoate. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

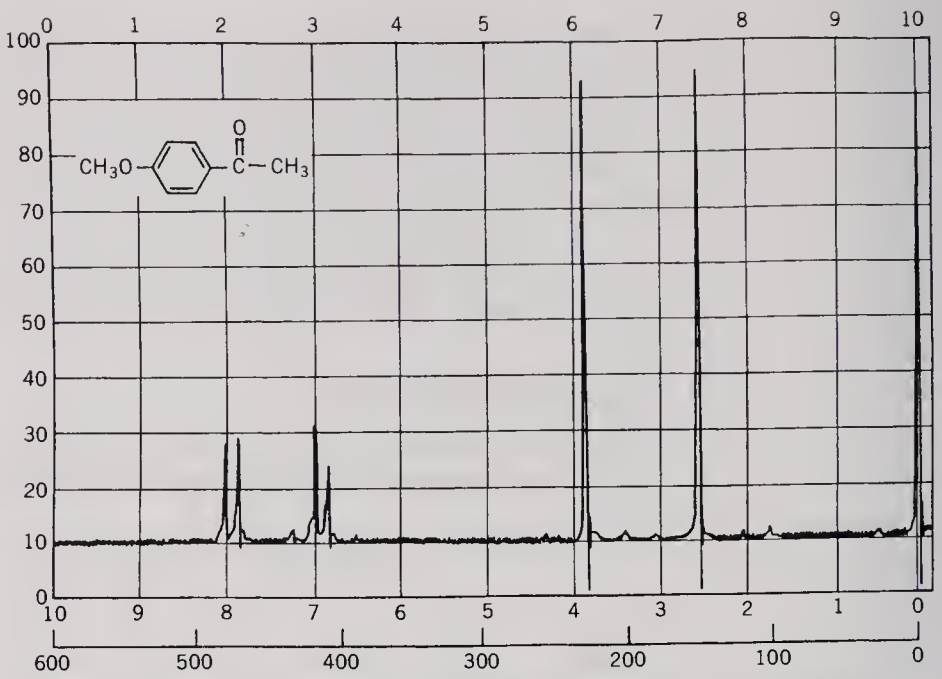


FIGURE 16.20 NMR spectrum of *p*-methoxyacetophenone. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

tiplets have been expanded to give greater detail by using a 200 Hz rather than a 600 Hz sweep.

Ethers

The characteristic absorption for ethers is that of the alpha protons, typified by the NMR spectrum of diethyl ether in Figure 16.6.

alpha protons, R—O—C—**H** 3.3–3.9 ppm

The shift downfield from typical alkyl absorptions is due to the electronegativity of oxygen.

See also the spectrum in Figure 16.20 for 1-(4-methoxyphenyl)ethanone (*p*-methoxyacetophenone), an aromatic ether-ketone.

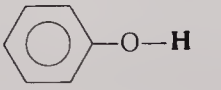
Ketones

The typical NMR absorption for ketones is due to the *alpha* protons, whose chemical shift is downfield from alkyl protons. The downfield shift is the result of the electronegative oxygen in the carbonyl and paramagnetic deshielding. The singlet at 2.55 in the spectrum of *p*-methoxyacetophenone (Figure 16.20) is due to the protons next to carbonyl carbon.

alpha proton, R—C(=O)—C—**H** 2.0–2.8 ppm

Phenols

The NMR spectrum of phenol at 5% concentration is shown in Figure 16.21. The hydroxylic proton shift is usually a sharp singlet, somewhat downfield from the hydroxyl proton of an alcohol because of resonance delocalization of electrons from oxygen into the ring. The position of absorption of the hydroxylic proton is highly dependent on concentration, ranging from 4.4 ppm at 1% to 7.4 ppm at 100%.

hydroxyl proton,  —O—**H** 4.0–7.7 ppm

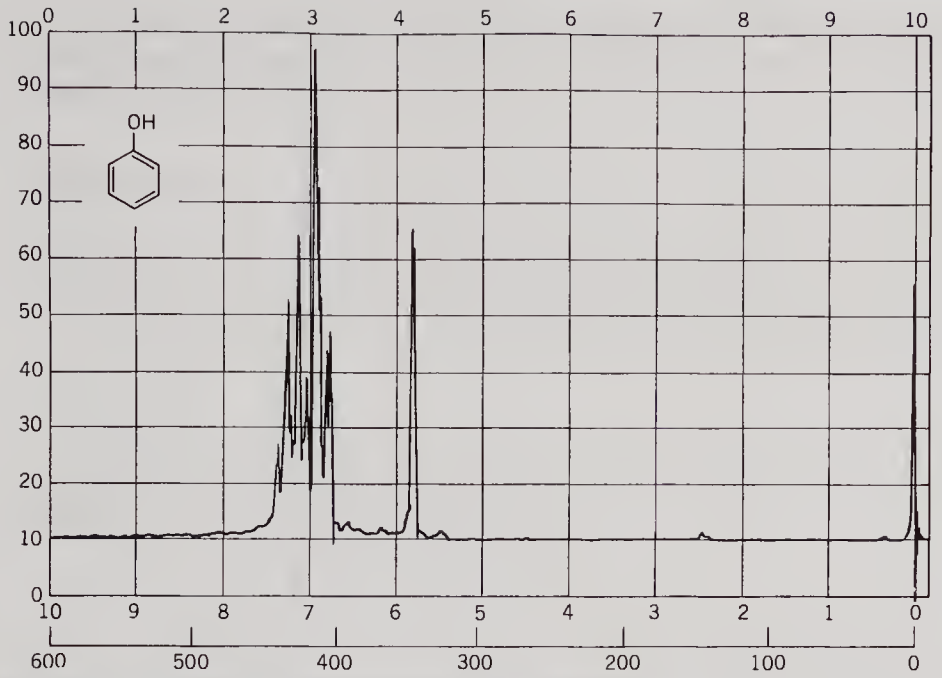


FIGURE 16.21 NMR spectrum of phenol. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

The position of the absorption varies with solvent, temperature, concentration, and other ring substituents. If it is necessary to determine which absorption belongs to the hydroxyl proton, the same procedures can be used as were described for the hydroxyl proton of alcohols.

Figure 16.21 is a spectrum of phenol at 5% concentration. The hydroxylic proton absorption at this concentration is the peak at 5.8 ppm. *Ortho* and *para* phenyl proton absorptions are somewhat upfield from the pure phenyl absorption at 7.2 because resonance donation of oxygen's electrons to the ring causes a greater shielding of the phenyl protons.

Anomalous Peaks

Almost always, spectra will exhibit certain peaks that have no meaning in terms of spectral interpretation.

Ringing

A regularly observed pattern of small peaks which you must ignore occurs in the phenomenon known as **ringing.** Ringing, also called relaxation wiggles, is a series of peaks of diminishing size which immediately follow singlet signals or peaks arising from first-order splitting. Figure 16.22 gives a good illustration of ringing. Ringing can be quite prominent when a fast sweep is made, and can be nonexistent for the same peaks at slow sweep. Actually, a symmetrical ringing pattern is an indication of good homogeneity.

The cause of ringing is related to the rate of nuclear relaxation. Recall that as soon as nuclei are excited from a low- to high-spin state, they start to relax as they lose energy to their surroundings. If the sweep rate (the number of ppm swept by per second) is slow, relaxation will be complete by the time a given peak is traced on the chart paper, and no ringing will be observed. On the other hand, if the sweep rate is fast, relaxation will be incomplete after the signal has been traced and the precessional frequency will be alternately in and out of phase with the rf frequency. Ringing is the recording of this phenomenon.

Satellites

A second kind of peak that you should disregard is the **spinning sideband,** or **satellite.** As shown in Figure 16.22, satellites always appear in pairs, one on each side of the

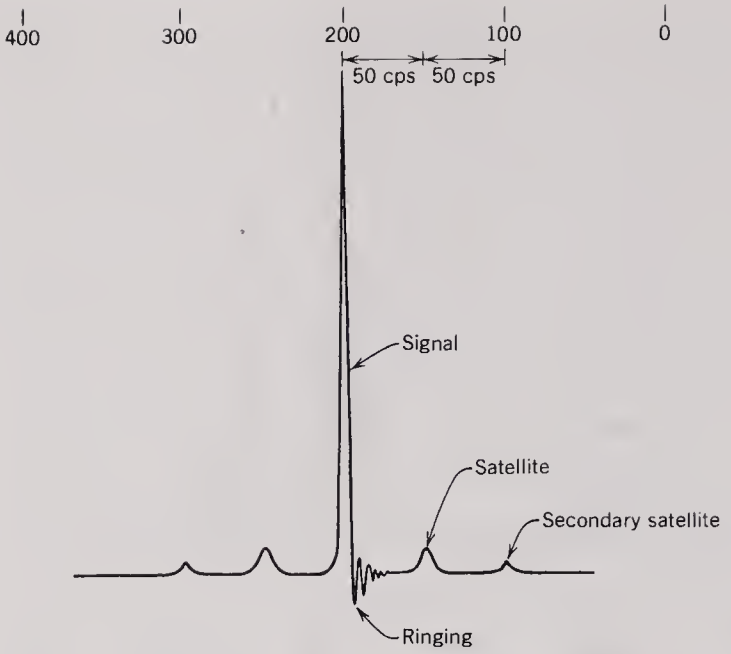


FIGURE 16.22 Satellites.

signal and equidistant from it. These satellites result from magnetic field inhomogeneities and are most noticeable when the sample tube is spun too slowly. Large spinning sidebands can also result from an improperly shaped NMR tube. If you use the Hertz scale of the chart paper to measure from the center of the signal to the first sideband, you find that the separation is equal to the rate of spin in cps. This makes it easy to identify spinning sidebands since their positions change as the sample spin rate changes.

It is also sometimes possible to observe secondary satellites at the same distance from the primary satellites as the latter are from the signal.

Deuterated Solvents

A third type of peak to disregard arises when deuterated solvents are used. Such solvents are never completely free of protons, and therefore give rise to small peaks. However,

TABLE 16.1 Some Useful NMR Solvents

Solvent	*Residual Proton Signal*[a]
$CDCl_3$	7.27
CD_3OD	3.47
	1.4
Acetone-d_6	2.10
D_2O	4.7[b]
p-Dioxane-d_8	3.70
Dimethylsulfoxide-d_6	2.62
Pyridine-d_5	7.6
	7.8
	8.60
Benzene-d_6	7.37
Acetic acid-d_4	11.37[b]
CCl_4	—
CS_2	—
Hexafluoroacetone	—

[a]Given on the *delta* scale in ppm relative to tetramethysilane.
[b]Highly variable, depending on solute and temperature.
From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compoudns*, 3rd ed.; Wiley: New York, 1974, Appendix F. Used with permission of John Wiley & Sons, Inc.

you can easily spot these peaks because you will know the chemical shift characteristic of the solvent you are using. Table 16.1 lists these residual proton signals for a number of deuterated solvents.

Electronic Noise

A fourth kind of peak occasionally arises as an artifact of **noise,** electronically induced vibrations of the recorder pen. If you suspect that a given peak is due to noise, make a second recording of the spectrum. The spurious peak should be absent.

Of course, noise increases as you increase the spectrum amplitude (Section 16.5).

Impure Samples

Impure samples will of course give rise to unexpected signals. The size of such signals is a reflection on your separations techniques.

16.5 THE TECHNIQUES

In brief, the technique involves preparing the sample and putting it into an NMR tube, recording the spectrum, and cleaning up.

Preparation of the Sample

Impurities

The sample to be analyzed should be as pure as possible because the recorded spectrum indicates the presence of impurities as well as the compound of interest. There are two kinds of impurities: (1) soluble materials which can give rise to NMR signals, and (2) insoluble particles such as filter paper fibers, dust, and fine metal fragments which might interfere with the homogeneity of the magnetic field. In the latter case ferromagnetic particles are especially a problem. They can arise from scrapings from spatulas against sintered glass funnels or even on test tube walls. Proper filtration is obviously important. You can often satisfactorily remove ferromagnetic materials by stirring the solution with a magnet.

Sample Form

If the substance to be analyzed is no more viscous than water, analyze it neat. Neat analysis produces a spectrum with taller peaks relative to base line noise (the tracings caused by a shivering pen). For the same reason, it is best to use as concentrated a solution as possible if a solution sample is required. A solution is necessary for solids and viscous liquids. However, it is a common practice to put nonviscous liquids into solution also, especially if not much of the liquid is available or if intermolecular interactions among the molecules of interest might cause line broadening or unexpected chemical shifts. Such interactions are most likely when hydrogen bonding or transfer is likely. You should be aware that chemical shifts change to some extent with concentration, subsequently requiring a shift correction of as much as 0.5 ppm. This is particularly a problem with aromatic solvents.

The solvent you select must satisfy several criteria: It must completely dissolve the sample because suspensions of solids produce broad peaks; it must be chemically inert; it should provide minimal interactions with the solute; and finally, it should have no protons that will produce an interfering spectrum. Tetrachloromethane (carbon tetrachloride) is the most common solvent. You can also use carbon disulfide. However, there are many organic compounds that are insufficiently soluble in these solvents, and require use of deuterated solvents, the most common of which is deuterated trichloromethane (chloroform). If you use deuterated solvents, you must be aware that residual

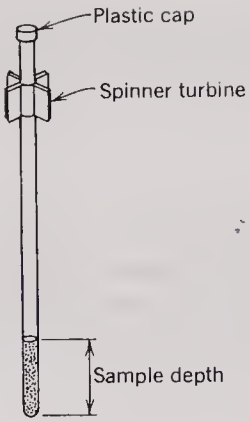


FIGURE 16.23 NMR tube with spinner.

protons from incomplete deuteration will give rise to small signals. Table 16.1 lists some useful NMR solvents.

In making a solution, the concentration is not critical (except as noted above). However, for a satisfactory spectrum, a minimum of 50–100 mg of compound per 0.5 ml of solvent is desirable. Otherwise the signal-to-noise ratio will be too low.

The minimum size sample that can be used with ordinary equipment is about 0.5 ml, whether neat or in solution. In a commercial NMR tube, this amount provides a column about 2.5 cm high. Smaller size samples are inadvisable because the small vortex due to spinning will be proportionately too large and create inhomogeneity in the critical region of the applied magnetic field. The depth of sample can be greater than 2.5 cm, but the tube should be no more than three-quarters full.

You can prepare a solution of nonviscous liquid directly in the NMR tube by "eyeballing" the measurements. An NMR tube, illustrated in Figure 16.23, is 0.3 to 0.8 cm in diameter and 15 cm long. Mentally mark on the tube the desired depth of the solution; then mentally divide the depth into five parts. Using a fine tip medicine dropper, fill the lower fifth of the tube with the liquid to be analyzed; then add solvent to the desired depth. Put the plastic cap on the tube and invert it several times to mix the contents thoroughly.

To prepare a solution of a very viscous liquid or of a solid, it is necessary to weigh the compound into a test tube or beaker and mix it with solvent prior to filling the NMR tube. The reason is that a very viscous liquid is difficult to get into an NMR tube; and it is difficult to estimate the volume of a powdered solid. Weigh about 0.3 g of compound for each milliliter of solvent.

Reference Standard

You must add the internal zero point reference standard, usually TMS, when preparing neat or solution samples. You need only a small amount of TMS because it has 12 protons. Because TMS boils at 26.5 °C it must be kept in a refrigerated, tightly stoppered bottle. You can best introduce TMS into a sample by adding two or three drops directly into the NMR tube just before obtaining the spectrum. Cool a clean, long-point medicine dropper or pipet in a refrigerator, draw a few drops of cold TMS into it, insert the long point into the NMR tube, and release the drops. *Immediately* cap the tube and invert it a few times to ensure good mixing. To avoid contaminating the TMS, *do not dip* the pipet back into the TMS after inserting it into the NMR tube. An alternate way for preparing solutions is to make the sample solutions from CCl_4 already containing 1 or 2% TMS. Such TMS/CCl_4 solutions in bulk must also be kept tightly stoppered and refrigerated.

Producing the Spectrum

In many chemistry departments beginning students are not permitted to use the NMR spectrometer. In such cases the instructor or a laboratory assistant operates the instrument to obtain the student spectra.

If your laboratory instructor expects you to record your own spectra, *you must receive special prior instruction.* Your instructor probably will not allow you to make homogeneity or coarse field adjustments but might expect you to be familiar with inserting and removing the sample, and with spectrum amplitude, sweep controls, and integration controls. Your instructor also might expect you to understand use of the spinner, and the rf field, filter, and phase controls. Alternately, your instructor might expect you to record your own spectrum once all controls have been set.

The NMR Tube

You must *take special care* not to break off the NMR tube in the instrument. You must follow your instructor's directions *exactly.*

Using the depth gauge supplied with the instrument, position a spinner turbine on the tube; then wipe the tube with a lint-free cloth. To prevent inhomogeneities, it is very important not to allow dust or lint to get on the faces of the magnet poles. Next, holding the tube directly and vertically over and almost in the opening of the tube holder (the sample probe) of the spectrometer, drop it in.

It is most likely that a tube will be broken when you are removing it from the sample probe. Remove the tube by holding one hand about the length of the tube above the tube holder opening, then eject the tube *completely* before gently grasping it. All movements must be made *slowly.* Depending on the model of the spectrometer, sit or stand directly next to the sample probe opening. Do *not* attempt to remove the tube from a sitting position somewhat removed from the sample probe.

Spinning Rate

The rate at which the NMR tube is spinning is very important. Figure 16.24 shows the effects on the resolution of two peaks under various spinning conditions. Notice that one broad peak (*a*) appears when the sample is nonspinning. If the sample is spinning too slowly you will observe two wide, poorly shaped peaks (*b*). The correct spinning rate produces two sharp, well-defined peaks (c). If the sample spins too rapidly, severe vortexing results (*d*). **Vortexing** is the production of a more or less conical indentation that appears at the top of a column of rapidly swirling liquid, such as that in a whirlpool. The problem with vortexing is that air is drawn down into the sample, creating an inhomogeneity because of the paramagnetic character of molecular oxygen and because

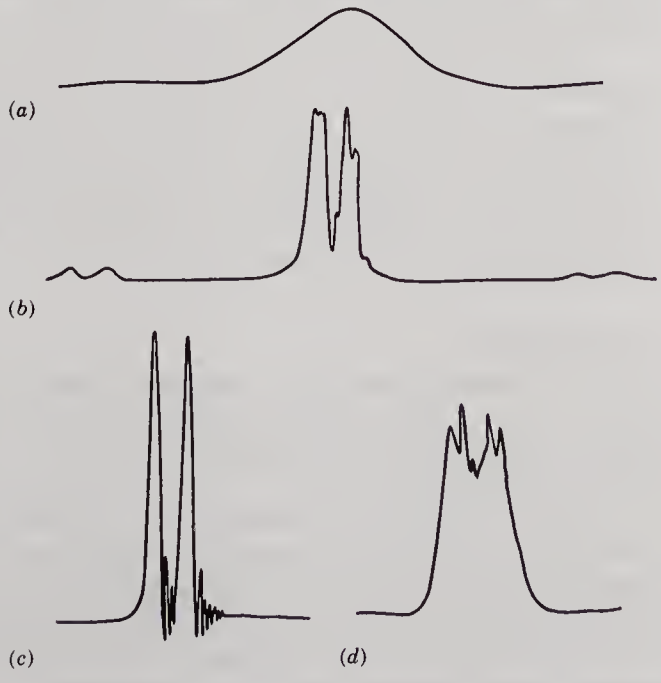


FIGURE 16.24 Spinning rate and peak resolution. (*a*) Nonspinning. (*b*) Slow spinning. (*c*) Correct spinning rate. (*d*) Fast spinning and vortexing. Varian Associates, Instrument Division.

the averaging of proton positions is disturbed within the sample. The correct spinning rate is between 30 and 60 cps.

Make the following adjustments with the sample spinning.

Spectrum Amplitude

The spectrum amplitude adjustment makes it possible to change the height of the signal. Using this control allows the operator to make the peaks of a reasonable size and yet to keep the tallest peaks on the chart paper. Different samples need different amplitude settings. For example, a solution sample requires a higher amplitude than a neat sample because there are fewer molecules of the compound to be analyzed, therefore fewer proton spins to flip. Higher amplitude settings cannot completely make up for dilution, however, because noise intensity increases as well as signal intensity.

Sweep Controls

The **sweep width** refers to the width of the spectral region that will be scanned. A sweep width of 10 ppm across the length of the chart paper is most commonly used since most resonance absorptions occur between 0 and 10 ppm. However, it is sometimes desirable to expand the size of a multiplet so that more accurate coupling constant values can be calculated. In this case you would change the sweep width to a lower number.

The **sweep zero** control allows you to position the signal of the reference substance at the chart paper's zero point.

The **end of sweep** or **sweep effect** control allows you to set the upfield end of the scan at some ppm value other than zero. For example, if an absorption occurred at 10.5 ppm it would be off scale. Setting the end of sweep at 2 ppm brings the absorption on scale at 8.5 ppm on the chart paper. Of course, at this setting, the TMS signal does not appear.

The **sweep time** adjustment changes the number of seconds it takes to sweep through the selected sweep width, that is, the time it takes for the pen to move from one end of the chart paper to the other. The most accurate information is obtained at slow sweep time. However, if the sweep time it too slow relative to the rf field setting, saturation can occur. Time is of the essence in the introductory organic laboratory and your instructor might suggest something other than the slowest sweep time available on your instrument. Commonly a rate of 1 Hz/s is used.

Make sweep adjustments on scrap chart paper. To save time, you should always make sweep adjustments at fast sweeps. The exception is setting the sweep zero, which you should set at the sweep time that you will use while recording the spectrum.

For best resolution, you need spinning rates in the range of 20–60 cps (rps). A simple way to check rate of spinning is to start spinning the sample slowly and then increase the rate until distinct revolutions can no longer be observed. Another way is to observe the positions of spinning sidebands of the signal relative to the center of the signal's tallest peak. The sideband is separated from that point by an amount in cps equal to the rate of the spin. Simply measure from center to center along the cps (Hz) scale at the top of the NMR chart paper.

rf Field Control

The rf field setting controls the intensity of the radiation, hence of the oscillating magnetic field. Up to a point, you can increase the height of a given signal by increasing the radiation intensity. However, saturation occurs more readily at high settings and gives rise to broader, lower peaks.

Saturation occurs more readily with some kinds of protons than others. Protons giving narrow absorptions saturate most easily; therefore you should use the narrowest line in the spectrum to set the rf field. Using scrap chart paper, scan the narrowest signal at several rf field settings to obtain maximum peak height. The exact setting is not critical. To some extent the rf setting depends on sweep width because at lower sweep width settings there is a greater probability of saturation.

Filter Control

By using the **filter control** you can decrease the high-frequency noise level associated with use of the spectrometer. However, you will broaden the signals if you use too much filtering. Electronic noise is most apparent at high-amplitude settings and low rf field settings.

Phase Control

The **phase control,** or signal symmetry control, adjusts the electronic phase so that you obtain a signal of good symmetry. Adjust the control so that the spectrum base line enters and leaves the signal at the same height. You might need to alter the phasing whenever you change the spectrum amplitude or rf field or when you have altered the phase for integration.

Recording the Spectrum

After you have correctly adjusted all of the controls, put a clean sheet of chart paper on the recorder and record the spectrum.

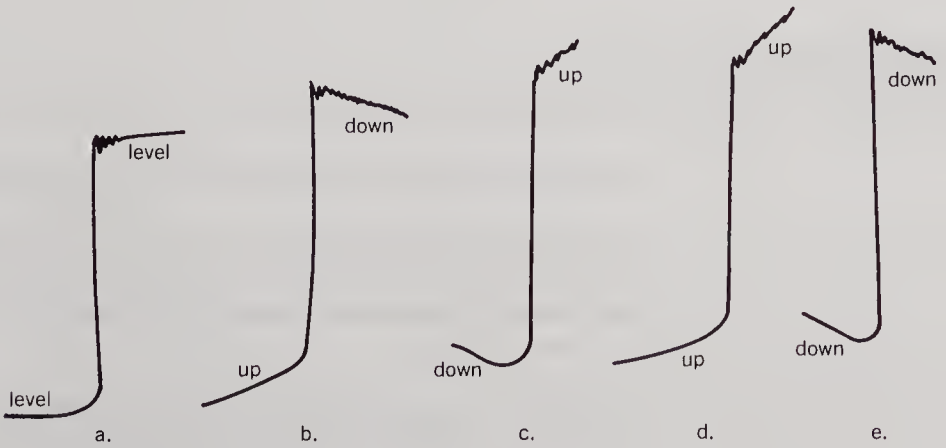
A complete NMR spectrum includes both the peaks tracing and the integrals tracing. Although it does not really matter, the peaks tracing is ordinarily made first.

After you have recorded the signals, put scrap chart paper on the recorder once more, and turn on the integration control. It is important that you use the same basic instrument control settings, although it is likely that you will have to adjust the spectrum amplitude. Small adjustment of rf phase and integrator balance controls might also be needed. Figure 16.25 shows correct and incorrect phase and balance for an integral. Notice that when the phasing is not correct, the base line will slant upward on approaching the integral and downward after integration, or down on approach and up afterward. By contrast, improper balance will yield a line that is either slanting up or down before and after the integral. The correct adjustments produce a horizontal line entering and leaving each integral. However, you should expect a slight rise just before and after the integrals since the spectral peaks themselves do not rise and fall suddenly.

Cleaning up

Pour the contents of the NMR tube into an appropriate container. Remember that NMR analysis is a nondestructive technique and the analyzed compound is as good as new.

Clean the sample tubes immediately after use by washing them or at least thoroughly rinsing them several times with an appropriate solvent. You can clean soiled tubes by



a. correct balance and phase
b. incorrect phase
c. incorrect phase
d. incorrect balance
e. incorrect balance

FIGURE 16.25 Phase and balance adjustments of integral.

introducing the solvent, a moderately hot soap solution, or other approved cleaning solution into the tube with a drawn out pipet. Then with the pipet still in the tube, alternately squeeze and release the rubber bulb so as to create currents within the tube. You can use a pipe cleaner to scrub the inside of the tube if necessary. Thoroughly rinse the tube in the same way, first with water after an aqueous wash, then with clean acetone. Gently blow it dry. You should be careful not to scratch the inside of the tube with a pipet or a pipe cleaner.

Never clean NMR tubes with dichromate cleaning solutions because a paramagnetic residue will be left in the tube. Remember, even small amounts of paramagnetic materials lead to line broadening.

Procedural Summary

The following procedure will be basically the same for obtaining an NMR spectrum on any NMR instrument.

1. Put the sample, including TMS, into the tube.
2. Place the spinner on the tube at the proper position.
3. Insert the tube into the instrument.
4. Align chart paper on the recorder.
5. Lay scrap paper over the chart paper.
6. Set the sweep width, end of sweep, and sweep time controls.
7. Sweep the field and locate the tallest peak.
8. Adjust the spectrum amplitude so as to keep the tallest peak on the scale at the sweep time of the final spectrum.
9. Set the sweep zero by lining up the TMS signal on zero of the chart paper. You will have to sweep through the signal and then accordingly adjust the zero point.
10. Set the recorder base line at the desired height.
11. Remove the scrap sheet and record the spectrum.
12. Replace the scrap and make adjustments for integration.
13. Remove the scrap sheet and integrate.
14. Lift chart paper from recorder.
15. Enter all control settings on the chart paper; and make and model of instrument.
16. Remove sample from instrument.
17. Clean up

16.6 EXPERIMENTAL PART
Identification of Unknown

Time Required: About 10 min/student on a pretuned spectrometer

You will be given about 1 ml of an unknown compound along with its molecular formula and an identifying number or letter. Your task is to identify the sample. Ask your instructor whether you are permitted to use additional techniques such as IR and refractive index along with NMR.

Procedure. Prepare the sample, obtain the spectrum, and clean up immediately. Do not forget to sign the instrument log book if your chemistry department uses one.

Writing the discussion. Identify the unknown and write a detailed analysis describing how you arrived at the identification.

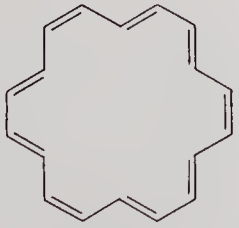
16.7 EXERCISES

Prelaboratory

1. Why is a sample analyzed neat if possible?
2. What are the minimum and maximum sample heights in an NMR tube?
3. How can ferromagnetic materials be removed from a sample?
4. Describe the introduction of your sample into the NMR tube.
5. Describe how you will introduce and mix the TMS into your sample.
6. List the controls on the NMR spectrometer with which your instructor has told you to be familiar; state the function of each.
7. Why is an NMR tube *always* wiped free of lint before insertion into the instrument?
8. When is an NMR tube most likely to be broken?
9. Describe how you will clean the NMR tube after use.
10. With what kind of solution will you never clean an NMR tube? Why?

Postlaboratory

1. 2-Aminoethanol possesses four kinds of protons. However, only three signals are observed because of an averaging of two signals. Explain, along with appropriate chemical equations and transition states, how this occurs.
2. Draw a diagram like that of Figure 16.10 showing how an aldehydic proton is paramagnetically deshielded.
3. Sketch the NMR spectrum of methanol, free of acid and water.
4. What would an NMR spectrum look like if the rf field setting is very high and the sweep time is very slow? What word is associated with this condition?
5. The chemical shift for the methyl protons on toluene is 2.31 ppm on the *delta* scale. Explain why they are so far downfield from the aliphatic methyl proton absorption at 0.9 ppm.
6. [18]Annulene absorbs on the *delta* scale at 1.9 ppm and 8.8 ppm when TMS is the standard. Draw a diagram like that of Figure 16.16 and explain the two chemical shifts.



[18] Annulene

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TECHNIQUE 17

MASS SPECTROMETRY

Mass spectrometry is a highly technical but extremely useful method of obtaining information about molecular mass and molecular structure. It can also be used for quantitative analyses of mixtures in concentrations of as little as parts per million.

Mass spectrometry is a prominent method of analysis in the chemical industry, and in university, government, and other research and analytical laboratories, and is becoming important in hospital and other medical laboratories. The field of mass spectrometry has been exhibiting an almost explosive growth in recent years, and it appears that this growth will continue.

Because of the burgeoning prominence of analysis by mass spectrometry, your education in organic chemistry is incomplete without an understanding of its basic principles. As you study mass spectrometry, you will also become better acquainted with carbocation (carbonium ion) and free radical chemistry.

Properly used, mass spectrometry is rapid and reliable. However, instrumentation is very expensive and it is unlikely that you, as a novice mass spectrometrist, will be able to get your hands on a real mass spectrometer. Therefore, *computerized simulations* have been prepared for you to use along with this textbook. They will teach you some of the basic skills of using a mass spectrometer and of interpreting mass spectra.

A **mass spectrum** is a recording of the masses of various positive ions that are produced when a compound is subjected to bombardment by high-energy electrons. The spectrum might appear in tabular form, as a pen tracing of peaks similar to GLC or IR curves, or as a bar graph. The bar graph is probably the most common form and represents a reconstruction of the areas under the curves of a pen tracing. Very often a mass spectrometer is run in conjunction with a computer that gives an almost immediate printout on a TV-like screen.

The mass spectrum of phosphine (PH_3) is shown in Figure 17.1. The abscissa (horizontal coordinate) of the bar graph depicts mass (actually mass to charge ratio, m/z) of ions. The ordinate (vertical coordinate) shows relative numbers of ions. The numbers of ions are all relative to the one found in greatest abundance. The peak (bar) of the most abundant ion is assigned a relative peak height of 100, and is called the **base peak.** In this case the base peak at m/z 34 is due to the ion PH_3^+, which has a molecular mass of 34 u (atomic mass units). This peak at m/z 34, corresponding to the molecular mass of phosphine, is called the **molecular ion peak** and is designated as M. The peaks at m/z 31, 32, and 33 correspond to P^+, PH^+, and PH_2^+ ions, respectively. The peak height of 35 for PH_2^+ at m/z 33 u tells us that for every 100 PH_3^+ ions there are 35 PH_2^+ ions.

17.1 INSTRUMENTATION

Mass spectrometers come in a variety of types and with varying degrees of sophistication. However, they operate on the same basic principles. Figure 17.2 is a schematic drawing of a simple mass spectrometer.

The operator puts the compound to be analyzed into the glass or stainless steel inlet system. The vapor pressure of the sample must be about 10^{-1} to 10^{-3} torr; therefore

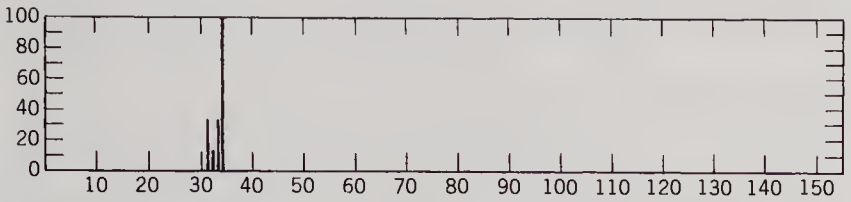


FIGURE 17.1 Mass spectrum of phosphine. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

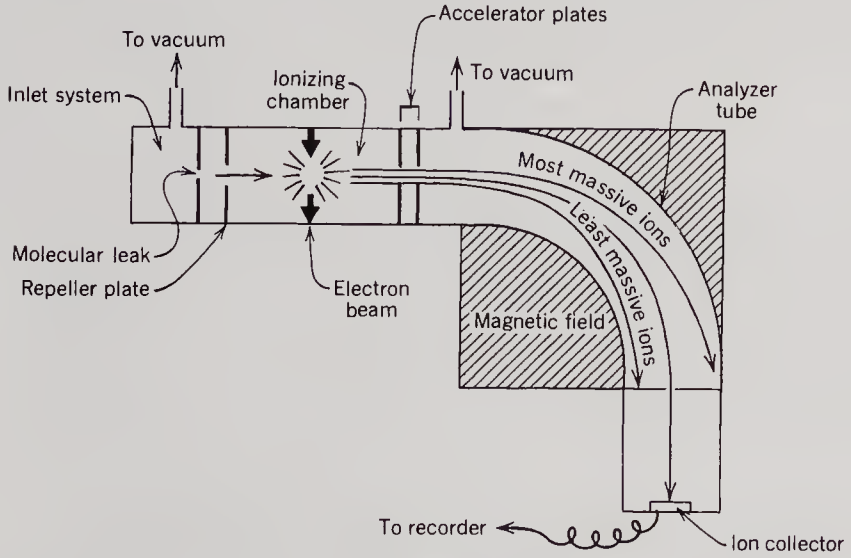


FIGURE 17.2 Schematic diagram of mass spectrometer.

the inlet system is contained in an oven. This arrangement permits adequate vaporization of many organic samples even if they are solids. The vapor then leaks into the ionization chamber through a small aperture often referred to as a **molecular leak.** This leak allows a steady stream of molecules to pass into the ionizing chamber.

The **ionizing chamber** is kept at a pressure of about 10^{-5} to 10^{-7} torr to minimize ionization of air and reduce the number of collisions between molecules, ions, and free radicals. After the sample molecules enter the chamber a few percent stray into the electron beam where about 0.1% of those few become ionized. Ionization occurs when electrons are knocked out of molecules by the beam electrons. The resultant radical cations are then pushed toward the ionizing chamber slit by a small positive potential on the **repeller plates.** The positive potential also serves to neutralize any negative ions that might form in the electron beam. Next, the cation radicals are accelerated by a potential of a few thousand volts between the **accelerator plates.** Passing through the slits at a high velocity, the beam of ions moves into the magnetic field of the **analyzer tube.** The field is at right angles to the beam of ionized particles and deflects them into a circular path whose radius varies in accord with their masses, the more massive particles being deflected least. At any one time only cations of a given mass can pass through the slit and impinge on the **ion collector.**

As ions strike the collector, electric impulses are produced which are amplified, then sent to a recorder. The mass spectrum is printed on a recorder and/or displayed on an electronic picture tube like a TV screen.

Operation of the Instrument

This text is designed to be used along with computer simulations that approximate the methods of actually using a magnetic scanning mass spectrometer. The type and arrangement of controls depend on the manufacturer of the instrument. However, Figure 17.3 illustrates a compact arrangement of all of the basic controls that would be found on a magnetic scanning instrument. The dial positions on Figure 17.3 are those most commonly used.

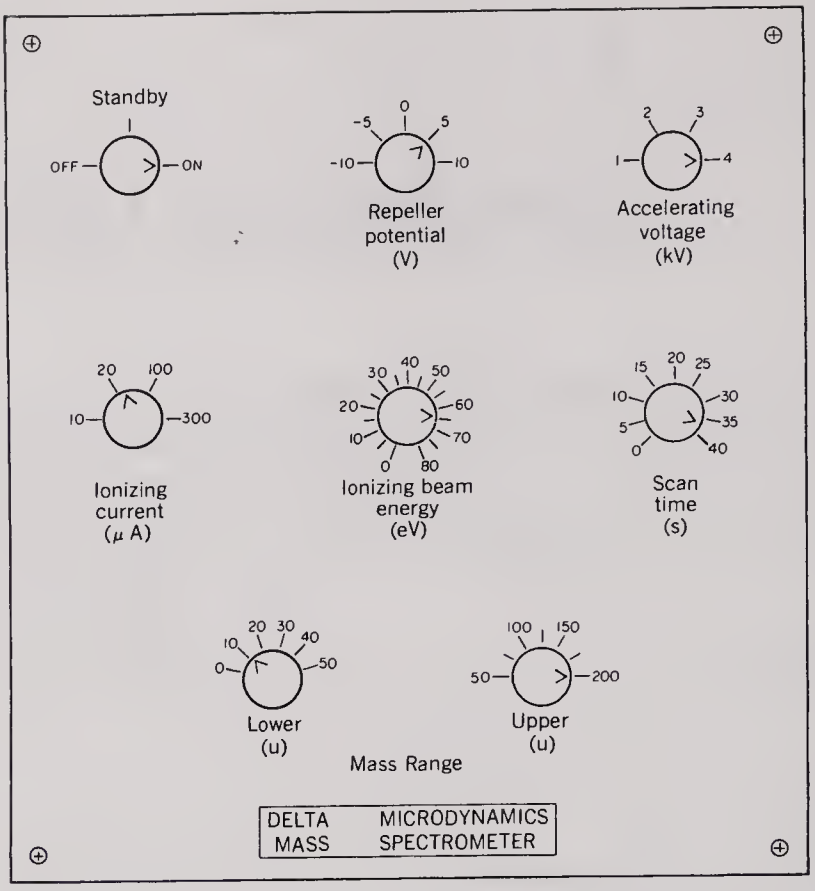


FIGURE 17.3 Control panel for magnetic scanning mass spectrometer.

Off-Standby-On

When the off-standby-on control knob is set to "off," the operating current to the instrument is shut off.

When the control knob is turned to "standby," current is supplied to the magnet. This current must be on well in advance of use in order to allow the magnet to reach temperature equilibrium so that reproducible mass spectra will be possible. The instrument is normally left on "standby" for weeks or months at a time when the instrument is in routine use.

The "on" position supplies high voltage current to the instrument and must be used during production of a mass spectrum.

In our computerized simulations, you must assume that the instrument is "off" when you begin work on a given program. You must therefore first turn the control to "standby" to warm up the magnet. After setting the other controls, turn the off-standby-on control to "on" in order to supply the high voltage current required to produce your spectrum.

Repeller Potential

The repeller potential control is used to alter the positive character of the repeller plates inside the ionization chamber. The repeller potential is given in volts (V). The higher the voltage, the greater the positive character of the repeller plates, and the shorter the time that the positive ions remain in the ionization chamber. The normal setting is 5 V.

Sometimes it is desirable to increase the repeller potential in order to observe the effect on what you think might be M + 1 peaks (please refer to Section 17.4).

Accelerating Voltage

The accelerating voltage provides the negative charge on the accelerator plates which causes the cations in the ionization chamber to gain speed and be propelled into and

through the analyzer tube. The accelerating voltage is given in kilovolts (kV), thousands of volts. Ordinarily, a 4 kV setting is used.

The accelerating voltage primarily changes the speed of positive ions: the higher the voltage, the greater the acceleration and final speed. The speed in turn affects the mass range and peak height that can be obtained.

Occasionally, it is necessary to operate beyond the normal upper mass range of the instrument in order to obtain a spectrum. This can be done by decreasing the accelerating voltage. An inverse proportion is roughly involved. For example, if you want to *increase* the mass range from 200 to 400 u, you will *decrease* the accelerating voltage from 4 to 2 kV. This tactic would in turn reduce the peak heights (or in other words the sensitivity of the instrument) on a pen tracing by roughly one-half.

Ionizing Current

The ionizing current determines the *number* of electrons passing through the ionizing chamber in a given time. It is measured in millionths of amperes (μA).

The ionizing current must be adjusted to give the bombarding electron beam sufficient intensity to cause peaks to be recorded for all positive ions of interest. With large samples (relatively high pressure), a low current can be used; but for small samples, a relatively high current must be employed so that enough ionization occurs to produce observable peaks in the spectrum. However, at high ionizing currents, background peaks from vacuum pump oil vapor, and so on, are also increased in height. Therefore, lower ionizing currents are used when possible.

For a pure sample of normal size producing a 10^{-6} torr pressure, a 20-μA current is normally used. When compounds are introduced directly from a GLC unit, the sample size and pressure might be very low. This is because the fraction of the compound in the GLC mixture being separated might be quite small. In general, a current of 100 μA is likely to be used for GLC samples. When the amount of GLC sample is 0.05% or less of the GLC mixture, it is necessary to increase the ionizing current to 300 μA.

Ionizing Beam Energy

The ionizing beam energy determines the *energy* of the electrons bombarding the sample. It is measured in **electron volts** (eV), the amount of energy gained by an electron when it falls through a potential of one volt. One **eV** is equivalent to 3.83×10^{-20} cal.

There are two regions of interest: (1) an energy of 7–15 eV and (2) an energy of 50–80 eV. Because the ionization energy of organic molecules is found in the 7–15 eV region, an electron is removed from the molecule and a molecular ion is formed. (Recall that **ionization energy** is the energy required to remove an electron without imparting any kinetic energy to it.) The molecular ion so formed theoretically has no excess energy, and hence *does not fragment.* In actual practice, the situation is not quite so clear cut. The 50–80 eV ionizing beam energy delivers enough excess energy to cause fragmentations in reproducible form. This is the ionizing beam energy ordinarily used.

Mass Range

The mass range, measured in atomic mass units (u), determine the upper and lower limits you want to measure for a given compound.

The mass range usually involves a scan (a systematic search for consecutive mass units) up to 50% beyond what appears to be the peak of highest mass for the compound. For example, if the molecular ion were suspected to be at 60 u, you would scan up to 60 + 0.5(60), or 90 u. The reason for the 50% excess is to establish that there is no peak at still higher mass. Occasionally, a scan beyond 50% is required when a massive fragment is severed from a large molecular ion.

It is necessary that you set a lower mass range limit and an upper mass range limit

before you begin the scan. If the spectrum obtained indicates that you did not scan to 50% beyond the last peak, you should repeat the scan, using an appropriately higher upper mass range limit.

Peak height ratios are most accurate if the scanned mass range is as small as possible for a given scan time. This is because more ions of a given mass will have time to impinge on the ion collector.

Scan Time

The scan time is the time it takes to scan the mass range of interest. The units used on our simulated instrument are seconds. An adequate scan time on our instrument is 36 s for a scan over a range of 200 u.

When there is a sufficient amount of sample to use, the longest possible scan time gives the most accurate peak height ratios. If the scan time is very short over a given mass range, very few ions of a given mass will impinge on the ion collector. Under such circumstances the peak on a pen tracing might be so small as to be confused with noise, or it might be missing altogether. On the other hand, in certain applications, you might *have* to use a shorter scan time: (1) If the sample is in the order of only 10 ng (nanogram, 10^{-9} g), you will be able to maintain the sample vapor pressure for only a short period of time. Under such circumstances, you would use a scan of 5–10 s duration. (2) Oftentimes a gas chromatograph is integrated with the inlet system of the mass spectrometer, and the mass spectra of GLC fractions are recorded as the fractions emerge from the gas chromatograph. In such cases the time interval between emerging fractions might be very short and you would want to scan the anticipated range of the compound in 1 to 3 s.

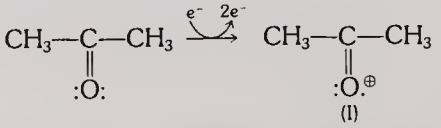
Starting the Scan

Set the off-standby-on control to "on."

17.2 FORMATION AND SEPARATION OF IONS

Formation of Ions

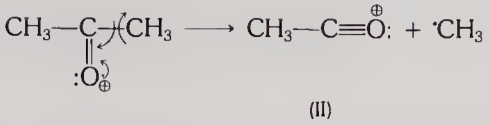
When an organic molecule is bombarded with electrons, it can react in several ways: It might accept an electron and become negative, it might lose one of its own electrons and become positive, or it might lose more than one electron and become multiply positive. The loss of one electron is by far the most likely event as illustrated for propanone (acetone):



(I) (17-1)

Notice that one of the nonbonding electrons has been removed in this example. A nonbonding electron of propanone is certainly the most easily removed, but does not represent the only possibility, as you will see later. When an electron is knocked out of a molecule, a radical cation called the **molecular ion** is created. It is illustrated by species (I) in equation 17-1. The symbol M or $M^{+\cdot}$ is often used for the molecular ion. Sometimes the molecular ion is called the parent ion, but IUPAC nomenclature specifies that these terms are *not* interchangeable.

Depending on the energy it possesses, the molecular ion might remain intact or it might fragment, yielding a **daughter ion** (II):

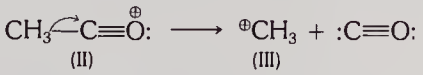


(17-2)

(II)

The ion that produced the daughter ion is often called the **parent ion.** In equation 17-2 the parent ion is the molecular ion. Fragmentation occurs when electron beam energy transferred to the molecule upon impact is greater than the ionization potential by an amount sufficient to break a bond. Fragmentation leads to formation of a daughter ion and a neutral fragment, which can be either a free radical or an uncharged molecule. It is possible for parent and daughter ions to rearrange before fragmentation, yielding fragments not directly related to the structure of the parent. Luckily, rearrangements within molecular ions containing hetero atoms are quite specific and follow principles of carbocation (carbonium ion) rearrangements with which organic chemists are familiar.

If enough energy is available in a daughter ion, it is possible for it to fragment again:



(17-3)

(II) (III)

Now daughter ion (II) has become the parent ion of daughter ion (III). The likelihood of fragmenting a given cation or radical cation depends on the energy of the bond to be broken, on the stability of the daughter ion, and on the stability of the neutral fragment. The most important of these factors appears to be the stability of the positive charge. The probability of producing a given positive species is of course enhanced if fragmentation produces a relatively stable neutral fragment as well.

In our study of mass spectra, we shall see that carbocation and free radical chemistry provide the foundation for fragmentation patterns. However, we cannot escape noticing that some rearrangements occur in mass spectrometric fragmentations which do not occur in ordinary organic reactions. This is because of the high energies supplied to the molecules by electron impact at energies between 50 and 80 eV.

An electron will be removed from a molecule by electron impact if the energy of the bombarding electron has an energy equal to or greater than the ionization energy of the molecule. Most organic molecules have ionization energies of 7–15 eV. If the energy of the electron beam is only equal to the ionization energy of the molecule, a molecular ion peak of low height is produced. Up to about 20 eV, increasing the electron beam energy increases the height of the molecular ion peak. Lower peak height occurs with beam energies greater than 20 eV because of increasing fragmentation of the molecular ion and production of doubly positive ions.

Separation of Ions

When the molecular ions and daughter ions are accelerated between the accelerator plates, they acquire kinetic energy and enter the magnetic field within the analyzer tube of Figure 17.2.

An important equation in mass spectrometry is

$$\frac{m}{z} = \frac{H^2v^2}{2V} \qquad (17\text{-}4)$$

wherein m is the mass of the ion and z is its charge, H is the magnetic field strength, v is the velocity of the ion, and V is the potential difference between the accelerator plates. This equation tells us that a peak position that is recorded on a mass spectrum for a given ion is actually the mass of the ion divided by its charge. However, since most ions are singly charged, m/z is equivalent in most cases to the mass itself. Equation 17-4 also shows us that at the fixed radius of the analyzer tube the variety of ions produced in the ionization chamber can be made to pass through the collector slit one mass at a time by varying either H or V. If the magnetic field, H, is varied, the process is called **magnetic scanning;** if the accelerating potential, V, is varied, it is called **electric scanning.** In a *magnetic scanning instrument,* V is held constant and H is gradually changed. Equation

17-4 tells us that if H is gradually increased, a spectrum will be produced in which masses are recorded from lightest to heaviest.

17.3 ISOTOPE EFFECTS

You probably recall that **isotopes** are atoms of the same element with different numbers of neutrons in the nucleus. The various isotopes of an element all have different masses. Therefore we should expect the mass spectrum of any given compound to record the mass of each ion in more than one place. And it will. However, most of the elements we are concerned with in organic chemistry exist primarily as one isotope, and therefore cause little confusion in mass spectral analysis. The presence of their other isotopes in small amounts helps to account for the many tiny peaks usually seen in mass spectra of organic molecules.

Table 17.1 lists the natural isotopic abundance of the most common elements in organic chemicals. You can see that the elements most likely to cause confusion are those of sulfur, chlorine, and bromine.

The ratios of peak heights relating to ions containing isotopes of a given element are the same as the ratios of the isotopes. This fact makes presence of isotopic peaks useful. Thus spectra containing chlorine and bromine are often easy to identify as such because of the peak height ratios 2 u apart. Also, the ratios of the peaks due to carbon isotopes can be used to help obtain molecular masses and formulas of ions.

Figure 17.4 illustrates a simple spectrum in which a telltale doublet appears. We readily see that the large peaks are separated by 2 u and that the one at 38 u is about one-third the height of the one at 36 u. Such an arrangement immediately suggests the presence of chlorine. The peaks at 38 and 36 u must be due to $H^{37}Cl^+$ and $H^{35}Cl^+$; the peaks at 37 and 35 u must be from the chlorinium ions $^{37}Cl^+$ and $^{35}Cl^+$. The compound analyzed must have been hydrogen chloride, HCl.

TABLE 17.1 Natural Isotopic Abundance of Elements Commonly In Organic Molecules

Element	*Mass*	*Fractional Abundance*	*Isotope*	*Ratios*
Hydrogen	1	0.999844	$^2H/^1H$	0.016/100
	2	0.00156		
Carbon	12	0.98892	$^{13}C/^{12}C$	1.08/100
	13	0.01108		
Nitrogen	14	0.9964	$^{15}N/^{14}N$	0.38/100
	15	0.0036		
Oxygen	16	0.9976	$^{18}O/^{16}O$	0.20/100
	17	0.0004		
	18	0.0020		
Fluorine	19	1.00		
Phosphorus	31	1.00		
Sulfur	32	0.9506	$^{34}S/^{32}S$	4.40/100
	33	0.0074		
	34	0.0418		
	36	0.000136	$^{33}S/^{32}S$	0.78/100
Chlorine	35	0.754	$^{37}Cl/^{35}Cl$	32.5/100
	37	0.246		
Bromine	79	0.5057	$^{81}Br/^{79}Br$	98.0/100
	81	0.4943		
Iodine	127	1.00		

From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974, Table IA. Used with permission of John Wiley & Sons, Inc.

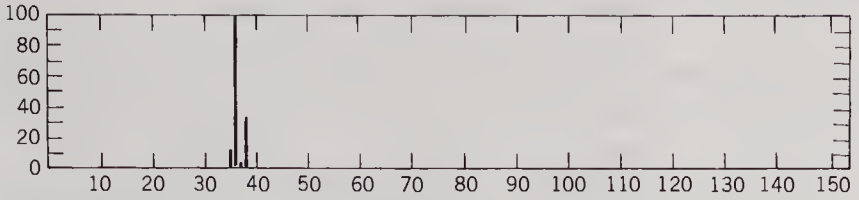


FIGURE 17.4 Mass spectrum of hydrogen chloride. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

Isotopic Clusters

We have seen that the presence in a compound of a single atom of an element with two isotopes of significant abundance leads to doublets in the mass spectrum. If there is more than one atom of that element in a molecule, groups of peaks appear in the spectrum, the number and heights of the peaks depending on the number of atoms and the natural abundance of the isotopes. Such groups are referred to as **isotopic clusters.** For a compound containing n isotopic atoms of a given kind there will be $n + 1$ peaks in a cluster. For example, $n = 1$ for Br in CH_3Br, and we should expect to see $1 + 1$, or 2 peaks. For Br in CH_2Br_2 we should observe $n + 1 = 2 + 1 = 3$ peaks in each cluster. It can be shown that the peak intensities are in accord with binomial coefficients.

17.4 THE MOLECULAR ION

Locating the molecular ion peak is very important for structure determination: First, it represents the molecular mass of the compound; second, it can often be used to calculate the molecular formula; and third, all fragmentations start with the molecular ion as the original parent.

Formation of the Molecular Ion Peak

The electrons of a molecule which are most loosely held are those which are most easily dislodged by electron impact:

(easy) nonbonding > pi > sigma (difficult)

Equations 17-5, 17-6, and 17-7 illustrate the dislodging of nonbonding, pi, and sigma electrons:

$$CH_3CH_2\ddot{O}H + e^- \longrightarrow CH_3CH_2\overset{\oplus}{\ddot{O}}H + 2e^- \qquad (17\text{-}5)$$

$$CH_2{=}CH_2 + e^- \longrightarrow \dot{C}H_2{-}\overset{\oplus}{C}H_2 + 2e^- \qquad (17\text{-}6)$$

$$H_3C{:}H + e^- \longrightarrow H_3\overset{\oplus}{C}.H + 2e^- \qquad (17\text{-}7)$$

We should of course expect that some electrons of a given type are more easily removed than others of that type. For example, a nonbonding electron of bromine is easier to eject than one of fluorine because the latter is more electronegative.

The height of the $M^{+\cdot}$ peak corresponds to the number of molecular ions arriving at the collector. If the molecular ion is not very stable it will fragment and reduce the number of molecular ions the collector can receive; therefore the molecular ion peak will be smaller. In 80–90% of cases, the $M^{+\cdot}$ peak is observable on a mass spectrum. Table 17.2 lists various classes of compounds with respect to the likely prominence of the molecular ion peak.

Locating the Molecular Ion Peak

The molecular ion peak must satisfy several requirements:

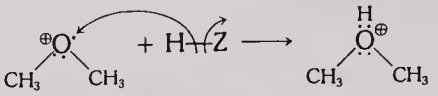
1. It must be the peak of greatest mass in the spectrum except for the M + 1 peak.
2. It must be produced by an odd-electron ion.
3. It must be produced by an ion that can yield by fragmentation the important peaks in the higher mass region of the spectrum.

TABLE 17.2 Prominence of Molecular Ions

Prominent	*Observable*	*Very Tiny or Undetectable*
Aromatics	Ketones	Alcohols
Alkenes	Esters	Amines
Cycloalkanes	Carboxylic acids	Nitriles
Short alkanes	Aldehydes	Highly branched alkanes
	Amides	
	Ethers	
	Haloalkanes	

4. It must have a relative peak height that is appropriate for the anticipated type of molecule.

With regard to the first requirement, you must be aware that it is not uncommon to find a peak 1 or 2 u higher than the mass of the molecular ion, $M^{+\cdot}$. An M + 2 peak sometimes arises from presence of isotopic atoms in the compound, as described in Section 17.3. In such cases $M^{+\cdot}$ is taken to be that of the lower mass ion. The second possibility involves an $(M + 1)^+$ ion, which is produced in the ionization chamber by capture of a hydrogen *atom* from a donor, HZ, as for example,



(17-8)

HZ is another molecule or fragment from the substance being analyzed. The rate of formation of $(M + 1)^+$ follows the second-order process

$$\frac{d[(M + 1)^+]}{dt} = \text{rate} = k[M^{+\cdot}][HZ] \tag{17-9}$$

wherein $[(M + 1)^+]$ is the concentration of the hydrogenated molecular ion, $[M^{+\cdot}]$ is the concentration of molecular ion, [HZ] is the concentration of the hydrogen donor, t is time, and k is a proportionality constant. Since the reaction is second order and the concentrations are proportional to sample pressure, the rate of $(M + 1)^+$ formation is proportional to the *square* of the sample pressure. Experimentally then, the $(M + 1)^+$ peak can be recognized in two ways: (1) by changing the sample pressure. An increase in pressure increases the relative M + H peak height. (2) By changing the repeller potential. An increase in repeller potential decreases the time $M^{+\cdot}$ spends in the ionization chamber, decreases its opportunity for hydrogen abstraction, and hence decreases the $(M + 1)^+$ peak height. On the other hand, decreasing the repeller potential increases the relative $(M + 1)^+$ peak height. For compounds with unstable $M^{+\cdot}$ ions but stable $(M + 1)^+$ ions, the $M^{+\cdot}$ peak might be quite small and the $(M + 1)^+$ peak might be of considerable height. Such relationships are common among esters, ethers, and amines.

With reference to the second requirement for molecular ion peak identification, use the principles found in Section 17.5 to determine the elemental composition (if possible) and to apply the odd-electron rule.

In terms of the third requirement, keep in mind that losses by fragmentation of masses of 4 to 14, 21 to 25, 33, 37, and 38 are very unlikely. Therefore, if significant peaks were to be observed at 46 and 32 u, it would be unlikely that the peak at 46 u is due to a molecular ion (46 − 32 = 14).

Finally, the relative peak height for what you believe to be the molecular ion must match the class of compound with which you are working. For example, if you know or strongly suspect that you are analyzing an alcohol, yet the molecular ion peak is large (Table 17.2), you know that you are mistaken about something.

There are two circumstances under which you might find identification of the molecular ion difficult. First, the molecular ion might be absent or very weak; and second, the molecular ion might be present but less dominant than a neighboring M − 1 peak.

Try

1. Reducing the ionizing beam energy to near the ionization potential of the compound.
2. Increasing the sample pressure (sample size), remembering that an M + 1 peak might become exaggerated in size.
3. Decreasing the repeller potential.
4. Increasing the repeller potential.
5. Simultaneously increasing sample pressure and decreasing repeller potential.

Items 1 and 4 should, alone or together, increase the *relative* size of the $M^{+\cdot}$ peak on a tabular output.

17.5 SPECTRUM ANALYSIS

In general, the most characteristic ions in the mass spectrum of a given molecule are related to the loss of an electron associated with the molecule's functional group. However, at 50–80 eV there is sufficient energy to knock out electrons of all kinds. Therefore a wide variety of ions can be produced. Even though ions caused by ejection of the more tightly held electrons are likely to be in lower abundance, a mass spectrum can be quite complicated, with many small peaks present. However, attempting to explain the formation of all peaks in a mass spectrum is neither practical nor necessary. Generally, consideration of the taller peaks will lead to valid conclusions about structure and molecular mass. This is because the taller peaks are due to fragments that form by an energetically favorable process and are easiest to interpret. Analyzing only important peaks is somewhat analogous to IR interpretation, wherein detailed analysis of the fingerprint region is not practical or necessary.

General Procedure

When analyzing the mass spectrum of an unknown substance, you will find this outline helpful. Following the outline are comments regarding the various steps.

1. Identify the $M^{+\cdot}$ peak, if present.
2. Note whether $M^{+\cdot}$ is of odd, or even, mass.
3. Determine from $M^{+\cdot}$ peak height how stable the molecular ion is.
4. Identify peaks due to odd-electron ions.
5. Identify homologous series of peaks.
6. Identify series of peaks due to low-mass ions.
7. Propose reasonable neutral fragments that accompany fragmentation to form high-mass ions.
8. Propose structures of ions and radical ions for the important peaks.
9. Determine elemental composition and formulas of ions if necessary to propose their structures.
10. Propose the molecular structure.
11. Analyze a few more peaks if possible to help confirm the structure.

Comment 1. Odd mass in the molecular ion *suggests* the presence of nitrogen because it is usually accompanied by an odd number of hydrogens.

Comment 2. The molecular ion peak can usually be distinguished from a daughter by noting whether the mass of the peak is odd or even. Unless the molecular ion contains an odd number of nitrogens it will have an even mass; daughters will have odd masses. Exceptions occur when fragmentation produces a neutral molecule, thereby removing an even mass from the molecular ion and leaving a daughter of even mass.

Comment 3. Remember that various classes of compounds yield molecular ion peaks of varying heights. See Table 17.2 for clues that might *help* you place your unknown within a given class.

Comment 4. It is useful to know that odd-electron ion fragments form in significant amounts only via special types of fragmentations such as when rearrangements and ring decompositions are involved. Such processes are often characteristic of molecular structure. Therefore it is important to note the presence of all odd-electron ion peaks greater than about 10% of the base peak height. Use the odd-electron rule (next section) to identify these peaks. Important odd-electron ion peaks are not likely to be found in the low-mass end of the spectrum. Therefore, even-mass peaks at the low end are generally due to ions containing an odd number of nitrogens.

Comment 5. A homologous series of peaks separated by 14 u is characteristic of straight chain alkanes.

Comment 6. Identification of low-mass ion fragments is useful in indicating general structural characteristics of the molecule. For example, a peak representing 15 u almost always indicates CH_3^+; masses of 29 u are usually $C_2H_5^+$ or CHO^+.

Comment 8. After determining the numbers of carbons and hydrogens in the ions of major peaks, look for the presence of a small peak 2 u higher than the masses of major peaks. Such peaks *might* indicate the presence of oxygen.

Ion Formulas

The ratio $^{12}C/^{13}C$ makes it possible to determine the maximum number of carbons in an ion. This in turn helps us to deduce the elemental composition of a molecular ion or fragment. The procedure is to divide the measured height of a major peak (p) into the measured height of the peak 1 u higher ($p + 1$), multiply by 100, and divide by 1.08 (1.08 comes from the $^{13}C/^{12}C$ isotope ratio):

$$\frac{(h_{p+1})(100)}{(h_p)(1.08)} = \text{maximum number of carbons} \qquad (17\text{-}10)$$

For example, if, relative to the base peak, peaks p and $p + 1$ have heights of 12 and 0.54, respectively, the maximum number of carbons in the ion is

$$C_n = \frac{(0.54)(100)}{(12)(1.08)} = 4.09, \text{ rounded to } 4$$

That is, there can be no more than four carbons in the ion. You can now deduce the formula of the ion in the following manner: Subtract the mass due to the maximum number of carbons from the mass at which peak p is found (mp) to obtain the mass that is in excess of carbons present:

$$mp - (12)(C_n) = \text{u in excess of C} \qquad (17\text{-}11)$$

For example, if p in the above example were at 58 u, the mass due to atoms other than carbon would be

$$58 \text{ u} - (12 \text{ u})(4) = 10 \text{ u}$$

Since oxygen and nitrogen both have masses greater than 10 u, there must be 10 hydrogens, and the formula of the ion must be $C_4H_{10}^+$.

This method of determining a formula obviously breaks down when a molecular ion forms (M + 1) peaks (see Section 17.4) or when other ions of the mass ($p + 1$) are present. Nevertheless, it is often a very useful technique.

Hydrogen Deficiency

Once the formula of an ion has been determined, you can determine the total number of rings and/or pi bonds that are present by finding the **hydrogen deficiency,** or **degrees of unsaturation.** In the generalized molecular formula $I_y II_n III_z IV_x$, the Roman numerals represent atoms with the valence of the numeral, and the subscripts are the numbers of the atoms. I can be any monovalent atom like hydrogen or halogen; II can be any divalent atom like O, S, Se; III can be any trivalent atom like B, N, P, As; and IV can be any tetravalent atom like C, Si, Sn, Pb; for example, C_4H_6O. The hydrogen deficiency is given by

$$x - \frac{y}{2} + \frac{z}{2} + 1 \qquad (17\text{-}12)$$

For C_4H_6O, the hydrogen deficiency would be

$$4 - \frac{6}{2} + \frac{0}{2} + 1 = 2$$

This means that there could be two rings, two pi bonds, or one ring and one pi bond.

Odd-Electron Rule

The **odd-electron rule** tells us that any cation with a formula yielding an integer in equation 17-12 must be a radical cation. That is, it must have an odd electron.

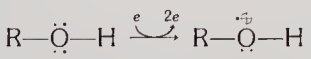
This information is of interest in mass spectral analysis because the molecular ion must be a radical cation. This follows since all neutral molecules have an even number of electrons and loss of one must produce a cation with an odd electron. If you suspect an ion of being the molecular ion and it does not fit the odd-electron rule, it must not be the molecular ion. Also, the odd-electron rule is important for identifying odd-electron ion fragments.

17.6 ANALYSIS OF COMPOUND CLASSES

The next several sections are devoted to providing you with mass spectral characteristics of the compound classes you will be asked to analyze: alcohols, aldehydes, and ketones. Lack of space in a book of this kind prohibits examining other classes of compounds. However, you will find that, after completing a study of these classes, you will have a sound foundation for further study of mass spectrometry.

Alcohols

Electron impact ionization of alcohols results in loss of a nonbonding electron from oxygen:

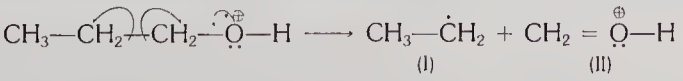


(17-13)

Typical ionization energies of alcohols are around 10.0 eV.

Primary and secondary alcohols usually exhibit very small molecular ion peaks; tertiary alcohols produce a negligible peak. However, the pressure-dependent $(M + 1)^+$ peak can often be used for molecular mass determinations. Also a prominent M − 18 peak often appears by loss of water.

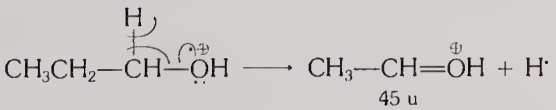
The mass spectra of alcohols are dominated by **α-cleavage** products (remember that α-cleavage is breaking of the carbon–carbon bond next to a functional group):



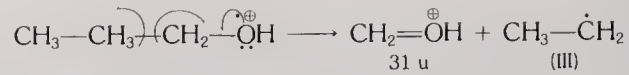
(17-14)

Notice that this process generates a free radical (I) of formula C_2H_5 and a cation (II) which is resonance-stabilized by the nonbonding electrons on oxygen. α-Cleavage is an energetically favorable pathway because formation of an oxonium ion is exothermic enough to easily compensate for the endothermic fracture of the carbon–carbon bond, or even of a carbon–hydrogen bond.

In general, during α-cleavage of primary alcohols, expulsion of a large free radical is favored over expulsion of a hydrogen atom. This is because the larger free radical is stabilized better by hyperconjugation or resonance. For example,



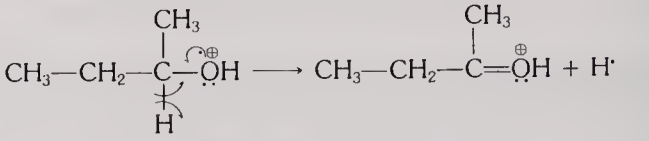
(17-15)



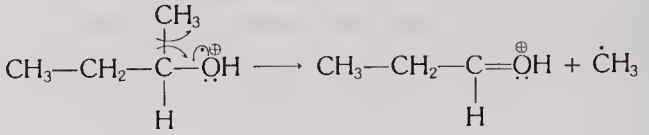
(17-16)

The ethyl-free radical (III) is stabilized by hyperconjugation, whereas there is no stabilizing effect for hydrogen. The peak at 31 u would therefore be taller than that at 45 u.

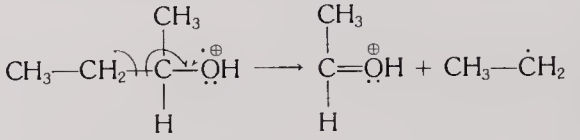
During α-cleavage of secondary and tertiary alcohols, the best-stabilized free radical also is preferentially lost. For example, 2-butanol (*sec*-butyl alcohol) can cleave three ways:



(17-17)



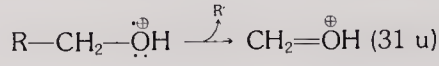
(17-18)



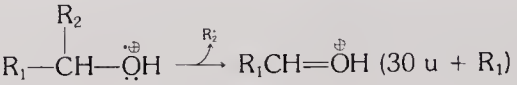
(17-19)

The process in equation 17-17 is least favorable and that in equation 17-19 is most favorable. Therefore, we should expect the spectral peaks at 45, 59, and 73 u to progressively decrease in height in the order given. Note, however, that the process in equation 17-17 yields the analytically important M − 1 peak.

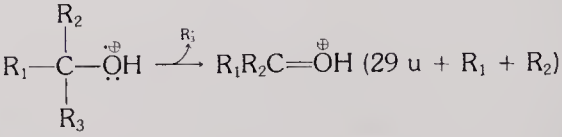
Equations 17-20, 17-21, and 17-22 illustrate α-cleavage for 1°, 2°, and 3° alcohols, respectively:



(17-20)



(17-21)

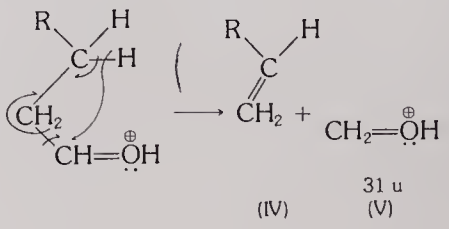


(17-22)

Notice that primary alcohols give a daughter of 31 u, that secondary alcohols produce daughters of 30 u plus the mass of the remaining alkyl or aryl branch, and that tertiary alcohols yield daughters of 29 u plus the masses of the two remaining alkyl or aryl branches.

Because α-cleavage directly results in only one possible primary alcohol daughter, whereas secondary alcohols yield two and tertiary alcohols give three, the number of peaks due to oxygen-containing ions increases in the order 1°, 2°, 3°. Consideration of this information can give valuable clues as to classification of the alcohol being investigated.

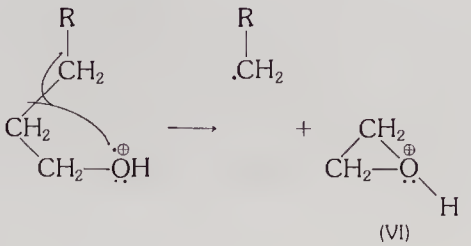
The α-cleavage daughter ion products often undergo further decomposition to yield an alkene (IV) and a smaller cation (V):



(17-23)

In this process, a hydrogen migrates to the carbon of the oxonium double bond.

For primary alcohols, cleavage of the molecular ion just beyond the β, γ, δ or other carbons is also observed. For example,



(17-24)

(VI)

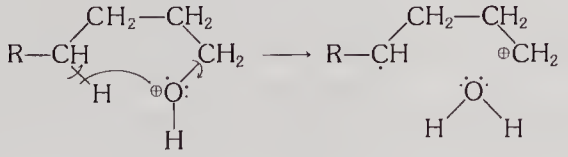
Here we observe a β-cleavage, yielding a free radical and protonated oxirane (VI) of 45 u. In primary alcohols, this sort of cleavage produces a homologous series of peaks separated by the 14 u due to CH_2. In straight chain primary alcohols, the peaks will exhibit a progressively diminishing height at 45, 59, 73 u, and so on. In branched primary alcohols, the series starts at higher mass number.

A peak at 31 u which is higher than any of its homologues suggests the presence of a primary alcohol. A peak at 31 u which is lower than any of its homologues is indicative of a secondary or tertiary alcohol.

Primary and secondary alcohols generally exhibit four very tiny peaks of about the same height at masses equal to $M^{+\cdot}$, $(M - 1)^+$, $(M - 2)^+$, and $(M - 3)^+$. The $(M - 1)^+$ peak always results from loss of hydrogen attached to the carbinol carbon (the carbon bearing the hydroxyl). It has the formula R—CH=O^+—H. The $(M - 2)^+$ and $(M - 3)^+$ peaks are thought to be R—CH=O^+ and R—C≡O^+:.

Secondary alcohols generally exhibit three very tiny peaks of about the same height at masses equal to $M^{+\cdot}$, $(M - 1)^+$, and $(M - 2)^+$, because of the formulas R_2=O^+H, R_2CH=O^+, and R_2C=O^+, respectively.

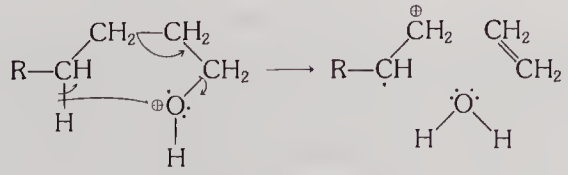
Another characteristic fragmentation of alcohols involves loss of water from radical cations. This process is believed to occur predominantly, but not exclusively, by a five- or six-member cyclic intermediate:



(17-25)

The product is a radical cation with a mass 18 u less than the molecular ion. Elimination of water from $M^{+\cdot}$ occurs easily in the case of 1° alcohols, but is a minor fragmentation process for 3° molecular ions.

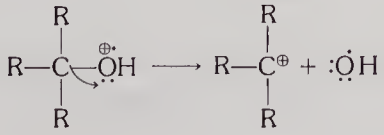
A similar fragmentation takes place with simultaneous loss of water plus an alkene:



(17-26)

This process yields peaks of substantial height for 1° alcohols of four or more carbons.

Because of the stability associated with 3° cations, 3° alcohols tend to lose a hydroxy-free radical rather than water:



(17-27)

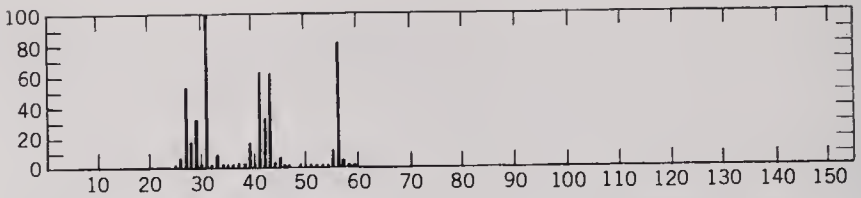
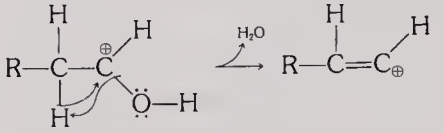


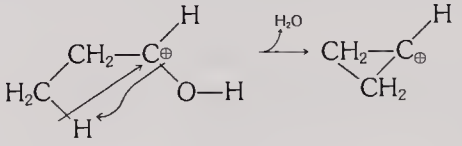
FIGURE 17.5 Mass spectrum of 1-butanol. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

Water can also be ejected from even-electron daughter ions:



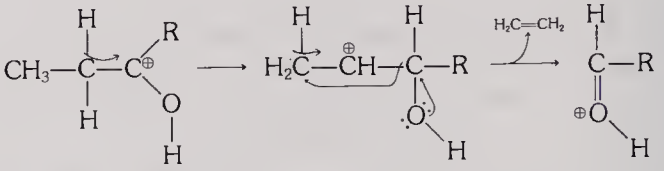
(17-28)

Cations lacking bonds that are easily cleaved tend to fragment with rearrangement:



(17-29)

or



(17-30)

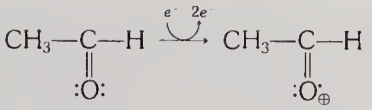
As alcohol chain length increases, hydrocarbon fragments become more abundant. This is especially so if the chains are branched and can give rise to the more stable 2° and 3° cations. In general, the longer the alkyl chain, the more the mass spectrum of an alcohol resembles that of hydrocarbons. Peaks will be found in homologous series 14 u apart and increasing in height with decreasing mass of the daughter fragment. This hydrocarbon character of mass spectra occurs by ionization at sites other than oxygen. In long chain alcohols, hydrocarbon type fragmentation might yield peaks that obscure the typical alcohol pattern.

Analytical Application

Now, analysis of an alcohol spectrum is in order. Figure 17.5 shows prominent peaks at 56, 43, 42, 41, 31, 29, and 27 u. The four very tiny peaks at 71, 72, 73, and 74 u suggest that the compound is a 1° or perhaps a 2° alcohol. Decreasing the repeller potential and increasing the sample pressure will help to confirm a molecular mass of 74 u by generating a peak at 75 u due to the $(M + 1)^+$ ion of formula ROH_2^+. The high peak at 56 u is 18 u below the molecular mass at 74 u. This suggests loss of water (18 u) as a neutral molecule and suggests that the alcohol is most likely primary. Because 56 u fits the ion radical formula C_nH_{2n} when $n = 4$, the chain appears to be butyl. The base peak at 31 u, probably due to $CH_2{=}O{-}H^+$, again suggests a primary alcohol. The peak at 43 u is most likely due to a propyl group, and that at 29 u to an ethyl group. The presence of an ethyl ion suggests a straight chain alkyl group. The peak at 28 u could have arisen from the molecular ion by simultaneous loss of ethene and water. Even without further analysis we can conclude that the sample is 1-butanol (*n*-butyl alcohol).

Aldehydes and Ketones

Electron impact on aldehydes and ketones most easily ejects a nonbonding electron from the carbonyl oxygen:



(17-31)

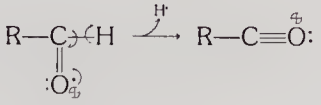
At somewhat higher energy, electrons can also be knocked out of the carbonyl pi bond, and at even higher energy out of the carbonyl sigma bond, as well as from other sigma bonds in the molecule. The fragmentations that are most characteristic of aldehydes and ketones are most easily understood in terms of the nonbonding electrons. Typical nonbonding electron ionization energies are between 9.4 and 9.8 eV.

Molecular ion peaks of aldehydes and ketones are generally small but present.

Aliphatic Aldehydes

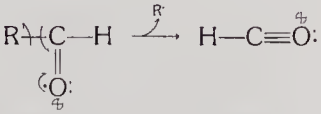
Several important modes of fragmentation are involved in producing the mass spectra of alphatic aldehydes.

Except for methanal (formaldehyde), any aldehyde can cleave in either of two ways at the carbonyl:



(17-32)

(I)

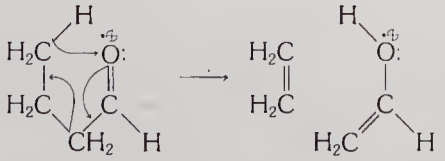


(17-33)

(II)

In equation 17-32, cleavage yields a hydrogen atom and an acyl ion (I) of mass (R + 28) u. By subtracting 28 u from the mass of the acyl ion, the mass of the alkyl group can be found. This is valuable information. Notice that the process in equation 17-32 yields an M − 1 ion. In equation 17-33 cleavage produces an alkyl-free radical and a methanoyl (formyl) ion (II) of 29 u. Here again, the mass of the alkyl group can be confirmed by subtracting 29 u from the molecular mass. In aldehydes of three carbons or less, the 29-u fragment produces the base peak. In larger aliphatic aldehydes, the mass at 29 u is roughly 40% of the base peak.

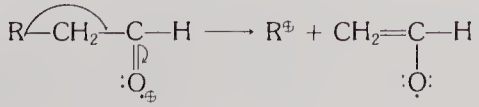
In aldehydes of more than three carbons, a hydride (or hydrogen atom in a homolytic process) can transfer from the number 4(γ) carbon in what is known as a **McLafferty rearrangement:**



(17-34)

This transfer results in expulsion of an alkene and an enol radical cation of 44 u. This ion is responsible for the base peak in saturated straight chain aliphatic aldehydes of four to seven carbons. If one or two alkyl groups are present on the number 2 (α) carbon, comparison of the proposed cleavage products from fragmentations of the types shown in equations 17-32, 17-33, and 17-34 can give valuable clues as to the substituents present on the number 2 carbon.

Another type of cleavage occurring between carbons 2 and 3 produces an alkyl ion of formula C_nH_{2n+1}:



(17-35)

This ion will have a mass M − 43 u if there are no substituents on the number 2 carbon.

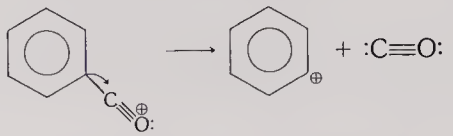
As the molecular weight of the aldehyde increases, the influence of the carbonyl on the mass spectrum decreases. The mass spectra of larger aldehydes are more like the spectra of hydrocarbons.

Aromatic Aldehydes

Aromatic aldehydes generally give an abundance of molecular ions. And the molecular ions fragment in relatively few ways.

A common cleavage involves loss of hydrogen from the carbonyl as shown in equation 17-38 for aliphatic aldehydes. The peak corresponding to M − 1 u is about the same height as that due to the molecular ion.

Further fragmentation of the M − 1 ion by loss of carbon monoxide readily occurs:



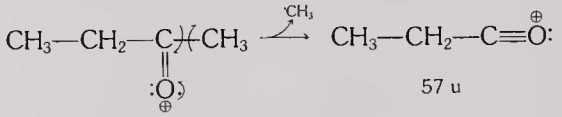
(17-36)

This cleavage produces a mass of 77 u. Further decomposition of $C_6H_5^+$ by loss of ethyne then occurs, yielding $C_4H_3^+$ of mass 51 u.

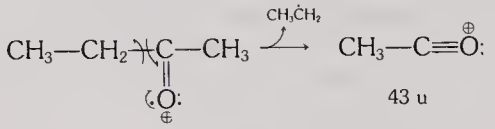
Substituted aromatic aldehydes exhibit the same general pattern of cleavages.

Aliphatic Open Chain Ketones

The spectra of these ketones can be interpreted on the same basis as that for aldehydes. The modes of fragmentation are the same. Cleavage between the number 1 and 2 carbons is relatively more important than in the case of aldehydes. The peak associated with loss of the larger alkyl group is likely to be higher than that associated with the smaller alkyl group. For example, look at these possible cleavages in butanone:



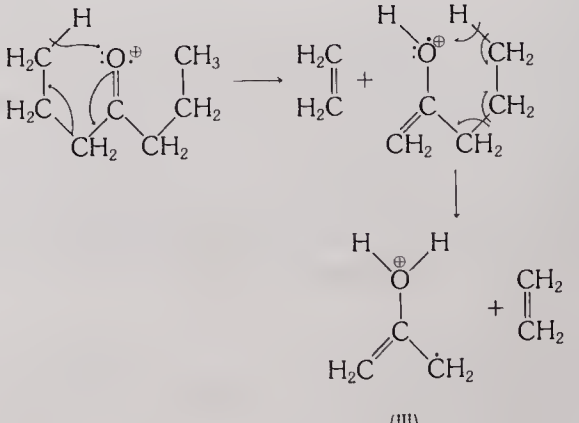
(17-37)



(17-38)

The loss of ethyl radical is favored because of its greater stability compared to methyl-free radical. Therefore we should expect the peak at 43 u to be higher than at 57 u.

McLafferty rearrangements take place in ketones as well as in aldehydes. In fact, a second rearrangement can follow the first if both chains attached to carbonyl contain three or more carbons:

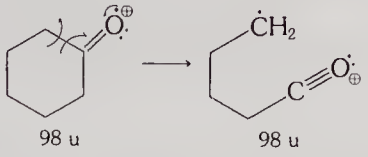


(17-39)

Note that if the two alkyl groups are different, there are two sets of successive McLafferty rearrangements that can occur. In the cases of longer alkyls or alkyls branched at the number 4 carbon, removal of hydrogen is preferred in the order 3° > 2° > 1°. Notice also that an obvious subsequent cleavage of (III) is loss of H_2O.

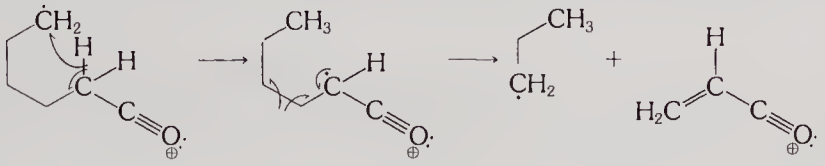
Cyclic Ketones

The molecular ion peak for a cyclic ketone is higher than that associated with its open chain counterpart. The reason is that cleavage would have to occur twice rather than once to reduce the molecular mass. Rupture of one bond in the cyclic structure leaves a structure that still retains the entire mass:



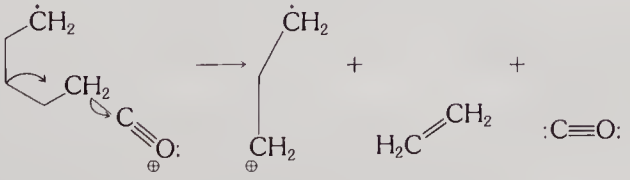
(17-40)

In the spectra of simple cyclic ketones, the highest peaks result from cleavage between carbons 1 and 2, followed by subsequent rearrangement and fragmentation:



(17-41)

or,

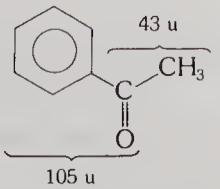


(17-42)

With substituted cyclic ketones, a combination of fragmentation modes for open chain and cyclic ketones is observed. If ethyl or larger groups are attached to cyclic ketones, McLafferty rearrangements can occur.

Aromatic Ketones

As for aromatic aldehydes, aromatic ketones have an uncomplicated fragmentation pattern. Molecular ion peaks are generally quite in evidence. Molecular ions of alkyl aryl ketones fragment in much the same manner as aryl aldehydes. Cleavage of the bond between alkyl group and carbonyl carbon occurs more readily than does the corresponding cleavage of the aryl-carbonyl bond. Therefore, in the fragmentation, for example, of 1-phenylethanone (acetophenone) a larger peak at 105 u will be observed than at 43 u:



The reason is primarily due to better stabilization of the acylium ion by resonance contribution of ring electrons.

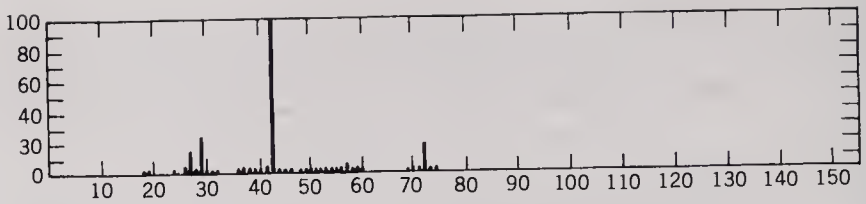


FIGURE 17.6 Mass spectrum of butanone. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

Analytical Application

Let us analyze the spectrum of Figure 17.6. If the peak at 72 u is the molecular ion peak, then we should expect that an $(M - 1)^+$ peak at 71 u would be observed if the compound is an aldehyde. Since there is none, we can proceed on the basis that the compound is a ketone. The base peak at 43 u, or M − 29 u suggests loss of an ethyl group in a cleavage between the carbonyl and the adjacent carbon:

(17-43)

The peak at 43 u suggests that R on carbonyl is methyl since 43 u minus the mass of carbonyl (28 u) is 15 u, the mass of methyl. The structure is apparently that of butanone, $CH_3—\overset{\overset{O}{\|}}{C}—CH_2—CH_3$. Confirmation is suggested by the small peak at 57 u due to loss of R in a similar manner to loss of ethyl in equation 17-43, and by the peak at 72 u, the molecular mass of butanone.

17.7 EXPERIMENTAL PART
Analysis of an Unknown

Your instructor will assign to you one or more unknown substances which are numbered from 1 through 36. Substances numbered 18 through 36 are introduced into the mass spectrometer directly from a GLC unit. You may assume that all unknowns represent pure samples containing one type of functional group. The substance will be an alcohol, aldehyde, or ketone.

Insert your mass spectrometry disk into disk drive No. 1. *Close the disk drive door,* and then turn on the computer, monitor screen, and printer. Follow the instructions the computer gives you. (Make sure the capitals lock is down.)

Using the mass spectrometer. The computer screen will display mass spectrometer controls and instructions for using them. You must set the controls to appropriate values in accord with your study of Technique 17. If you set the controls correctly, your "mass spectrometer" will function and the printer will then display a mass spectrum of your unknown either as a bar graph or table. If you set even one control incorrectly, the computer will respond by ringing a bell, displaying a message, or displaying a bad spectrum. It will not tell you which control is erroneously set, but you will have the opportunity to try again.

To make the most efficient use of your time at the computer, follow this procedure.

1. Scan using a mass range that you believe will be 50% higher than the molecular ion peak.
2. Optimize conditions to obtain the best information available about the molecular ion peak and run spectra that deliver this information.

3. Using standard instrument settings, obtain a final spectrum over a mass range up to about 5 u beyond the molecular ion peak.

To obtain values useful for calculating ion formulas, you will have to use a tabular printout.

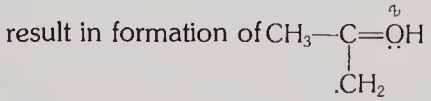
Writing the discussion. Identify the unknown and discuss your reasoning. Write ion fragmentation mechanisms that illustrate the formation of the important peaks leading to identification.

17.8 EXERCISES

Prelaboratory

1. What will you do immediately after inserting the mass spectrometry disk into the disk drive?
2. Make a detailed outline of your approach to using the "mass spectrometer." Include the control settings you intend to use for all three steps of the procedure suggested in the experimental part.
3. *Ken Dooit* suspected that a 1-cm peak of mass 79 was due to $(M + 1)^+$. He changed the sample pressure from 10^{-5} to 10^{-4} torr. If the peak was indeed $(M + 1)^+$ what did he observe in the spectrum?
4. *Norma Lee Good* obtained the spectrum of a compound with the ionizing potential at 70 eV. She then set the ionizing potential at 10 eV and obtained no spectrum. However, at 12 eV she obtained a large peak at mass 72 u along with many smaller peaks at lower mass. Explain.

Postlaboratory

1. Look at equation 17-4 and explain how voltage would be varied during electric scanning at fixed magnetic field in order to obtain a spectrum in which masses are recorded from lightest to heaviest.
2. Explain why loss of simple fragments are likely to leave daughter ions with odd-numbered masses when parents have even-numbered masses.
3. The mass spectrum for a compound shows a very small peak at m/z 74. Under proper conditions, the peak at m/z 75 can be made to increase significantly in intensity. What are these conditions? What do these results suggest for the molecular weight?
4. Equation 17-34 illustrates a hydride transfer from a γ carbon to carbonyl oxygen. Illustrate this same rearrangement with single-headed arrows for a homolytic transfer of a hydrogen atom.
5. Equation 17-39 depicts two McLafferty rearrangements, one following the other. Show mechanistically how the second one could result in formation of  rather than the ion radical shown. (Hint: Use another resonance form of the first McLafferty product.)
6. Draw resonance structures to show that an aryl acylium ion is more stable than an alkyl acylium ion.
7. The molecular ion radical for butanal can via a pseudo-six-member ring, lose a molecule of ethene and form an enol radical cation in a McLafferty rearrangement. Show the mechanism of this process. Also show mechanistically the likely fate of the enol radical cation in terms of further fragmentation.
8. Determine the structures of the compounds in Figures 17.7 through 17.10. Figures 17.7 and 17.8 are alcohols, aldehydes, or ketones; Figures 17.9 and 17.10 are bifunctional in carbonyl and/or hydroxyl.

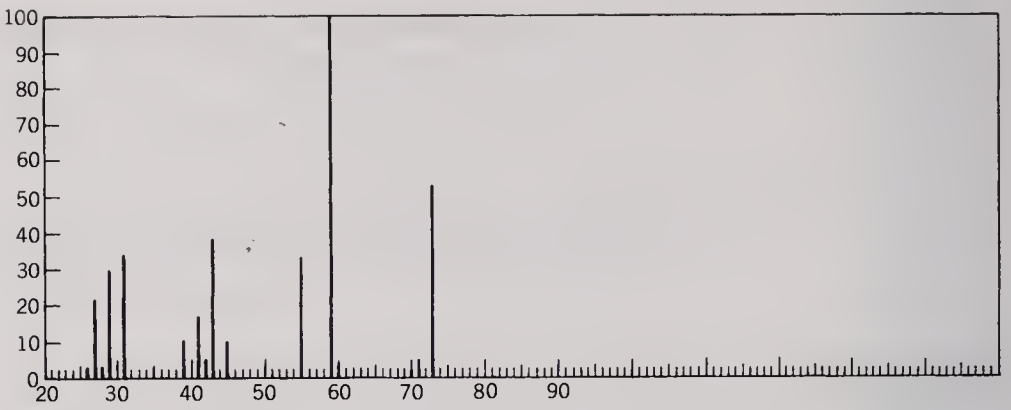


FIGURE 17.7 Mass spectrum of unknown substance. From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974, p 23. Reprinted by permission.

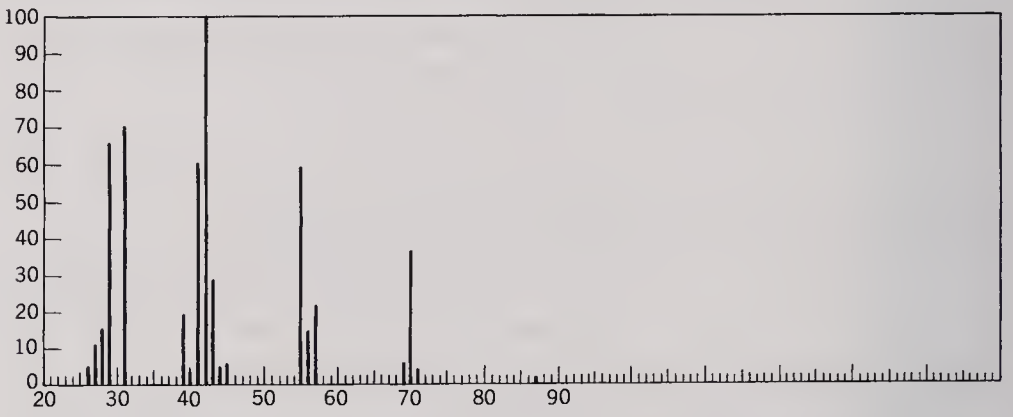


FIGURE 17.8 Mass spectrum of unknown substance. From Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974, p 23. Reprinted by permission.

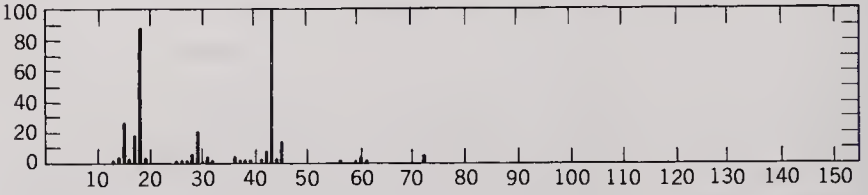


FIGURE 17.9 Mass spectrum of unknown substance. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

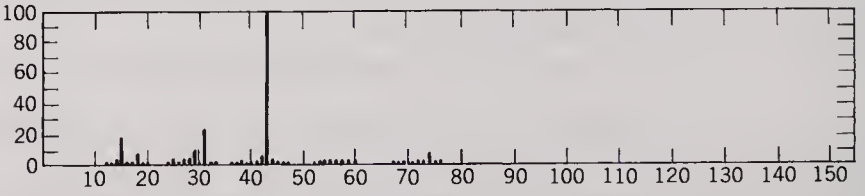


FIGURE 17.10 Mass spectrum of unknown substance. From NSRDS-NBS63, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand. (U. S.), 63, Vol. 3, 1978.

9. Draw lines on a mass scale from 0 to 105 to indicate where the major peaks would occur in the mass spectrum of 1-phenylethanone. Write fragmentation equations, showing the origin of the peaks.

REFERENCES

1. McLafferty, F. W. *Interpretation of Mass Spectra*, 2nd ed.; Benjamin: Reading, MA, 1973.
2. Budzikiewicz, H.; Djerassi, C.; Williams, D. H. *Mass Spectrometry of Organic Compounds*; Holden-Day: San Francisco, 1967.

3. Beynon, J. H. "Recommendations for Symbolism and Nomenclature for Mass Spectroscopy." *Pure Appl. Chem.* **1978,** *50,* 65.
4. Biemann, K. *Mass Spectrometry,* McGraw-Hill: New York, 1962.
5. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds,* 3rd ed.; Wiley: New York, 1974.
6. Heller, S. R. *EPA/NIH Mass Spectral Data Base,* NSRDS-NBS 63, Vol. 3, (Dec. 1978).

Acknowledgment
The writer thanks Ronald Robinson of Dow Corning Corp., Midland, MI for helpful discussions.

TECHNIQUE 18

THE CHEMICAL LITERATURE

As you are undoubtedly aware by now, what appears to be a simple, one-step process in your textbook can entail many hours of detailed procedure in the laboratory. Such procedures are not found in organic chemistry textbooks, but must be sought in the organic chemical literature.

The organic **chemical literature** consists of all of the written works concerning organic chemistry. The literature is very extensive, and has increased rapidly over the past 10 years. The purpose of this chapter is to acquaint you with the literature that is most likely to be of interest to you until you get to a more advanced level of research. For a more comprehensive treatment of the literature you should refer to the references at the end of this chapter.

Spending time in the library might seem to be a tedious chore. However, time spent searching the literature can save you many hours in the laboratory. If a good chemical library is available, an experienced person can find in a couple of hours whether a given compound has been prepared before; and if so, what preparative methods were used, what spectroscopic information is available, and what some of its physical and chemical properties are.

There are two major reasons why literature searches might prove to be frustrating experiences: First, library facilities are often limited and second, you might not know how to proceed. If your library has a relatively small selection of chemical literature, you might find it necessary to travel to another more complete library. Or, alternatively, your librarians can borrow books or obtain reprints of articles from the larger libraries. If you have a small chemical library it would be wise to begin literature searches far in advance of the time when you will need the information: Processing requests, mailing time, and lack of immediate availability of a certain book can result in long, discouraging delays.

18.1 SOURCES OF INFORMATION

There are two categories of sources: primary and secondary. **Primary sources** are those sources in which the original work is published, such as professional journals, certain books expressing new ideas, doctoral and masters degree theses, reports by and for some government agencies, and industry reports. Most industry reports, however, are private property of the companies and are not available to the public. **Secondary**

sources include all of the other literature that used the information of the primary sources. They include textbooks, handbooks of chemistry and physics, toxicology books, books on synthesis and analysis, and so on. The source categories most likely to be useful to you are summarized below.

Primary Research Journals

These journals, such as the *Journal of the American Chemical Society, Journal of Organic Chemistry, Chromatography,* and *Journal of Applied Polymer Science,* contain the original work and give preparative and analytical details. There are hundreds of journals that might be of interest to an organic chemist. Because of this large number and the time required to search through them, the journals themselves are obviously not the place to start a literature search. They are more likely to be the sources to which secondary sources finally refer you.

Review Journals and Monographs

Reviews are collections, summaries, and evaluations of original work published in the primary sources. **Monographs** are scholarly books or pamphlets that are devoted to a specialized topic. Reviews and monographs are valuable sources of information, and give references to all of the original works they encompass. In addition, review journals generally provide an annual author and subject index. However, you should not assume that all possible primary sources have been quoted in a review or monograph. Some of the more important review journals you are likely to find of interest are:

1. *Accounts of Chemical Research*
2. *Annual Reports on the Progress of Chemistry* (London)
3. *Chemical Reviews*
4. *Quarterly Reviews*
5. *Synthesis*

Also, reviews are often found in *Angewandte Chemie* (English edition available).

The *Journal of Organic Chemistry* since 1978 has biennially published a section called "Recent Reviews," which is a referenced list of reviews and monographs related to organic chemistry. Also, references to reviews on topics of interest can be found in *Index to Reviews, Volumes, and Monographs in Organic Chemistry,* Kharasch, N; Wolf, W., Eds.; Pergamon.

Laboratory Books

Laboratory books, like this one, are often a good source of information on techniques and synthetic methods. Such references can be particularly helpful to the novice because more extensive and easy-to-understand information is likely to be given.

Encyclopedias and Dictionaries

A **chemical encyclopedia** is a comprehensive reference to a wide variety of alphabetically arranged topics in chemistry. A **chemical dictionary** is an alphabetically arranged list of chemically related words (including compounds) and their definitions, and might include short explanations, physical properties, biological properties, chemical properties, structures, and references. In such volumes, only relatively small amounts of information are usually given on any one subject. Some dictionaries and encyclopedias you are likely to find most useful are:

1. *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical Co.: Milwaukee, WI, 1985–1986 and earlier editions.
2. *Atlas of Spectral Data and Physical Constants for Organic Compounds*; Grasselli, J. G., Ed.; CRC: Cleveland, OH, 1973.
3. *Beilstein's Handbuch der Organischen Chemie*; Springer-Verlag: Berlin, 1918 to present. (This work is of such importance that Section 18.4 is devoted to its description.)

4. *Chemistry of Carbon Compounds*; Rodd, E. H., Ed.; Elsevier: New York, 1951 to present.
5. *Dictionary of Organic Compounds* Heilbron, 4th ed.; Pollack J. R. A.; Stevens, R., Eds.; Oxford University Press: New York, 1965 with annual supplements.
6. *Handbook of Chemistry and Physics,* various annual or biennial editions; Chemical Rubber Publishing Co.: Cleveland, OH.
7. *Handbook of Tables for Identification of Organic Compounds,* 3rd ed., Rappaport, A., Ed.; Chemical Rubber Publishing Co.: Cleveland, OH, 1967.
8. *Kirk-Othmer Encyclopedia of Chemical Technology,* 3rd ed.; Grayson, M., Exec. Ed.; Wiley: New York, 1978. 25 volumes.
9. *Lange's Handbook of Chemistry,* 11th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, 1974.
10. *Merck Index of Chemicals and Drugs,* 9th ed.; Merck and Co.: Rahway, NJ, 1976.
11. Patterson, A. M.; Capell, L. T.; Walker, D. F. *The Ring Index,* 2nd ed.; American Chemical Society: Washington, DC, 1960 with supplements.
12. *Industrial Hygiene and Toxicology,* 2nd rev. ed.; Patty, F. A., Ed.; Interscience: New York, 1958. Three volumes.
13. Sax, N. I. *Dangerous Properties of Industrial Materials,* 3rd ed.; Reinhold Publishing: New York, 1968.
14. *Handbook of Laboratory Safety,* 2nd ed.; Steere, N. V., Ed.; Chemical Rubber Co.: Cleveland, OH, 1971.

Volumes of Spectral Data

These volumes provide standard spectra with which you can compare spectra generated in your laboratory. Some volumes you are likely to find useful are:

1. *The Aldrich Library of Infrared Spectra,* 3rd ed.; Pouchert, C. J., Ed.; Aldrich Chemical Co.: Milwaukee, 1981.
2. *The Aldrich Library of NMR Spectra,* 2nd ed.; Pouchert, C. J., Ed.; Aldrich Chemical Co.: Milwaukee, 1983. Two volumes.
3. *Sadtler Spectra Handbook of Reference Spectra*; Sadtler Research Laboratories: Philadelphia. Volumes on IR, UV, NMR.
4. *Atlas of Spectral Data and Physical Constants for Organic Compounds*; Grasseli, J. G., Ed.; CRC: Cleveland, OH, 1973.

References on Synthesis, Methods, and Techniques

Some of the most useful books fall into this category. Here are a few that are likely to be of particular interest:

1. *Organic Syntheses*; John Wiley & Sons: New York, 1932 to present. Many volumes.
2. *Organic Reactions*; John Wiley & Sons: New York, 1942 on. Many volumes.
3. Vogel, A. I. *Practical Organic Chemistry,* 3rd. ed.; Longman Group, Ltd: London, 1956.
4. Fieser, M; Fieser, L. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967.
5. Wagner, R. B.; Zook, H. O. *Synthetic Organic Chemistry*; John Wiley & Sons: New York, 1953.
6. *Technique of Organic Chemistry,* 3rd. ed.; Weissberger, A., Ed.; Interscience: New York, 1959. Many volumes.

Abstracts and Alerting Services

Abstracts are concise summaries. The first two journals listed below are devoted to summarizing all of the pertinent chemical literature. Because abstracting and printing the

abstracts might take as much as a year after the original work was published, **alerting services** have been developed to make interested parties aware of new publications at an earlier date. The abstracts will be of greater use to you unless you are watching for something very recent. The most notable abstracting and alerting journals are listed below:

1. *Chemical Abstracts.* This is one of the places to look for information when the easier-to-use sources listed above do not yield the information you need. This service is of such importance that its use is discussed in some detail in Section 18.3.
2. *Chemisches Zentralblatt.* This abstracting journal is written in German. *Chemisches Zentralblatt* is more thorough in its coverage of material published prior to 1939 than Chemical Abstracts. Also, the journal originated in 1856, whereas *Chemical Abstracts* did not begin publication until 1907. Today, the two journals complement each other; what is not found in one is likely to be found in the other. Author, subject, formula, and patent indexes are provided.
3. *Chemical Titles.* Each issue consists of three sections: a list of publication titles, an alphabetical listing of journals from which the titles were obtained, and an author index.
4. *Current Chemical Papers.* Each issue contains a list of titles, authors, and sources of articles in pure chemistry. Organic chemistry is one of about a dozen areas involved.
5. *Current Contents.* Each issue is made up of photostated title pages of journal articles from three areas: life sciences, physical sciences, and chemical sciences.
6. *Index Chemicus.* This is a more comprehensive, more expensive alerting service which contains an abstract of the original article in the language of publication.
7. *Science Citation Index.* This journal provides a means of searching the literature from a given data *forward* to current times, whereas other services search only *backward* in time.
8. *Computer Search Profiles.* This service supplies references when a keyword profile is supplied to a computer with stored information excerpted from current sources. If you are willing to pay for it, the most up-to-date information is available long before it gets into the printed indexes.

18.2 MAKING A LITERATURE SEARCH

While making a literature search, you should have your notebook with you. Use it to list under appropriate headings all references that *might* be of interest to you. List along with the references the name and page of the abstract, index, or other source in which you found them. It is easier to make these lists when the source volume is open than to later wish you had after you can not remember where you saw the reference.

The method of searching the literature depends somewhat on whether you are looking for information about a specific compound, or a certain topic, reaction, or class of compounds.

Search for a Specific Compound

If your goal is to obtain information about a compound, your best plan of attack is probably to first consult Wagner and Zook's *Synthetic Organic Chemistry,* where you might find some general information about synthesis and also some references to the primary journals or books on synthesis. You should also consult the *Dictionary of Organic Compounds, The Ring Index,* (if your compound is cyclic), and *Chemistry of Carbon Compounds.* For physical properties, look in the various handbooks, the *Merck Index,* and the *Aldrich Catalog.* Also, do not forget to look in laboratory textbooks and manuals. If, after proceeding this far, your search has not yet turned up the information you need, proceed next to *Beilstein's Handbuch.* Then, look in *Chemical Abstracts* and *Chemisches*

Zentralblatt. If the compound is a very new one, or you want the most recent information, refer to the alerting services.

If your compound is one that has been known for a long time, Beilstein is likely to give the best information. If the compound is relatively new (but not newer than one or two years ago), *Chemical Abstracts* or *Chemisches Zentralblatt* is a more likely source.

A complete up-to-date search, of course, requires use of *Beilstein, Chemical Abstracts, Chemisches Zentralblatt,* and the alerting services.

Search for a Topic, Reaction, or Class of Compounds

When you need to find information of this sort, you should go directly to the subject indexes of *Chemical Abstracts* and *Chemisches Zentralblatt.* You must try to second-guess the thought processes of the abstracters with respect to the way they would have cataloged the entries. For example, suppose that you want information about the reaction

$$CH_3MgBr \xrightarrow[2)\ H_3O^+]{1)\ CH_3CHO} CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3. \qquad (18\text{-}1)$$

You might find it under any one or more of the following headings: methylmagnesium bromide, reactions; ethanal, reactions; 2-propanol, preparations; Grignard reactions; perhaps even acetaldehyde, reactions; and isopropyl alcohol, preparations since the chemical abstracting services uses some common names of long standing.

It is probably most efficient to start with the indexes of the latest abstracts and work back. Using this approach may call to your attention reviews and monographs that are helpful in summarizing information and supplying more references. However, if you know the time period when most of the interest developed about the topic, it might be more advantageous to start your search in abstracts dated no more than a few years later than the active period.

18.3 CHEMICAL ABSTRACTS

An **abstract** is a summary of the important parts of an article or text.

Chemical Abstracts is one of the largest services of its kind, regularly publishing abstracts from over 10,000 scientific journals and other sources worldwide. Although a complete discussion on the use of this service is impossible in this book, enough information will be presented to point you in the right direction.

The way to use *Chemical Abstracts* is first, to find the item of interest in an appropriate index; second, to use the index to locate the abstract; and third, to use the abstract to determine the content value, and then to locate the original paper.

After you locate the abstract you will of course read enough of it to determine whether it supplies the information you need. Sometimes the abstract itself gives all the information you require. However, this is unusual, and you will need to read the primary source. The abstract includes a reference to the source, stating the name of the author, the title of the journal, the volume number, page number, and year of the publication.

The Indexes

The index and abstract formats have been differently arranged during different time periods.

Until 1934 the abstracts were arranged in a single column per page. The index to these abstracts refers to the volume, page, and region on the page on which the desired abstract is found. For example, **28**, 314^3 tells you to look in Volume 28, page 314, down the page to near the number 3 in the margin.

From 1934 to 1947 the page was divided into two columns, and the notation **51**, 314^5 means that you should look in Volume 28, column 314, down the page to near location 5 in the margin.

From 1947 to 1967 the superscript page position numbers were replaced by non-

superscript letters of the alphabet from a to i. The notation, for instance, might be **68**, 1758g.

Since 1967, a new listing system has been used. There are no column numbers or letters. Instead, each abstract is given a number, the numbers being assigned consecutively throughout each volume. For example, the index might list **80**, 3127 d. This means to look in volume 80 for entry number 3127. The letter at the end of the number no longer has any meaning in your search. It is there for computer usage.

The capital letter P which sometimes precedes a page, column, or entry number, such as **45**, P 1755 h, means that the entry refers to a patent.

Chemical Abstracts provided formula, subject, author, and patent indexes up until 1972. Since 1972, the Chemical Abstracting Service has produced an index guide, general subject index, formula index, ring index, patent index, and author index. Use of the various indexes is described in Volume 76 starting on page 1 l.

In addition to the annual indexes, there are decennial indexes up until 1956 and collective indexes for each five-year periods since then.

Also, each weekly issue of *Chemical Abstracts* includes an author index, a keyword index, a patent index, and a patent concordance (an alphabetical index of important words).

Which index to use depends somewhat on what kind of information you are seeking. Generally, you should concentrate your attention on the subject index. The formula index is a little easier to use, but is not as reliable. For a complete search, both should be used, as well as the patent index. Because the five-year and decennial indexes cover the same information as annual indexes, you should always consult them when they are available.

Use of the Formula Index

When your search involves a specific compound, the formula index is the easiest place to start. You should remember, however, that the formula index is not as reliable as the subject index. For carbon compounds, the molecular formula is listed in the order C, H, then other elements in alphabetic order (the **Hill system**). The formulas are indexed beginning with small subscripts and proceeding in order of increasing subscript size. For example, C_4H_8O appears before C_8H_{16}.

After the formula has been located in the index, you will find a list of many isomeric compounds. You must determine which is the one of interest to you. This of course demands some knowledge of organic nomenclature as used by *Chemical Abstracts,* but it is not usually too difficult to pick out your compound.

Use of the Subject Index

In using the subject index, your first job is to determine the name of your compound as listed by *Chemical Abstracts*. The *Chemical Abstracts* system is given in the Volume 56 subject index. It is basically the same as IUPAC nomenclature. However, some common names and trivial names are employed when they have been widely used for a long time.

In *Chemical Abstracts* indexes, the parent portion of the compound is listed first, followed by the substituents in alphabetic order. For example, 1-chloro-3-methyl-2-pentanone is listed as 2-pentanone, 1-chloro-3-methyl-. So, in the subject index you look under pentanone. Sometimes the most important function is given as part of the parent name and not as a substituent: In the above example, the compound could be called chloro 3-methyl-2-oxopentane. Because the doubly bonded oxygen is considered to be the main function it is incorporated into the parent name. For multifunctional compounds, an arbitrary order of priority is employed; acid, acyl halide, amide, imide, aldehyde, nitrite, ketone, alcohol, phenol, thiol, amine, imine, ether, sulfoxide, and sulfone, the last named being the lowest priority.

You will often have to use your imagination and try all possibilities. One way to obtain a name is to look for it in the formula index; references to the compound in subject indexes will most likely appear as named in the formula index. The *Ring Index* is helpful for naming cyclic compounds.

18.4 BEILSTEIN'S HANDBUCH

Beilstein's Handbuch der Organischen Chemie, commonly referred to simply as *Beilstein* is far from being a simple handbook, although the first edition in 1883 did consist of only two volumes.

Even though *Beilstein* is more of an encyclopedia of organic compounds than it is an abstracting journal, it serves much the same purpose. It is an index of organic compounds along with such information as structural formula, physical and chemical properties, syntheses, and references.

Beilstein covers the compounds from the beginning of organic chemistry in the 1800s up to 1930. It is the most thorough reference of organic compounds. You can confidently use *Beilstein,* knowing that if a given compound is not cataloged it was unknown before 1930.

Although a comprehensive discussion of *Beilstein* is impossible in this book, enough information will be given so that you will be able to use this important reference. Since it is written in German, you will want to have a German-English dictionary handy.

Safety hazards can result from mistranslations. If you have little facility with German, have synthetic procedures translated for you or have your translations reviewed by a competent chemist.

Organization of Beilstein

In 1909 the fourth edition of *Beilstein* was published. No new editions have been published since then. Instead, supplements to the fourth edition were published. The fourth edition therefore forms the basis of *Beilstein* as we know it today. The fourth edition is called the Hauptwerk (the main work), and is abbreviated as H in each supplement (Ergänzungswerk). The Hauptwerk consists of 27 volumes. Each Band (volume) covers certain classes of compounds, which are sometimes, but not always, listed on the spine of the book. The classes of compounds are subdivided into 4877 subclasses; each subclass has a Systemnummer (system number) assigned to it, and these are always listed on the spine. Page XXXI of Band I of the Hauptwerk lists the volume, class, and Systemnummer assigned to the class.

The Erstes Ergänzungswerk (first supplement, EI, or I) covers the years 1910 through 1919. The same classes of compounds appear in the same-numbered volumes as in the Hauptwerk; the Systemnummer for each class is also the same.

The Zweites Ergänzungswerk (second supplement, EII, or II) covers the period 1920 through 1929 and also has the same organization as the Hauptwerk. However, two additional volumes appear in the Zweites Ergänzungswerk. Band XXVIII (volume 28) is a General Sachregister (cumulative name index), and Band XXIX (volume 29) is a General Formelregister (cumulative formula index). These indexes include all compounds of the Hauptwerk, Erstes Ergänzungswerk, and Zweites Ergänzungswerk.

The Drittes Ergänzungswerk (third supplement, EIII, or III), still incomplete, will cover the period 1930 to 1949. The Viertes Ergänzungswerk (fourth supplement, EIV, or IV) was begun in 1972, and will cover the period 1950 to 1959. Beginning with Band XVII (volume 17), the Drittes Ergänzungswerk and Viertes Ergänzungswerk are published within the same volume and together will cover the years 1930 to 1959.

There are four major sections in Beilstein: (1) Acyclische Reihe (noncyclic series), (2) Isocyclische Reihe (carbocyclic series), (3) Heterocyclische Reihe (heterocyclic series), and (4) Natürlich Produkte (natural products). Each section is found in the volumes of the Hauptwerk and each Ergänzungswerk in that order. Within these sections, compounds are subdivided into classes such as Kohlenwasserstoff (hydrocarbons); Oxy-Verbindungen (hydroxy compounds like alcohols, glycols, phenols, etc.); oxo-Verbindungen (aldehydes, ketones, and aldols); carbonsäuren (carboxylic acids); Sulfonsäuren (sulfonic acids); Amine (amines and related compounds); Azo-, Diazo-, and diazonium Verbindungen (azo-, diazo-, and diazonium compounds); and so on.

Compounds that have two or more like functional groups are found in the same

class as for the single function. Those that have two or more unlike functional groups are found among that class that appears latest on the list of class subdivisions. For example, *p*-hydroxybenzoic acid is classified as a carboxylic acid, but *p*-aminobenzoic acid is classified as an amine because the amines class is found farther down the list than the carboxylic acids class. Compounds containing functional groups like halogens and nitro groups that are not listed in the various classes are listed in the class with the parent compound. Compounds that yield hydrolysis products that can be found among the listed classes are put into that class that contains the hydrolysis product of latest listing. For example, methyl benzoate is listed with alcohols; benzoic anhydride is listed among carboxylic acids; and *N*, *N*-diethyl toluamide is listed with amines.

When you have located a compound, you will find various properties and syntheses listed along with references. The references are much abbreviated; the abbreviations (abkurzungen) used can be found in the introductory section of each Band. Sometimes some literature source abbreviations will appear in a table of commonly used abbreviations, and others in a table of additional abbreviations.

Indexes

There is a name index in each volume. However, the indexes of the Zweites Ergänzungswerk should be used for all work before 1929 since these indexes are cumulative. These indexes indicate where to find a compound in the Hauptwerk or either Ergänzungswerk. For example, having located $C_{12}H_{10}O$ in Band XXIX (29), we see the notation Diphenyläther 6, 146, I 84, II 148. This means that information about diphenyl ether will be found in the Hauptwerk in Band 6, on page 146, in the Erstes Ergänzungswerk in Band 6 on page 84, and in the Zweites Ergänzungswerk in Band 6 on page 148. You should note that although volume numbers in the indexes are in Arabic numerals, the volume number on the Band itself is likely to be a Roman numeral.

Using the Formelregister

For someone who does not read German, the easiest approach to obtaining information from *Beilstein* is to use the Formelregister. This is especially the case because lack of knowledge of the language is compounded by frequent use in Beilstein of nonsystematic nomenclature.

The cataloging of formulas in the Zweites Ergänzungswerk and thereafter follows the same method as used in *Chemical Abstracts* (the Hill system). But cataloging in the indexes of the Hauptwerk and Erstes Ergänzungswerk is according to the **Richter system,** wherein the order of listing elements is C, H, O, N, Cl, Br, I, F, S, P, then an alphabetic arrangement for other elements.

The Formelregister refers to various isomers by systematic names, but the numbering system for substituents and functional groups is likely to be different from that used by *Chemical Abstracts*. Drawing the formulas of the isomers in accord with good reasoning and judgment will help you decide which isomer is the one you want.

Using the Sachregister

A better acquaintance with German is required for this approach. Furthermore, there is no distinguishing among structural isomers in any of the name indexes. If the index lists a compound and refers you to several volumes and pages, you must look at all of them to determine which isomer is discussed on each page. For example, if pentane were listed along with a number of volume and page locations, you would not know until you read part of the page whether the reference was to *n*-pentane, *i*-pentane, or neopentane.

Using Functional Group Classes

If you become thoroughly familiar with the organization of Beilstein as noted above, you can omit the indexes and take your search directly into the volumes where your compound is described. This method requires a reasonable familiarity with German but with some practice is the fastest method of all.

Using the Systemnummer

Once you have located at least one reference to a given compound, you will see on the page a notation "Syst. Nr. XXXX." Once a compound's Systemnummer (system number) has been located, you can find reference to that compound by selecting the volume of any supplement that includes the system number of the compound. Then search the pages until you find a page with the same system number notation. This method works even for the Drittes Ergänzungswerk and Viertes Ergänzungswerk where there are no indexes.

Using Aldrich or Lange

A relatively easy way to find information about a compound is to refer to the *Aldrich Catalog* or *Lange's Handbook* as listed in Section 18.1. These sources include a *Beilstein* reference, if any, along with each listed compound. Of course, if the compound you are interested in is not listed in these sources, you will have to go directly to *Beilstein*.

18.5 EXPERIMENTAL PART
Literature Search

Search the literature to obtain information to satisfy the following assignments, as directed by your instructor. In each case cite all references, including *Chemical Abstracts* and *Beilstein*.

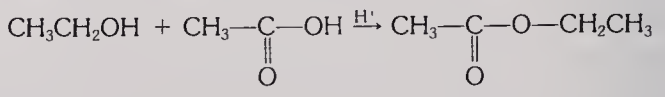
1. Find the melting point, boiling point, refractive index, and density, of quinoline. Cite the reference.
2. Report the chemical hazards of isopropyl glycidyl ether. Cite the reference.
3. Determine whether cyclobutadiene has ever been prepared, and if so give the complete reference for the first synthesis.
4. Find a review that discusses organic and inorganic cubanes.
5. Locate an article that discusses Friedel-Crafts reactions. Give your reference.
6. Find the solubility of acetylene in water at 12 °C and 755 mm. List the primary reference.
7. Find the melting point of *trans*-1-amino-2-methylcyclohexane after crystallization from benzene-ligroine. List the primary reference.
8. Find the color and shape of crystals of 2,3,4,6-tetrabromoaniline; also the corrected melting point. Give the primary reference.
9. Describe briefly what you find in *Beilstein*, I, 27, 267.

18.6 EXERCISES

Prelaboratory

1. State the fundamental purpose of each of the following secondary sources: handbooks, toxicology books, monographs, and review journals.
2. Write the definition of "journal" as found in a large dictionary and in the context of this chapter. Report the derivation of the word and how it applies to the definition as used herein.
3. Define chemical encyclopedia and chemical dictionary.
4. What is an "atlas" of spectral data? Define the word as given in a large dictionary and in the context of this chapter. Look in such an atlas and list the type of information contained.
5. What kind of secondary source is *Accounts of Chemical Research?*
6. List the kinds of information available in *Beilstein*. Is this a simple "Handbuch"?

7. Define "abstract." List the titles of two major abstracting services.
8. List the English words that correspond to the following German words: Hauptwerk, Ergänzungswerk, Band, Erstes, Zweites, Drittes, Viertes, Sachregister, Formelregister.
9. In what Beilstein class would you expect to find (a) 1,3-propanediol, (b) 4-methylbenzenecarboxylic acid, (c) 3-amino-2-methylbutanal, and (d) ethyl 2-methylpentanoate?
10. How might the following reaction be entered in *Chemical Abstracts?*



11. What does the notation *27,* 412^4 mean in a *Chemical Abstracts* index?
12. How would you expect 3-phenylhexanal to be listed in a *Chemical Abstracts* index?
13. Under the listing for imidazole in an *Aldrich Catalog Handbook of Fine Chemicals* the notation "Beil. *23,* 45" appears. What does this notation mean?
14. If you wanted information about methyl anthranilate would you first consult the decennial indexes of *Chemical Abstracts?* Explain your answer.

Postlaboratory

1. *Hal Ogen* looked in the *Aldrich Catalog Handbook* for information on tetrachloromethane. List all of the informative items he found.
2. *Annie Won* can get a lot of information from *Beilstein* if it is properly used. She has heard about a new analgesic drug put on the market in 1983 and is contemplating searching *Beilstein* for details on the drug's physical properties. What is your advice to her? Explain.
3. A student was looking for information about a new organic compound he suspected had been synthesized a few months earlier. He began his search with the indexes of recent issues of *Journal of Organic Chemistry.* Critique his approach.
4. *Polly Ester* chose benzocaine, a long-known compound, to prepare and identify for a laboratory project. She listed the following references to consult in the order given: Wagner and Zook's *Synthetic Organic Chemistry,* Heilbron's *Dictionary of Organic Compounds, The Ring Index,* Rodd's *Chemistry of Carbon Compounds,* the *Merck Index,* a handbook of chemistry and physics, and Sax's *Dangerous Properties of Industrial Materials.* Critique her approach.
5. *Al Kaloid* wanted information about a compound which he was quite certain was a known substance. In order to get information quickly he consulted all available review journals and monographs from their inception to the present. The compound was not discussed in any of them; so he concluded that it was an unknown substance. Is this what you would have done? Explain.
6. A student concluded that because he could not find $C_{13}H_{12}N_2O$ in the Erstes Ergänzungswerk of *Beilstein* that compounds of this formula were not known prior to 1919. Do you agree? Explain.

REFERENCES

1. Hancock, J. E. H. *J. Chem. Educ.* **1968,** *45,* 193, 260, 336.
2. Huntress, E. H. *A Brief Introduction to the Use of Beilstein's Handbuch der Organischen Chemie*; Wiley: New York, 1938.
3. *Searching the Chemical Literature*; Gould, R. F., Ed.; Advances in Chemistry *30*; American Chemical Society: Washington, DC, 1961.
4. Weissbach, O. *The Beilstein Guide: A Manual for the Use of Beilstein's Handbuch der Organischen Chemie*; Springer-Verlag: New York, 1976.
5. Sunkel, J.; Hoffmann, E.; Luckenbach, R. *J. Chem. Educ.* **1981,** *58,* 982.

TECHNIQUE 19

REPORT WRITING

After completing your literature search and your laboratory research you must intelligibly communicate to your colleagues what you have discovered and what its significance is. Otherwise your work is likely to be of little value to the world.

The object of this chapter is to acquaint you with the fundamental features of report and journal writing. You can find additional details in the references at the end of this chapter. Furthermore, each journal's first issue of the year usually gives manuscript contributor instructions. For example, such instructions can be found in *J. Org. Chem.* **1986,** *51,* 9A.

19.1 THE FORMAT

Each journal or chemical company subscribes to a particular format for its written work. The **format** is a basic ordering of topics and form of presentation. Its purpose is to generate uniformity so that the regular reader of the journal or report knows what to expect and how to quickly find information.

Another important aspect of journal and report writing is the style of writing. For example, it is generally a requirement that articles be written concisely and in the third person.

It is important to follow the format and style of the journal for which you are writing. Otherwise, your article might be returned to you by the editor without even having been read.

There is some latitude in the format of a scientific report, but in general your article will contain the following elements in the order given: title, name of author, abstract, introduction, results and discussion, experimental part, acknowledgements, and references. It is not uncommon for the experimental part to precede the results and discussion.

As you continue to read, you will notice that the format used in this book generally parallels that of journal writing.

The Title

The title should be descriptive of the main thrust of the article but should be as short as possible. You should not use symbols and formulas in titles.

The Abstract

An **abstract** is a concise summary of the article, and is sometimes called the summary, or synopsis. Only rarely should it contain more than 200 words. There are two reasons for the abstract: First, the reader can quickly determine whether the article is of interest without wading through a lot of words; and second, an abstract already written by the author alleviates pressure on the American Chemical Society's *Chemical Abstracts* in providing a speedy abstracting service.

Notice how the abstract of the sample report in Figure 19.1 at the end of this technique summarizes the article, very concisely relating its three fundamental parts: First, it tells what the experimental part contains; next, it describes the results; and finally, it provides a brief summary of the conclusion.

The Introduction

The purpose of this part of the paper is to provide the reader with background. The **introduction** should clearly state the problem being investigated. It ought to tell why the current article is of interest, what similar work was done in the past, and why the currently reported research was undertaken. It should cite appropriate literature, but avoid including semirelevant information.

In the sample report the author has met most of these conditions, but could have made the statement of purpose more obvious.

Sometimes, in some journals, the introductory section is not formally captioned by the word "Introduction."

The Experimental Part

The **experimental** section provides a description of materials, instrumentation, unusual apparatus, methods, and data obtained. It should also note any *unusual* safety hazards. The experimental part should be complete enough that the reader could repeat the work and obtain the same results.

If the method has already been published elsewhere, it should not be described again in the current work. It is only necessary to state, for example, that "The method was that according to Vogel[2]." The superscript reference number refers the reader to Vogel's work. If you use a method primarily taken from someone else's work but modify it, you might say something like, "The method was that of Vogel[2] with the following modifications." An exception to the rule of not repeating already published work is the instance where you know that the method is available only by reference to some obscure source or to an article written in a little-known language. Under such circumstances, you should describe the entire procedure, but nevertheless preface the description by reference to the original work.

In some journals the experimental part is simply referred to as "Experimental," as it is in the sample article of Figure 19.1.

The Results and Discussion

The **results and discussion** section presents the results of the current research. It then proceeds to discuss the meaning of these results in terms of past and newly acquired knowledge. The discussion centers on the conclusions that can be drawn from the author's research.

This section of the paper includes all relevant data, and main points and limitations of the work. It uses formulas, equations, figures, and tables to make the article clear and concise. Notice how the writer of the sample article has used these media, and how he has referred to them in his presentation.

In some papers the author presents the results in one section and discusses them in a subsequent section. The mode of presentation is at the discretion of the writer.

In some chemical journals the results and discussion section precedes the experimental section. Such sequencing probably arose from the idea that the reader is normally more interested in the results and author's comments than in the experimental methods. After all, the results of the work and the discussion of them are the heart of the article and provide the main reasoning for writing it.

Acknowledgments

The **acknowledgment** gives recognition to people or institutions that gave the author assistance in terms of finances, gratis laboratory work, and helpful discussions. The acknowledgment is a matter of courtesy and professionalism.

Notice how the writer handles this in Figure 19.1.

Referencing

A **reference** is a source to which the publication refers the reader. Proper and adequate referencing is essential, being the service that directs the reader's quest for further information.

From your experience in literature searches, you already know how important

references are, and how frustrating it can be when you can not seem to find what you need.

A reference should be made for every informational item that the writer thinks is not normally in the possession of the reader. Whenever such an item is introduced, the writer places a superscript Arabic number at a position in the statement which most clearly indicates the thought that is being referenced. Notice the positioning of the superscripts, for example, in the first paragraph of the Introduction in Figure 19.1, where the reference numbers relate to the foregoing statement. On the other hand, when other authors are named, it is often more convenient for the reader to find the reference number following the name of the other authors, as in the final paragraph in the discussion section of Figure 19.1. The superscript refers the reader either to the bottom of the page or to the end of the article, where the corresponding number gives the reference. The location of the references depends on the practice of the journal.

It is important to notice that the references are listed in the order in which they appear in the article, not alphabetically. Whenever a reference is repeated, the writer uses the *same* superscript number. Notice, for example, that references 4–7 were used twice by the author in Figure 19.1: in the second paragraph of the Introduction, and at the beginning of the final paragraph in the Discussion.

All journal references should include the authors, journal, year, volume, and at least the first page of the report in that order (see references 2–10 in Figure 19.1). *J. Am. Chem. Soc.* strongly recommends that you list both the first and last pages. When referencing a journal that begins every issue with page 1, include the issue number in parentheses following the volume number:

Stinson, *S. C. Chem. Eng. News* **1985,** *63* (25), 26.

All book references should include all of the following elements that are appropriate: authors, title of book, edition, editor, publisher, city and state of publication, year of publication, and location of information (volume, chapter, page), in that order (see reference 11 and 13 in Figure 19.1). An example is

Handbook of Chemistry and Physics, 53rd ed.; Weast, R. C., Ed; CRC: Cleveland, OH, 1972; pC-135.

Notice that a colon is used between publisher and place of publication; that semicolons precede editor, publisher, and location of information; that commas are used to separate the various parts between semicolons; and that a period separates author from name of publication.

References to corporate publications should include the authors (if any), title, name of corporation, publication number, and date, in that order (reference 12 in Figure 19.1).

Patent references should include the authors, the patent number, and year, in that order (reference 1 in Figure 19.1).

When you obtain information from a reference as described by someone other than the original authors you must so indicate, for example, if you refer to the work of P. R. Story who cites the work of Teetem and Bell, you would record

Teetem, H. M.; Bell, E. W. *Org. Syntheses* **1952,** *32,* 20; Story, P. R. *J. Org. Chem.* **1961,** *26,* 287.

You must use abbreviations when referencing. Always use authors' initials, not their full names; and never include titles, such as "Dr." and "Professor." When writing the reference use the following abbreviations: 1st, 2nd, 3rd, and so on, for first, second, third, and so on; ed. for edition; Ed. for editor; ch. for chapter; and p for page. Most journal names are abbreviated. Table 19.1 lists the accepted abbreviations for some of the journals to which you will most commonly refer. *Chemical Abstracts Service Source Index* and its quarterly supplements provide a complete list of recommended journal abbreviations.

TABLE 19.1 Journal Abbreviations

Abbreviation	*Name of Journal*
Angew. Chem.	*Angewandte Chemie*
Ann. Chem.	*Annalen der Chemie*
Ann. Chim. (Paris)	*Annales de Chimie*
Ber.	*Berichte der deutschen Gesellschaft*
Can. J. Chem.	*Canadian Journal of Chemistry*
Chem. Abstr.	*Chemical Abstracts*
Chem. Ber.	*Chemische Berichte*
Chem. Commun.	*Chemical Communications*
Chem. Ind. (London)	*Chemistry and Industry*
Chem. Rev.	*Chemical Reviews*
Helv. Chim. Acta	*Helvetica Chimica Acta*
J. Am. Chem. Soc.	*Journal of the American Chemical Society*
J. Appl. Chem. (London)	*Journal of Applied Chemistry*
J. Chem. Educ.	*Journal of Chemical Education*
J. Chem. Soc.	*Journal of the Chemical Society*
J. Med. Chem.	*Journal of Medicinal Chemistry*
J. Org. Chem.	*Journal of Organic Chemistry*
J. Pharm. Sci.	*Journal of Pharmaceutical Science*
Nature[a]	*Nature*
Naturwissenschaften[a]	*Naturwissenschaften*
Tetrahedron[a]	*Tetrahedron*
Tetrahedron Lett.	*Tetrahedron Letters*

[a]Titles with single names are not abbreviated.

19.2 PREPARING YOUR MANUSCRIPT

If you are writing a report based on your own laboratory work, your laboratory notebook forms the basis of the formal written article. Notice that the format of your laboratory reports is very similar to that of the article.

After you select the journal in which you want to publish your work, first investigate the journal's manuscript contributor instructions, usually found in the journal's first issue of the year. Do not begin to write until you know the required format.

After you have written the report, have it typed double-spaced; then proofread it to ensure that it is entirely correct. Put tables, figures, and references on separate pages and append them to the end of the report. The actual placement of these elements will be determined by the publisher.

Since typewriters normally do not have italics and bold type, underlines and wavy underlines, respectively, are used to indicate the same. For example, reference number 6 in Figure 19.1 was originally typed as:

Barrer, R. M.; Chio, H.T. J. Polym. Sci C 1965, 10, 111.

After your manuscript is completed, you will send it to the editor as prescribed in the journal. The editor will in turn send it to one or two **reviewers,** competent scientists in your field who will read and critique your paper. They will consider such factors as whether the work is important and/or novel enough to justify publication, whether sufficient experimental work has been completed, and whether the report is intelligibly written. In effect, the reviewers will "read and understand" your paper in the same manner as does the witness to your laboratory report. If the reviewers agree that the report is ready for publication, they will so inform the editor. Notice that at the end of Figure 19.1 the date the manuscript was received has been noted, also the date the revised manuscript was received. In this instance, the manuscript was originally written as a preliminary communication to alert investigators of diffusion phenomena to the

inadvisability of using an unmodified time lag approach for determining diffusivity in silicone rubber. The reviewer agreed to the merit of publication but suggested that additional data be obtained and incorporated into the report, making it a longer, full-fledged paper rather than a preliminary communication.

19.3 EXPERIMENTAL PART
Writing an Article

Write an article in a format and style that (if it were new research or novel information) would be acceptable to a professional scientific journal or as an intracompany publication. Your instructor will assign the journal or advise from which journals you may choose. The assignment will be of the following sort:

1. Write a formal report to be used as an in-house publication that can be distributed to your classmates detailing the importance of and the information available from a given secondary literature source such as *Heilbron's Dictionary*. Include directions and examples of using the source.
2. Write an abstract of a journal article from a reprint supplied by your instructor.
3. Survey the literature and prepare a review article on a subject of particular interest to you or assigned by the instructor.
4. Write a paper describing and discussing a two or three step synthesis that you performed in the laboratory.

19.4 EXERCISES

Prelaboratory

1. *Vera Long* wrote a paper describing the condensation polymerization of ethandioyl chloride with 1,2-diaminoethane. The title of her paper was "Loss of HCl During Polymerization of Ethandioyl Chloride with Ethylenediamine at Temperatures at and Below 30 °C." Critique.
2. Why is the abstract of a paper found at the beginning of an article?
3. In the results and discussion section of a report describing his synthesis of benzenol, *Hal Ogen* centered his attention on the results of the Dow process of benzenol (phenol) synthesis. Was this a legitimate presentation of information? Explain.
4. *Ms. Taken* repeated the experimental work described by an Arabian article translated by a friend. In the experimental section of her own paper, she gave a thorough description of the instrumentation, apparati, methods, and data she obtained. Critique her method of presentation.
5. *Stu Dent* gave the following book reference: Dr. Linus Pauling, *Nature of the Chemical Bond*, Second Edition, Cornell University Press, 1948, page 80. Criticize the referencing.

Postlaboratory

1. Pick out three articles in a *Journal of Organic Chemistry*; list the order of the format elements for each article.
2. In the results and discussion section of a report describing his synthesis of benzenol, *Hal Ogen* discussed the merits of his laboratory process relative to those of the Dow process. Was this a legitimate presentation? Explain.

REFERENCES

1. *The ACS Style Guide*; Dodd, J. S., Ed.; American Chemical Society: Washington, DC, 1986.

JOURNAL OF APPLIED POLYMER SCIENCE VOL. 14, PP. 1019–1024 (1970)

Some Filler Effects on Diffusion in Silicone Rubber

C. F. MOST, JR., *Dow Corning Corporation, Midland, Michigan 48640*

Synopsis

Experimental / Results / Conclusion: The diffusion of ethyl *p*-aminobenzoate in silicone rubber membranes containing varying amounts of a high surface area fumed silica filler is described, as is a new apparatus for assaying multiple samples. It is shown that increased filler loading results in what appears to be a linear decrease in transmission rate, but that apparent diffusivities fall off drastically as a result of adsorption of the permeant on the filler. Distribution coefficient measurements suffer from the same result. The results suggest that neither an unmodified time lag technique nor a direct solubility method can be used to determine diffusivities of polar or unsaturated molecules in silicone rubbers, since they generally contain silica fillers.

INTRODUCTION

The relatively high diffusivities and minimal body tissue response exhibited by polydimethylsiloxane rubber has led to its exploitation as an implantable sustained-release carrier for medicaments.[1–3]

Diffusion coefficients have been calculated for a number of hydrocarbons and gases in silicone rubber,[4–9] but in general, in spite of the considerable current interest in drug diffusion, little effort has been made to determine the relationship between observed transmission rates and diffusivities.

Statement of problem being investigated

Before a steady state is reached, there is a variation of permeant concentration within the membrane with respect to time, and a time lag is experienced before any permeation into the desorbing medium is observed and before the mass flux becomes constant. This time lag has been used by Daynes[10] and Barrer[11] to develop what has in the past been the most popular method for experimentally determining diffusivity and solubility terms.

EXPERIMENTAL

The entire procedure is described because it is not already in the literature

Dow Corning vinyl-functional polydimethylsiloxane and Cabot Corporation Cabosil MS-75 were used in preparing permeation cell membranes. Ethyl *p*-aminobenzoate, purchased from Aldrich Chemical Co., Inc., was used in the permeation cell in dry form as supplied, with an average particle size of 60-110 m. Freshly distilled water was used as desorption medium.

The fillerless membranes were prepared by adding *tert*-butyl perbenzoate, 0.4000 g, to the gum, 100.0 g; blending thoroughly on a two-roll mill; and molding between Teflon without release agent at 138°C and 2000 psi for 10 min. The filled membranes were prepared by milling vinyl-functional polydimethylsiloxane gum with the filler, total 100.0 g, and blending thoroughly with 2,5-dimethyl-2,5-di(*tert*-butylperoxy)hexane, 0.5000 g, on a two-roll mill. The stocks so prepared were molded between Teflon without release agent at 100°C for 1 hr at 2000 psi followed by 10 min at 177°C. All membranes were postcured 16 hr at 150°C, cut from the vulcanized sheet with a cork borer, and rinsed with ethanol. A schematic view of the permeation cell assembly is shown in Figure 1. A nickel-plated or aluminum screw top cap (A) with a centered hole of 1.00-cm diameter sealed the membrane to the end of the permeant-containing chamber (B) attached to a glass tube (C). The glass tube was held by friction fit to a Teflon gasket (D) inside the cap (E) of a 2 oz. French square bottle (F) containing 25.0 ml of desorbing solution (G) and a 0.5 in. diameter stainless steel ball (H).

A machine screw soldered to the cap was secured by a wing nut (I) to a large aluminum disc (J) designed to accomodate 12 permeation cells of the described size. The disc was inclined at an angle of 35° to the horizontal and was rotated at a rate of 30 rpm by an air motor with reducing gear box. The permeation cells were at all times submerged in a Sargent Model S-8470 water bath at 27.0°C. A side arm (K) with

FIGURE 19.1.

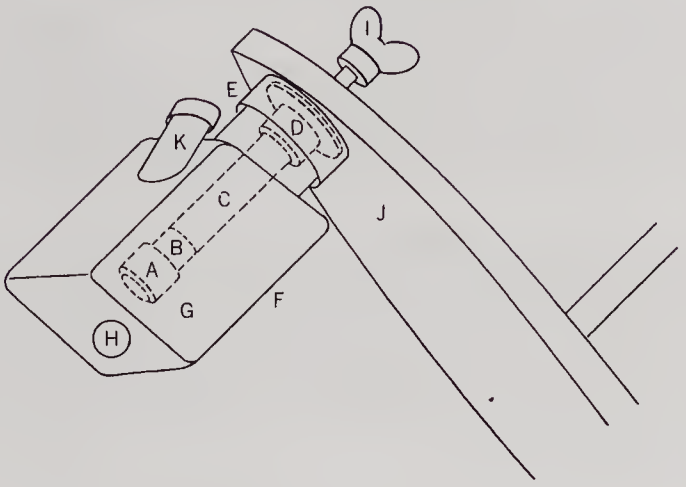


Fig. 1. Permeation cell assembly. (See text for key.)

screw cap and Teflon gasket was provided for ease of sampling at intervals. Measurements were effected by periodically stopping the rotation of the disc, blowing dry the underlip portion of the sidearm cap, withdrawing a small sample, and immediately directly assaying for permeant at 285 mm. The sample was then returned to its cell and incubation was continued. The motion of the rotating disc was resumed during the assay period. Ultraviolet spectra were obtained using a Cary Model 14 recording spectrophotometer, employing a 0.0–0.2 slideware for nonsteady state measurements for the fillerless membrane, or a Beckman DU-2 spectrophotometer. Four or six replicate samples were used for each membrane.

Distribution coefficients between an aqueous solution of ethyl *p*-aminobenzoate, 5.30 mmoles/ml, and silicone membranes were determined by washing the carefully weighed rubber, ca. 5 g, twice in distilled water, then in ethanol; drying at 70°; and immersing in 35.0 ml of aqueous benzoate solution at 27°C in the previously described permeation cells. The samples were kept in the constant temperature bath four days, a period found sufficient for equilibrium distribution, and the aqueous solution was analyzed at 285 mm. The ratio of ethyl *p*-aminobenzoate concentration in the rubber, found by difference of drug in the aqueous phase before and after, to that in the final aqueous solution was taken as the solubility coefficient.

RESULTS AND DISCUSSION

Ethyl *p*-aminobenzoate was chosen as a model for the work reported herein because it has reasonable solubility in both aqueous and nonaqueous systems, prossesses a satisfactorily high extinction coefficient in

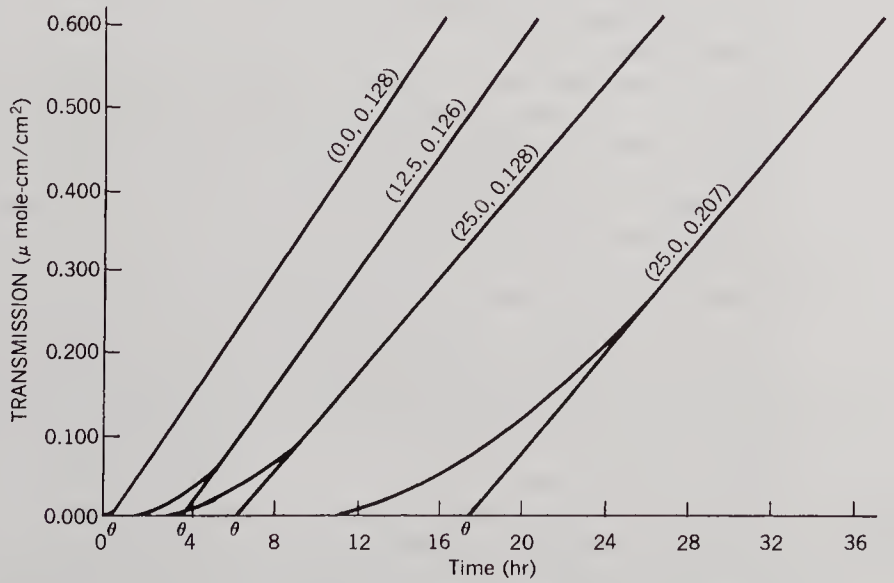


Fig. 2. Time lag plots for ethyl *p*-aminobenzoate in membranes with varying filler content. Parenthetical expressions refer to % filler, thickness of membrane.

FIGURE 19.1 (*Continued*)

the ultraviolet (λ_{max} 285 mm, ϵ 18,200 ± 600, water), and is a relatively small drug molecule, hence commanding a fairly high diffusivity.

Although a quasisteady state system was employed, it was found that the correction for nonlinearity in the benzocaine–water system was so small as to be negligible for the illustrated period and was therefore ignored. A further assumption was that a diffusion coefficient would probably be constant inasmuch as ethyl *p*-aminobenzoate is soluble only to the extent of 4.5–5.4mmoles/cm^3 in high molecular weight silicone fluids.

Cabosil MS-75 is a fumed silica with no internal surface area[12]; hence its entire surface area of 265 m^2/g is readily available to the silicones present and to the permeant. In preparing the membranes, attention was given to thorough milling and heating processes during membrane preparation in order to obtain the good filler-polymer contact essential to illustrating the phenomena reported herein.

The curves in Figure 2 illustrate the transmission of ethyl *p*-aminobenzoate through membranes with varying amounts of filler. The transmission rates shown in Table I were calculated from the slopes of the steady state portions of such curves, and the time lag diffusivities according to Daynes[10] and Barrer[11] were calculated from the equation

$$D = \frac{l^2}{6\theta}$$

wherein l is the membrane thickness and θ is the time lag obtained by extrapolating the steady state portion of the curve to the time axis.

Note the use of equation, graphs, and tables to lend conciseness and clarity to the article

TABLE I
Composition and Properties of Silicone Rubbers

Filler, wt-%	Thickness, cm	Transmission rate,[a] (mmole·cm)·(hr·cm^2)$^{-1}$	Time lag, min	Apparent diffusivity,[a] cm^2/hr
0.0	0.128	0.038 ± 0.003	25	0.0064 ± 0.0005
12.5	0.139	0.035 ± 0.003	220	0.00087 ± 0.00005
15.0	0.197	0.033 ± 0.001	749	0.00052 ± 0.00001
15.0	0.134	0.033 ± 0.001	396	0.00053 ± 0.00001
25.0	0.207	0.030 ± 0.001	1054	0.00041 ± 0.00001
25.0	0.128	0.030 ± 0.001	375	0.00043 ± 0.00001

[a]95% Probability level.

A good agreement in values between membranes of different thickness for both transmission rates and apparent diffusivities is observed in Table I, indicating that initial absorption of the permeant into the rubber and desorption therefrom are not rate-limiting steps and that Fick's laws are obeyed.

Contemplation of Figure 2 and Table I immediately makes evident a severe displacement of time lag values for membranes containing filler. The disparity in time lag intervals is reflected in a considerable diminuation of calculated diffusivities, as compared to the moderate decrease in transmission rates as filler loading is increased. For example, comparing the unfilled membrane with that containing 25.0% of filler, a 15-fold decrease in diffusivity is observed whereas only a 21% drop in transmission rate is seen. This relationship is graphically depicted in Figure 3. Such results can be attributed to adsorption of permeant on the filler, the adsorbed permeant no longer taking part in the diffusion process. Such a conclusion is quite reasonable in that the nonsteady state period, during which adsorption of permeant on silica occurs, should be more susceptible to variation than the steady state.

It is obvious that in the systems described, wherein a solid permeant is in contact with the membrane, a direct measurement of a solubility coefficient can't be made. However, in order to further demonstrate the highly adsorptive capacity of the silica, distribution coefficients were measured as a function of an aqueous solution containing 5.30 mmoles/ml of the permeant. The coefficient so obtained was 0.97 ± 0.02 for the fillerless rubber, but 3.8 ± 0.2 for the rubber containing 25.0% filler, thus giving additional evidence for the filler adsorption phenomenon.

Note the reference—to other authors; and the second-time use of the same references

Barrer and co-workers[4–7] have recorded small differences in diffusivities in silicone rubber when the time lag method is compared to solubility methods. That such differences were slight is probably the result of the relatively nonpolar character of the gases used since, although almost all classes of organic compounds can be separated by silica gel chromatography, the more highly adsorptive capacity of silica depends on

FIGURE 19.1 (*Continued*)

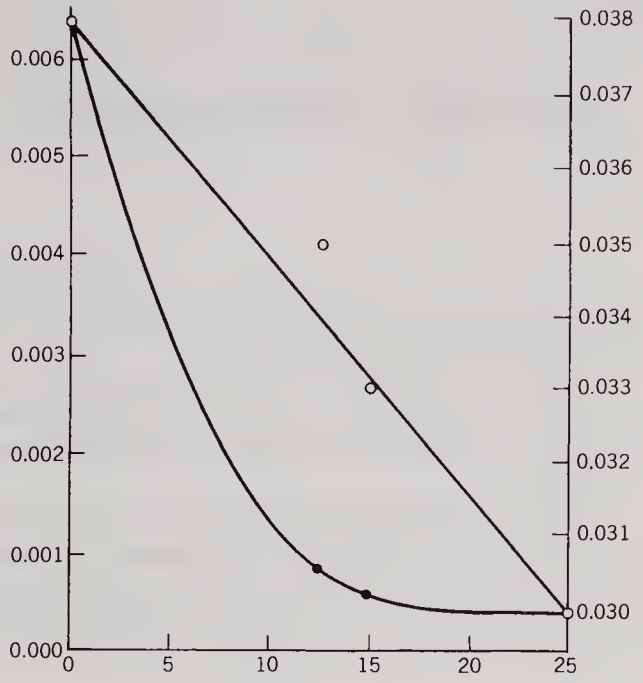


Fig. 3. Change in transmission rate and diffusivity as a function of filler content: (●) diffusivity; (○) transmission rate.

interaction of its surface hydroxyls with polar or unsaturated molecules.[13] It is probable that all chemicals which are good candidates for silica gel column chromatographic methods of purification would show a more or less severe time lag displacement in a diffusion experiment. Thus, for polar and unsaturated chemicals in general, it is suggested that an unmodified time lag technique will not be valid for determining diffusivities in silicone rubbers, which generally contain silica fillers. It also appears that use of a direct solubility technique will also be inapplicable for the same reason. One is led to anticipate that for the time lag method of determining diffusivities in silica-filled membranes as compared to membranes containing a nonadsorbing filler, Fick's second law would require modification by terms which are functions of filler surface area and activity.

The author thanks M. G. Kasperski for his careful assistance with membrane preparation, also J. L. Duda and J. S. Vrentas for a helpful discussion.

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Received September 10, 1969
Revised November 19, 1969

FIGURE 19.1 (*Continued*)

TECHNIQUE 20

PROCESS ECONOMICS

In a capitalistic society, the reason for existence of a chemical or drug company is to make a profit. Products must be made which are profitable and the processes used in their manufacture must be economical.

Although the burden of profit making falls on managers, all laboratory personnel should have some feel for costs and the attendant production volumes that are necessary to make profits. Then they will better understand why some very interesting projects are not feasible.

In this chapter, we shall very briefly explore the sorts of relationships that are involved in making decisions like: How many pounds must be manufactured in order to make a profit? Could I afford to start a small chemical company? Can the company afford to continue employing me at my current level of efficiency?!

20.1 COST ANALYSIS

There are many considerations that go into a complete cost analysis. We shall consider a number of them here in simplified form. The following discussion is directly related to use of Table 20.1, which is an adaptation of a form used in industry. The first thing that might catch your attention is the use of pounds and gallons. Perhaps you will be surprised to know that the chemical industry uses the English system of measurements in engineering and production. The metric system is used in research, however.

In Table 20.1, the product is the substance to be prepared, the building or plant refers to the location, annual capacity is the amount of product to be made in a year, the evaluator is the person preparing the report, and the **direct manufacturing capital** (DMC) is the cost of the equipment itself directly used in the process. The average DMC to produce 15,000,000 lb of a given compound annually is likely to be in the neighborhood of $3,000,000. Actual DMC varies, of course, in accord with individual processes.

20.2 PROCESS COSTS

Raw Materials

One of the most obvious costs is that of the raw materials. Enter these materials, the reactants, in Table 20.1. A **batch process** is a process designed to be terminated after each production of product, as opposed to a **continuous process,** wherein reactants are continually fed into the reactor and product is continually removed. Most of your laboratory work involves batch process.

In the laboratory, you would list the reactant, the number of moles required for the reaction, and the mass or volume to use. The **unit cost** is the cost per gram or milliliter. The **batch cost** is found by multiplying the unit cost by the number of grams or milliliters used.

The production section of Table 20.1 refers to the scaled up process used in the chemical plant. The annual amount of raw material to be used depends on the annual amount of product desired and, of course, the percent yield obtainable. The unit cost in production is the cost per pound or gallon of raw material. The annual cost is the annual amount multiplied by the production unit cost.

TABLE 20.1 Economic Evaluation of Cost and Capital

Product _____ *Bldg/Plant* _____
Annual Capacity _____ *Evaluator* _____
Direct Mfg Capital, lab: _____ *plant:* _____ *Date* _____

	Laboratory			Production		
Raw Materials	*Quantity, Mass or Vol per Batch*	*Unit Cost*	*Batch Cost*	*Amount per yr, lb or gal*	*Unit Cost*	*Annual Cost*
Total Raw Materials			$			$
Utilities, electricity	kWh	$	$	kWh		$
steam	lb	$	$	lb		$
gas	ft^3	$	$	ft^3		$
water	gal	$	$	gal		$
ice	lb	$	$	lb		$
Total Utilities			$			$
Direct labor	hr	$/hr	$	hr	$/hr	$
Indirect labor		%DL	$		%DL	$
Labor-related overhead		%TL	$		%TL	$
Total Labor-Related			$			$
Location overhead		%DMC	$		%DMC	$
Quality assurance		%DMC	$		%DMC	$
Maintenance		%DMC	$		%DMC	$
Waste disposal		%DMC	$		%DMC	$
Taxes and insurance		%DMC	$		%DMC	$
Depreciation on direct mfg. capital		%DMC	$		%DMC	$
Total Capital-Related			$			$
Grand Total			$			$

Raw materials costs in industry are obtained by direct quotations from suppliers, but a good idea of current prices can be found in various issues of the weekly *Chemical Marketing Reporter,* Schnell Publishing Co, Inc., 100 Church St., New York.

Raw materials include intermediates that your company manufactures. When using intermediates, you must make a complete economic evaluation of cost and capital for the intermediate; then use that cost as a raw materials cost for the final product.

Utilities These utility costs are for the process only, not for the building. The utilities are the public services—electricity, gas, water, steam, and so on. These services are purchased respectively in units of cents per kilowatt hour, cents per 100 cubic feet or cents per 100,000 BTU, dollars per 1000 gallons, and dollars per pound. The actual unit costs for utilities vary from one location to another, but in 1985, respective costs in central Michigan were \$0.07 kWh of electricity, \$0.55/100,000 BTU or \$0.55/100 ft^3 of natural gas, \$1.28/1000 gal of water, and \$3.85/1000 lb for steam.

Labor Labor is divided into two categories: direct and indirect. **Direct labor** is work performed by the people directly running the reactions, the operators. The amount of direct labor depends on the type of process, the amounts of materials, and the number of shifts. The cost of labor per operator is about \$8 per hour. So, assuming 40 hr/week for 50 weeks, the cost of an operator would be \$16,000. (The number of weeks worked would probably be 50 because of vacation time.) **Indirect labor** includes services directly related to the process: those of foremen, process supervisors, quality control personnel, and the like. Indirect labor costs are in the neighborhood of 30% of direct labor (DL on Table 20.1). **Labor-related overhead** includes such costs as operating the personnel department, running the cafeteria, the telephone switchboard, the plant manager's salary, and so on. Such overhead is about 15% of total labor (TL on Table 20.1), that is, 15% of the sum of direct and indirect labor.

20.3 PLANT COSTS

Location Overhead Location overhead includes the items that relate to the operation of the building housing the process equipment: building depreciation, taxes, lights, and maintenance of the building. These costs might be in the neighborhood of 8% of DMC.

Quality Assurance Quality assurance, or quality control, is the service that analyzes the product to see that it meets the standards set for it. This adds about another 3% of DMC to the cost of the operation.

Maintenance This category includes maintenance on the manufacturing equipment and machinery, such as repairs, replacing filters, changing pump oil, and so on. This cost might run approximately 4% of DMC.

Waste Disposal Waste disposal is an important consideration. Water, byproducts, waste acids and bases, tars, and residues must be disposed of in a nonhazardous way. Charges for this service are likely to be about 3% of DMC for processes that do not involve disposal of particularly hazardous or unusual materials.

Taxes and Insurance These costs apply to the manufacturing equipment and can be estimated to be 1% of the DMC.

Depreciation **Depreciation** is the decrease in value of a property due to wear and tear. Such a decrease is allowed in computing the value of property for tax purposes. This cost can be calculated in a number of ways. A commonly used method is straight line depreciation. In this method, the usable life (in years) of the equipment is decided on and DMC is divided by that amount to get the annual depreciation. Eleven years is a common period used for depreciating manufacturing equipment. Using 11 years as a basis gives an annual cost of 9% of DMC.

20.4 COST, SALES, AND PROFIT

Two categories of costs are generally considered: fixed and variable. **Fixed costs** are those that do not change over a given time period (say a year) no matter how great the volume of production. Examples of fixed costs are depreciation on the laboratory or production building, property taxes, fire insurance, and managerial salaries. **Variable costs** change with the volume of production. For example, the cost of raw materials and salaries for a greater number of equipment operators increase as product volume increases. Fixed and variable costs can be graphed as shown in Figures 20.1 and 20.2. Figure 20.3 shows a composite of the two types of costs.

Another side of the picture is sales. In order to make a profit, what is manufactured must be sold. The sales dollars depend of course on the volume that can be produced.

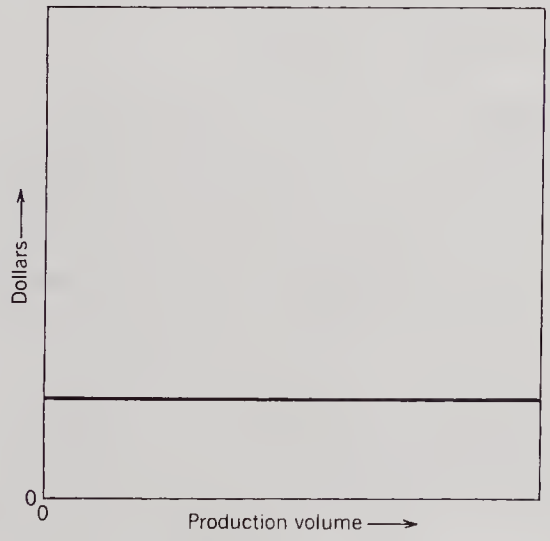


FIGURE 20.1 Fixed costs.

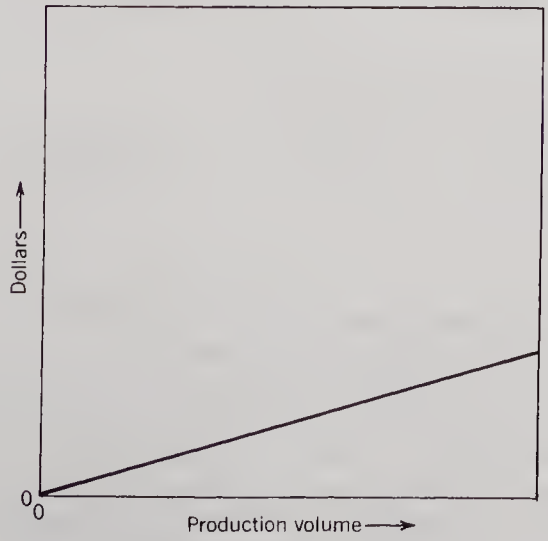


FIGURE 20.2 Variable costs.

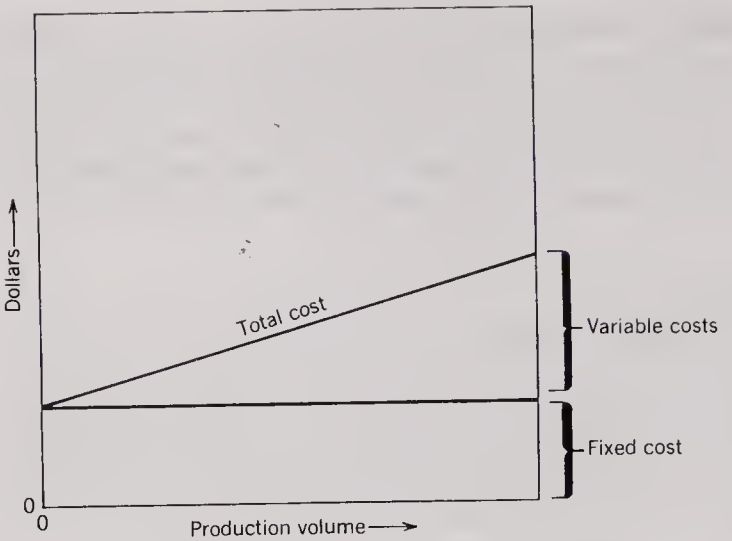


FIGURE 20.3 Total costs.

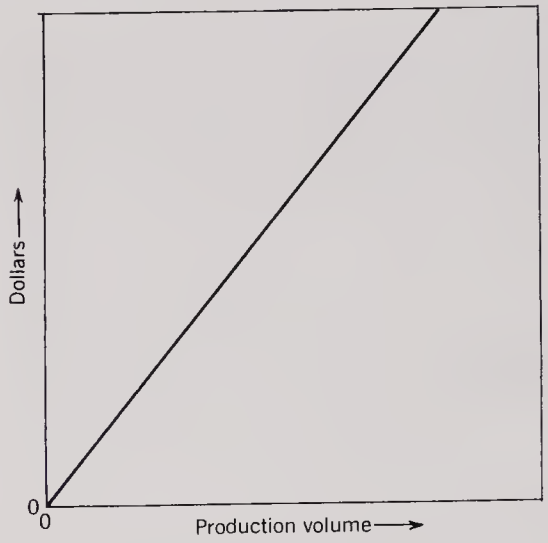


FIGURE 30.4 Sales.

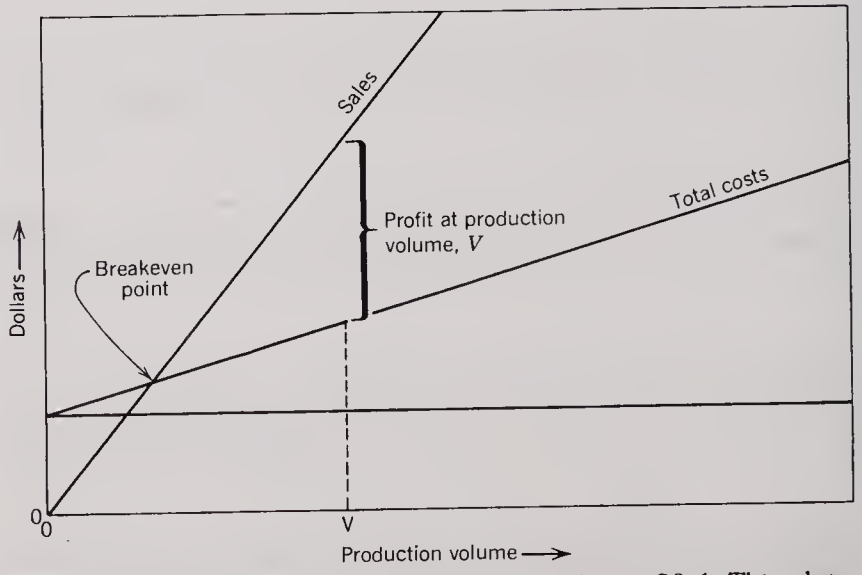


FIGURE 30.5 Breakeven chart.

A graphic representation of sales is shown in Figure 20.4. This plot assumes that there is no limit to the demand for the product.

Figure 20.5 is called a breakeven chart. It is simply a combination of the plots of fixed and variable costs, and of sales. A point of considerable interest is the breakeven point, that point in volume above which profit can be made. The **breakeven point** is the point where the sales line intersects the total costs line. Until the breakeven point is reached, you operate at a loss for a given product. Notice that in order to make a profit, the slope of the sales line must be greater than that of the total costs line.

20.5 COST ANALYSIS LAB TECHNIQUES

Proceed with your synthesis in the usual manner. However, there are certain additional steps that you will have to take.

Keep track, to the nearest 5 min, of your total time input from beginning to end. You must have a complete record of amounts of *all* materials and utilities used, including the volumes of water involved in separatory funnel washes, the amount of water used during water aspiration, the time a hot plate was used, and so on. The amount of steam used can be estimated by measuring at about 4 °C the volume in milliliters of condensate in the steam bath and adding 25% for steam that escaped as vapor. The volume of gas passing through a Bunsen burner can be measured with a flow meter, or by bubbling a small amount of gas for a timed period into an inverted, water-filled graduated cylinder supported in a water trough, then using this volume to determine the volume over the period of actual use. To dispose of the gas in the graduated cylinder, use an air hose to blow the gas from the cylinder into a hood.

Keep the gas away from flames, electrical switches, and static electricity. Work behind a shield.

The cost of using electrical equipment can be calculated if you know the following data: local cost/kWh, the rating in watts of the equipment in use (found on the nameplate), and the time the equipment is in use. For example, if you use a 180-W (250-ml-size) heating mantle for 2.0 hr at \$0.45/kWh, the cost is \$0.016.

$$\left(\frac{\$0.045}{\text{kWh}}\right)(2.0\text{ h})(180\text{ W})\left(\frac{1\text{ kW}}{1000\text{ W}}\right) = \$0.016 \qquad (20\text{-}1)$$

Keep track of the amounts of materials wasted, such as excesses of acids, bases, excess reagents, water, and so on. Assume for simplicity in making calculations that the difference in theoretical and actual yield is due to unreacted raw materials; include in your waste calculations the unreacted portion of the raw materials. Make a table like that shown in Table 20.2 and attach it to your notebook or report.

To calculate the amount of raw materials needed in production and their annual cost, first calculate a multiplication factor that you can apply to all of the raw materials used, to utilities, and to labor. Do *not* use this multiplication factor on labor, DMC, or plant costs (location overhead, quality assurance, maintenance, waste disposal, taxes, insurance, and depreciation). To calculate the multiplication factor, divide the annual production capacity by the yield you obtained in your laboratory preparation, and multiply by the appropriate metric/English conversion factor. For example, let us assume

TABLE 20.2 Waste Disposal

		Production Annual Waste		
Waste Material	*Laboratory Waste Moles, Mass or Vol., g or ml*	*Weight, lb or Volume, gal*	*Unit Cost, \$/lb or gal*	*Annual Cost, \$*
Total annual chemical waste, lb and \$.		lb		\$
Total annual water waste, gal and \$.		gal		\$

that the production capacity is 10,000.0 lb and your yield is 1.35 g. The multiplication factor is given by

$$\frac{(10{,}000.0 \text{ lb})\left(\frac{454 \text{ g}}{\text{lb}}\right)}{(1.35 \text{ g})} = 3.36 \times 10^5 \qquad (20\text{-}2)$$

This factor tells you that you need on an annual basis 3.36×10^5 times as many grams of product as you prepared. To make this much product you will need 3.36×10^5 times as much of every raw material that you used. So, multiply by the factor; then change the laboratory metric units to the production English units using appropriate metric/English conversion factors.

To figure the annual direct labor cost, assume that you have a reactor (industrial reaction vessel) of 500-lb or 500-gal capacity, and the overall production process to make 500 lb or gal of product requires the same amount of time as the laboratory procedure. Thus

$$\$ \text{ direct labor cost} = \frac{\text{annual capacity (lb)}}{\left(\frac{\text{batch}}{500 \text{ lb}}\right)\left(\frac{\text{hr}}{\text{batch}}\right)\left(\frac{\$}{\text{hr}}\right)}$$

Fill out an Economic Evaluation of Cost and Capital for laboratory and for production at an assigned annual capacity. Assume the direct manufacturing capital for production is in the ratio of \$1.00 per 6.00 lb of product. (More elaborate and larger equipment than laboratory equipment is necessary for production.) For production raw materials use the *Chemical Marketing Reporter* or, if necessary, the costs as found in chemical supplies catalogs. For laboratory, use the prices found in chemical supplies catalogs. Calculate the labor requirements based on your own time input.

Calculate fixed and variable costs, and also the total dollar sales based on an assigned annual capacity. In assigning fixed and variable costs, assign each item to that category that appears most appropriate. Or assign a reasonable percent of fixed and variable costs to those items that might not be totally fixed or variable: quality assurance, maintenance, and waste disposal. Assume that there is an unlimited demand for sales of the product. Use as the sales price the price per pound from a current chemicals catalog. To obtain sales dollars, multiply the price per pound by the production volume. Using graph paper and your calculations of fixed costs, variable costs, and sales, construct a breakeven chart and attach it to your notebook or report.

20.6 EXPERIMENTAL PART
Analysis of Aspirin Synthesis

Time Required: 2–3 hr lab time; $\frac{1}{2}$-hr microcomputer time

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.12)
Swirling	(0.14)
Heating	(0.5)
Vacuum filtration	(4.3)
Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.3)
Labeling	(0.23)
Storing	(0.4)

In this experiment you will prepare aspirin and make an economic analysis of the process.

Preliminary work. Turn on your water aspirator full blast and collect the water for 10 s. Record the amount of water collected. You will use this information to calculate the amount of water used during suction filtration.

Make a table in your notebook with a column for given uses of water and a column for amounts used.

Record the cost of your laboratory drawer equipment and the hot plate used in this experiment. This amount represents the DMC of the process you are about to begin.

Now that you are ready to begin the synthesis of aspirin note the time and record it. You have now punched in on your company's time clock!

Aspirin preparation. Put 2.0 g of salicylic acid in a 125-ml Erlenmeyer flask. Add 5 ml of acetic anhydride; then five drops of concentrated sulfuric acid. (Enter these amounts on the economic evaluation table.) Swirl the flask until the solid dissolves, then heat it gently in a 100 °C hot water bath for 10 min. (Record the time the hot plate is turned on and its watt rating. To calculate the amount of electricity used to heat the water, multiply the time the hot plate is used by the watt rating of the plate. Change to kilowatt hours.) Allow the mixture to cool to room temperature. You should observe precipitation of aspirin. If no precipitate forms, scratch the inside of the flask below the surface of the liquid with a sharp stirring rod and cool the mixture in an ice bath. (Record the milliliters of water and weight of ice used in the ice bath.) If necessary, seed your mixture with a crystal or two of aspirin borrowed from another student or the stockroom. Allow the mixture to sit on the bench top until precipitation appears complete.

Workup. Add 50 ml of ice-cold water (Record the water amount), stir the mixture, and cool it in an ice bath until precipitation appears to be complete. (Is this the same ice bath as before? Did you add more ice? Keep track!) Using vacuum filtration, collect the precipitate in a Büchner funnel. (Record the amount of water used in aspiration.) Rinse with filtrate all ppt from the Erlenmeyer flask. Wash the ppt with a small amount of ice-cold water (Record the amount of water) and put the ppt into a 150-ml beaker. Make up 25 ml of saturated aqueous sodium bicarbonate (Record the amount of bicarbonate and water used; record the bicarbonate as a raw material) and cautiously, with stirring, add it to the 150-ml beaker. Stir until all evidence of gassing has ceased; then filter the mixture through a Büchner funnel (Record the water used for aspiration). Rinse the beaker and pour the filtrate back into the beaker. Cool the filtrate in an ice bath and add, with stirring, cold 6*M* hydrochloric acid (Record this as a raw material) until the pH of the mixture is 1. Filter the crystals, wash them lightly with ice-cold water (record the amount used), and dry them. Recrystallize the dry crystals from a minimum amount (ca. 2 ml) of hot ethyl acetate (Record this as a raw material). Cool the mixture gradually to about 5 °C. Seed or scratch if necessary to induce crystallization. Collect the product in a Hirsch funnel by vacuum filtration. (Record the amount of water used for aspiration.) Put the filtrate in an ethyl acetate recovery container. Dry the crystals, weigh them (The weight of product is crucial in cost calculations), obtain a melting point, and turn in the product in a labeled vial. Calculate the percent yield based on the limiting reagent, salicylic acid.

Record the time that you complete the experiment.

Economic evaluation. Record the masses or volumes of all raw materials on an Economic Evaluation Table like that of Table 20.1. Enter the unit cost from a chemicals catalog, noting in your notebook the catalog used. Calculate the laboratory batch costs.

Total the amount of electricity used in kilowatt hours and record it in the table. Multiply kilowatt hours by your local unit cost of electricity to obtain the batch cost.

Sum the amount of water used, change it to gallons, and enter it on the table. Enter the local unit cost of water and multiply times the gallons of water used.

Enter ice as a utility, the number of pounds used, the unit cost in cents per pound, and batch cost. Obtain the price of ice from a grocery store.

Enter the number of hours worked, your wage per hour as a technician (ca. $8 per hour) as direct labor.

Enter the indirect labor as a percentage of direct labor and labor related overhead as a percentage of the sum of direct plus indirect labor.

To calculate the plant costs, enter the percent DMC for each plant costs item on Table 20.1; then multiply the DMC by the percent (do not forget to divide by 100).

Sum up the laboratory batch cost.

Now you are ready to scale up for production. Assume in your report that you want to produce 10,000 lb of product annually. Calculate a multiplication factor as in equation 20-2 and use it to determine how much of each raw material will be required. Also scale up utilities by applying the multiplication factor to the corresponding lab cost. Scale up labor-related costs by assuming a 500-lb or 500-gal reactor batch capacity. Apply the same percentages of direct labor and total labor as used for the laboratory costs. Apply the same percentages of DMC to capital-related production costs as to the capital-related laboratory costs.

The grand total batch and annual costs are the sums of the columns.

Put on a waste disposal table like that of Table 20.2 all amounts of materials discarded (including water) down the drain or into recovery containers and unreacted raw materials. Complete the table in the same way as you did for the raw materials section of Table 20.1.

Separate the various expenses into fixed and variable costs. Use these costs and your assumed annual production to construct a breakeven chart.

As directed by your instructor, securely attach your economic evaluation, waste analysis, and breakeven chart to your laboratory notebook or submit them as a separate report.

Computer analysis. If your chemistry department has a personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR,* and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations. To save computer time, you should have the following information ready when you arrive at the computer:

1. Your name, the date, and the name of the product.
2. Annual production capacity in lb or gal.
3. Lab product yield in g or ml.
4. Sales price of the product in $/lb or $/gal.
5. Direct mfg capital for the laboratory.
6. Name, quantity in g or ml, lab cost in $/g or $/ml, and production cost in $/lb or $/gal for each raw material.
7. If you used electricity: the price in cents/kWh, time in hr each electrical device was used, and the watt rating of each electrical device.
8. If you used steam: the price of steam in $/1000 lb, and the volume in ml of condensate in the steam bath.
9. If you used gas: the price of natural gas in cents/100 ft^3, the rate of gas use in ml/s, and the time in min during which gas was used.
10. If you used water: the price of water in $/1000 gal, and the liter amount of water used.
11. If you used ice: the mass in g of ice used, and the price of ice in cents/lb.
12. The total number of hours you worked, your wages in $/hr, the percent of direct labor for indirect labor, and the percent of total labor for labor-related overhead.
13. The percent of DMC for location overhead, quality assurance, maintenance, waste disposal, taxes and insurance, and depreciation.
14. The percentage of quality assurance, of maintenance, and of waste disposal which is a fixed cost.

Writing the discussion. Your discussion should address the following questions: What is the breakeven point? Can your company make a profit on producing aspirin? Discuss the amount of product relative to waste, and various means of increasing annual profit such as the possibility of decreasing labor time, decreasing the amount of wastes or utilities used, and increasing yields. Be specific as to the dollar increase in profit that such changes would make. Write a summary recommendation, as if to your plant manager, relative to the economic impact of the process you analyzed.

20.7 EXERCISES

Prelaboratory

1. Is steam that is used for evaporation of solvent from a reaction mixture a fixed, or variable, cost? Explain.
2. Is direct labor primarily a fixed, or variable, cost? Indirect labor?
3. What should be the relationship between the slopes of the sales curve and total costs curve in order to make a profit?
4. Make a flowchart for the preparation of aspirin.

Postlaboratory

1. Is the cost of an intracompany mail clerk direct, or indirect labor?
2. Which of the following items would be likely to involve a higher percentage of DMC for waste disposal: (a) aqueous ethanol or mercury salts? (b) soapy water or nonbiodegradable silicone polymeric wastes? (c) calcium sulfate hydrate or benzene?
3. The laboratory batch cost approximates the cost in an industrial research laboratory. Calculate the percent difference in total annual production cost of aspirin which would be involved in using chemicals at the laboratory supply rate rather than production supply rate as given by the *Chemical Marketing Reporter*. Use the cost of your laboratory drawer equipment as DMC for lab calculations.
4. Based on your work in this experiment, what appears to be the largest single item in annual production cost?
5. *Sally Sillik* obtained 3.00 ml of a liquid product and wants to scale this up to a production capacity of 4000.0 gal. Using a calculation similar to that of equation 20-2, determine what multiplication factor she should use.

REFERENCE

1. Horngren, C. T. *Cost Accounting*, 4th ed.; Prentice-Hall: Englewood Cliffs, NJ, 1977.

Acknowledgment
The writer thanks Jim Gray and John Churchfield of Dow Corning Corporation and Paul Stright of Lake Michigan College for helpful suggestions.

PART II

THE EXPERIMENTS

I LABORATORY SAFETY

Concerns about laboratory safety have increased in recent years, partly as a result of better methods of diagnosis and testing, and partly because of a greater awareness of hazards and drive to comply with standards set by OSHA (Occupational Safety and Health Administration).

If you have not already done so, be sure to read the section on safety in the Introduction and to become familiar with Appendix C.

In this section there are two exercises on safety: one to help you become aware of the safety features of your laboratory, and the other to acquaint you with a property of liquids to which we commonly refer: flash point. Needless to say, the need for safe practice is involved every time you set foot in the laboratory.

EXPERIMENT 1 LABORATORY SAFETY FEATURES

Time Required: 15 min

Review Techniques and Principles:

Lab notebook	(1)
Laboratory safety	(Introduction)

Laboratory safety is a vital part of any chemistry program. It is important that you are fully acquainted with safety features in your laboratory and procedures to use in case of emergency.

Study the section on safety in the introduction thoroughly if you have not already done so.

E1.1 EXPERIMENTAL PART

You will be given a sketch of your laboratory with the word "FIRE" somewhere on it. From your own observations, locate the various safety features in your laboratory and mark them and your own location on the laboratory diagram. Do not ask for help in finding safety features. You will remember their locations better if you locate them yourself. You should look for the following items: safety shower, eyewash station, fire blanket, fire extinguishers, and acid and base neutralizers (if any). Draw a long arrow from your location showing your proposed route of escape from the laboratory if a large fire, explosion, or other serious mishap occurred at the point labeled FIRE. Also draw an arrow showing the most direct route from your location to the eyewash and shower.

List on the laboratory sketch sheet the location of the nearest telephone for emergency use, the emergency number to call in case of fire or injury, and the location of the nearest general fire alarm.

Paste the completed laboratory sketch on the inside cover of your laboratory notebook.

E1.2 EXERCISES

Prelaboratory

1. List the suggested kind of clothing you should wear in chem lab.
2. What piece of apparel must you always wear in the laboratory?
3. What is the rule about eating, drinking, and smoking in the laboratory?
4. How long should eyes or skin be washed after contact with acids? With bases?

Postlaboratory

1. Find the structure of 2,4,6-trinitrophenol (picric acid). Explain why it is not necessary for the compound to be in presence of oxygen in the air in order for it to be oxidized.
2. Describe an implosion and outline the conditions leading to it.

EXPERIMENT 2 DETERMINATION OF FLASH POINT

Time Required: 10 min/student at the apparatus

Review Techniques and Principles:

Lab notebook (1)
Heating (0.5)

E2.1 DISCUSSION OF FLASH POINTS

The flash point of a substance is the temperature at which sufficient vapors accumulate above it so that an ignitable mixture with air is formed. Introduction of a small flame into the gaseous mixture causes it to suddenly ignite, a phenomenon known as **flashing.** At the flash point all of the vapors above the substance ignite, not just those next to the flame. Flash points normally apply to liquids, but some sublimable solids also have flash points.

There are two types of flash points: closed cup and open cup. The cup is the device that holds the liquid being tested, and for closed cup flash points, there is a lid that can be closed during the test. Most flash points are closed cup points, but for liquids with relatively high flash points, the open cup method is often used. Open cup flash points are usually a bit higher than closed cup flash points for the same liquid; they are indicated by the notation "oc" following the temperature. Flash points are most commonly given in degrees Fahrenheit.

The approximate closed cup flash point in degrees Fahrenheit for unsubstituted hydrocarbons can be calculated by

$$\text{flash point} = 0.73 \times (\text{boiling point}) - 122 \qquad \text{(E2-1)}$$

The importance of knowing flash points lies in knowing what to expect in terms of fire hazards when using liquids in the laboratory.

Another term that you might encounter is **fire point,** the lowest temperature at which vapors of a liquid in an open container are evolved rapidly enough to maintain a continuous burning (rather than a flash). The fire point is a few degrees above the flash point.

E2.2 THE TECHNIQUES

It is unlikely that your laboratory has a flash point testing device. However, you can easily construct a very simple apparatus for open cup flash point determinations which

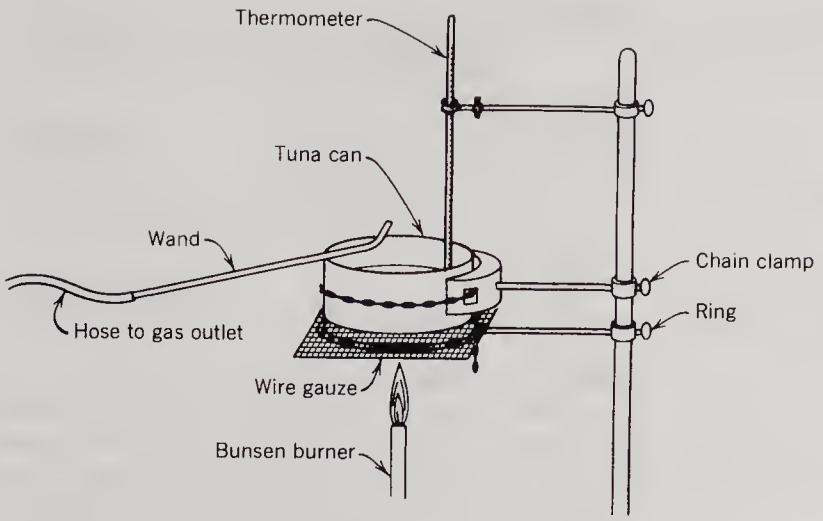


FIGURE E2.1 Inexpensive open cup flash point apparatus.

will give results within 5 F° of the literature value. Figure E2.1 illustrates the equipment, which consists of a 85-mm-diameter, 40-mm-high tuna fish can held in place by a chain clamp or snap lock clamp. Suspend the thermometer so that it is not touching the bottom of the can but so that its bulb is immersed in liquid. Figure E2.2 depicts a slightly more sophisticated piece of equipment, which has a metal reinforcing strap fastened at a 90° angle with bolts to the upper part of the cup. A finger clamp holds the strap so that the cup is bathed in a water bath. Notice that the rim of the can must extend above the beaker rim. This arrangement makes possible the use of a water bath for heating, which is preferable especially for liquids boiling below 100 °C because it gives better heat control and decreases the fire hazard.

The wand is a 30-cm section of ordinary glass tubing with a 3-cm 90° bend at one end, which is drawn down to a 1-mm opening.

Put the liquid to be tested into the cup to a depth of 0.5 cm. The depth of the liquid is important for getting true and reproduceable results. If a can of different size than described is used, you must determine the proper depth with a liquid of known flash point. Use a scratch mark on the inside of the can to identify the proper level.

Next, *slowly* heat the liquid with a *low* Bunsen burner flame or hot plate if the heating control on the hot plate allows gradual changes in temperature. It is easy to overheat the liquid to a temperature beyond the flash point.

Connect the unbent end of the wand to a natural gas source, introduce into it a slow stream of gas, and light it. Hold the wand so it rests on the rim of the cup with all

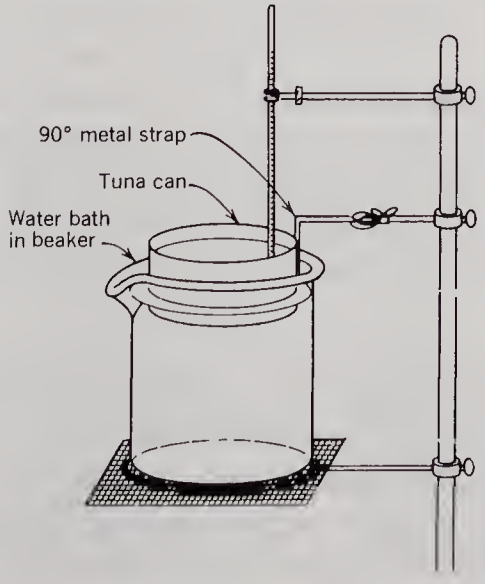


FIGURE E2.2 Inexpensive open cup flash point apparatus with water bath as heating sources.

TABLE E2.1 Flash Points of Ethanol-Water Mixtures

Vol% Alcohol	*Flash Point, °F*
10	180
20	115
40	90
70	72
95	60

portions of it parallel to the bench top and the bent tip pointing away from the cup. Then slowly move it horizontally across the center of the cup, at all times maintaining the parallel position. Repeat the movement across the cup at every 2–3 C° rise in temperature on the thermometer. Watch carefully for a nonsustained flash. Record as the flash point the temperature at which the flash is first observed.

Work with a shield between you and the flash point apparatus.

Heat the liquid slowly, so as not to reach the fire point.

Immediately extinguish any sustained fire in the cup by covering the cup with a watch glass held by a tongs.

E2.3 EXPERIMENTAL PART

You will be given an unknown aqueous mixture of ethanol (ethyl alcohol) at one of the concentrations listed in Table E2.1.

Determining flash point. Set up the apparatus in Figure E2.1 or preferably Figure E2.2.

Determine the open cup flash point, taking the flash point as the average of three trials. After each trial, immediately remove the water bath and cool it about 10 or 15 F° below the observed flash point; then repeat the procedure.

Writing the discussion. Report the flash point and identify from it the unknown mixture, justifying your conclusion.

E2.4 EXERCISES

Prelaboratory

1. What are the requirements for suspending the thermometer in the flash point cup?
2. Why must the liquid in the cup be at a specified level?
3. Why is a water bath preferable as a heat source?
4. Why must the liquid in the cup be heated slowly?
5. Describe the position and movement of the wand during the flash point determination.

Postlaboratory

1. Calculate the approximate flash points of pentane, octane, dodecane, and hexadecane in degrees Fahrenheit. Make a plot of molecular weight (abscissa) versus flash point (ordinate). Is there a linear relationship?
2. Do flash points in general seem to be above, or below, boiling points?
3. Which should have a lower flash point, cyclohexane, or cyclohexene? What are they? Look up the flash points or calculate them from equation E2-1.

4. Explain in terms of LeChatelier's principle why closed cup flash points should be lower than open cup flash points.

REFERENCE

1. *N.F.P.A. Handbook of Fire Protection,* 11th ed.; Moulton, R. S., Ed.; National Fire Protection Association: Boston, 1954.

Acknowledgment
The author thanks A. G. Smith of Delta College for assistance in devising this project.

II ISOLATIONS

In a broad sense, isolation is the process of obtaining a substance in a form uncombined with anything else. In this sense, isolation applies to separating a product from any reaction mixture and is almost synonymous with the workup that follows every organic chemical transformation.

In a more restricted sense, isolation is taken to mean the process of obtaining a natural substance from its origin.

Until recent times, techniques for isolation of natural products were extremely important because there were few synthetic chemical processes known. The branch of pharmacology known as pharmacognosy once was an important part of a medical student's preparation for becoming a physician because in this study the student became acquainted with the origin of natural drugs and how to isolate them.

Even today, isolation techniques continue to be important because we are still unable to synthesize many materials that we need in industry and commerce. For example, the very important adhesive, casein glue, has only one origin: milk.

In this section, there are four isolations of compounds from natural sources. You will notice that the fundamental isolation techniques are those with which you may already be familiar: filtration, recrystallization, extraction, and distillation.

EXPERIMENT 3 ISOLATION OF CAFFEINE FROM COFFEE

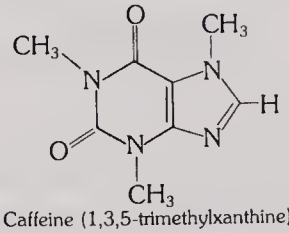
Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Solid-liquid extraction	(6.2)
Liquid-liquid extraction	(6.2)
Filtration	(4.3, 4.5)
Simple distillation	(7.2)
Drying liquids and solids	(2.1, 2.2)
Sublimation	(Appendix A2)
Melting points	(3.3)
Recrystallization	(5.3)
Labeling	(0.13)

INTRODUCTION

Sometimes when we have worked late we become tired, but find that a cup of coffee revives us. The main compound responsible for this effect is caffeine, an alkaloid. **Alkaloids** are organic compounds of natural origin which contain basic nitrogen and usually exhibit physiological properties. It is the basic properties of these compounds which led to their being called alkaloids, which means "alkali-like."

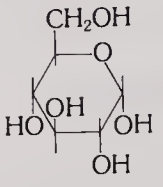


Caffeine (1,3,5-trimethylxanthine)

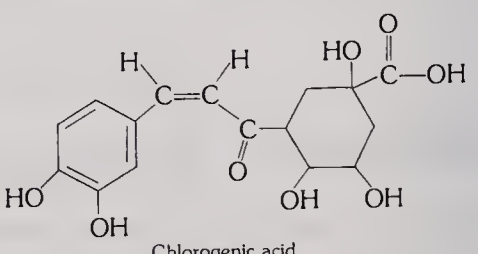
Caffeine is used medically to stimulate the central nervous, respiratory, and cardiac systems. Because of its stimulating effect, it is frequently included in certain pharmaceutical preparations to counteract sleepiness produced by other components. Although caffeine can be a useful drug, it has the potential to produce side effects like nervousness, restlessness, insomnia, ringing ears, diuresis, muscle tenseness, and rapid heartbeat. Caffeine is a mildly addicting drug, possessing all components of drug addiction: physical dependence, psychic craving, and tolerance. Caffeine has also been shown to induce chromosomal breakage in microorganisms and therefore has a mutagenic effect. However, for a normal coffee drinker, the number of mutations, if any, presumably would be negligible. However, caffeine has been implicated in promoting growths of cysts in some women. The lethal toxicity of caffeine is quite low, an adult fatal dose being about 10 g; since an average cup of coffee contains about 0.2 g, there is little danger of a fatality from coffee drinking.

E3.1 DISCUSSION OF THE ISOLATION

The isolation of caffeine in this experiment is an excellent exercise in separation techniques because caffeine is not the only compound that is extracted from the coffee grounds by hot water. Glucose, chlorogenic acid, and tannins are also extracted.

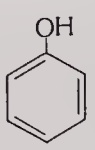


α-D-glucose

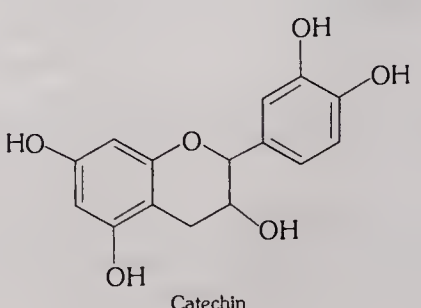


Chlorogenic acid

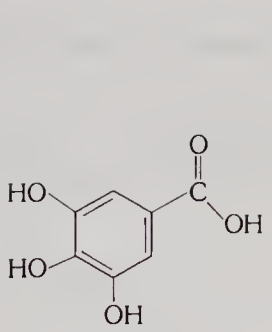
Tannins vary considerably in structure, but are phenol-like compounds with molecular weights up to 3000 g/mole. Some are polymeric forms of catechin. Others are glucose esters of dimerized gallic acid in which more than one hydroxyl of glucose might be attached to a dimer.

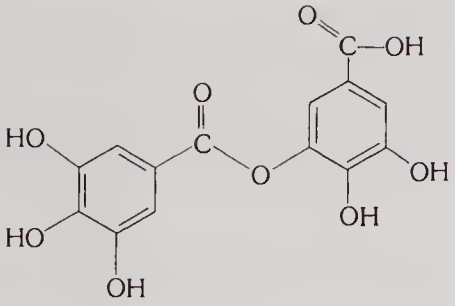


Phenol

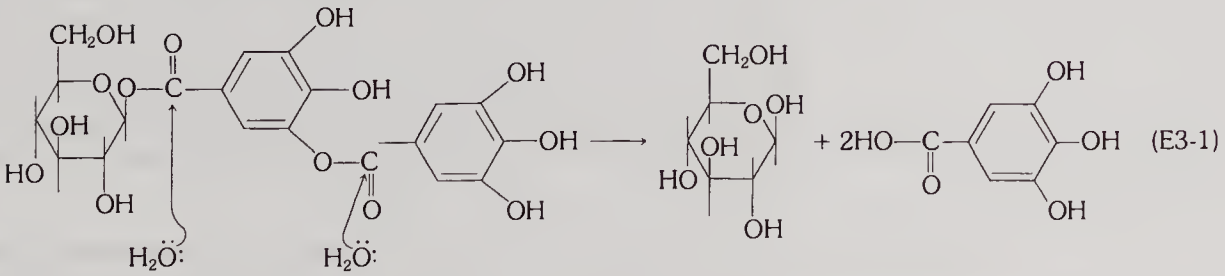


Catechin

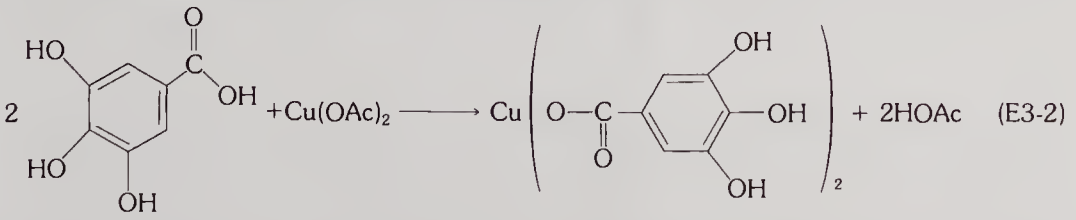

Gallic acid


Gallic acid dimer

During the aqueous extractions of coffee grounds, these tannins undergo at least partial hydrolysis to gallic acid and glucose or a partly substituted glucose, depending on the degree of hydrolysis:


(E3-1)

The phenolic hydroxyls and the carboxyl of chlorogenic and gallic acids are acidic functions and react with certain heavy metal compounds like lead (II) acetate, copper (II) acetate, and tin (II) chloride to form insoluble precipitates in water:


(E3-2)

You can remove the precipitated salts by filtration, but because they are very finely divided and somewhat gelatinous in nature, they rapidly clog the filter paper and render the process extremely tedious. By using a filter aid, you can circumvent this difficulty.

After filtration, the filtrate contains glucose and caffeine along with small amounts of other organics, including pigments. By extraction from water into chloroform (IUPAC trichloromethane) you can separate the caffeine from glucose and most of the other organics, since only the caffeine is very soluble in chloroform. Subsequent removal of chloroform by simple distillation yields crude caffeine. The caffeine is considered to be crude because it has not yet been purified.

E3.2 EXPERIMENTAL PART

Liquid-solid extraction. Put 40 g of regular grind coffee, a boiling chip, and 150 ml of water into a 500-ml round-bottom flask. Attach a condenser in the reflux position and let water flow through the jacket. Reflux the mixture for about 15–20 min, using a Bunsen burner, hot plate, or heating mantle as heat source. Using a water aspirator, filter the hot mixture through a relatively fast filter paper in a Büchner funnel. Press the coffee grounds in the funnel with a large cork or with the bottom of an appropriate size beaker. Put the coffee grounds in the assigned container, not down the drain. A 15–20 min time-saving alternative is to start with 15 g of instant coffee in 150 ml of water.

Check with your instructor to ascertain whether burner flames will be permitted in your lab or in a flame-permit area of the lab.

Extinguish burner flames when they are not in use.

If you are not using ground glass equipment, use accepted methods of inserting glass tubing and thermometers through stoppers: glycerine for lubrication, a cloth or paper pad to protect your palm, holding the tube near the stopper, twisting while pushing.

Removal of tannins. Prepare 25 ml of a hot 10% plumbous acetate (IUPAC lead (II) ethanoate) solution or 25 ml of a hot 6% cupric acetate (IUPAC copper (II) ethanoate) solution. Put the coffee filtrate from the liquid-solid extraction or the instant coffee solution into a 250-ml Erlenmeyer flask and add the acetate solution. Bring it to a boil and keep it hot for 5 min, stirring occasionally. Filter the hot solution through a Büchner funnel prepared with a diatomaceous earth filter from an aqueous slurry. Be sure to wet the filter paper before pouring in the suspension of filter aid, and to empty the filtering flask prior to the filtration of your hot solution. If the filtrate comes through muddy in appearance rather than colored but clear, stop the filtration and pour the filtrate back into the funnel. Rinse the flask and commence filtration once more. Rinse with about 20 ml of hot water; then release the vacuum and cool the filtrate in a cold water bath. If the diatomaceous earth and/or copper or lead components are to be recovered, put the filter cake into the assigned container.

If you use a beaker to press coffee grounds into a Büchner funnel, use a pad of cloth or paper to protect your palm from potential breakage of the beaker.

Liquid-liquid extraction. Pour the filtrate into a separatory funnel of appropriate size and gently extract the solution with 20 ml of trichloromethane (chloroform), taking care to avoid formation of an emulsion. Use about a 3- or 4-min contact period, then allow the layers to separate. If a large emulsion layer develops, add another 20 ml of trichloromethane, agitate gently about 30 sec, then drain it down. If the emulsion layer is still very large, drain it down also and depend on the sodium hydroxide wash to help break it up. Add another 20 ml of trichloromethane to the separatory funnel and repeat. Combine the two trichloromethane extracts. Empty the aqueous layer from the funnel, rinse the funnel, then pour the 40 ml of trichloromethane extract back into the funnel. Wash for 3–4 min with 10 ml of 5% aqueous sodium hydroxide to remove traces of acids not removed by the ethanoate treatment, and then with 10 ml of water to remove traces of sodium hydroxide. Keep track of the liquid layers as you pour the washes in, so you always know which layer to keep!

Do not inhale the solvent vapors. Work in a hood.

Do not forget to cool the product solution before addition of extraction solvent, to periodically release pressure in the separatory funnel, and to point the tip away from yourself and others when releasing pressure.

Put the washed trichloromethane layer into a small Erlenmeyer flask or beaker and add enough anhydrous sodium sulfate to dry the solution (probably 0.5–1 g will do it). Swirl the mixture occasionally during about a 10-min period (longer will not hurt). Decant or gravity filter the solution into the smallest tared distilling flask compatible with the amount of liquid present. Add a boiling chip and distill almost to dryness, using a steam or water bath to keep the temperature low enough to circumvent caffeine decomposition. Put the trichloromethane distillate in its assigned recovery container.

Working in a hood, blow out the remainder of the trichloromethane with a gentle stream of air introduced through a glass tube. Weigh the flask to determine the yield of the crude caffeine. Put enough in a melting point capillary to get a melting point, and save 0.05–0.10 g for sublimation.

Recrystallization of crude caffeine. Recrystallize all but the amount of caffeine saved for sublimation. Use the mixed solvent method, employing toluene as the primary solvent, and 60–90 °C petroleum ether or ligroine as the second solvent. △△ Collect the crystals on a filter paper in a Hirsch funnel, using vacuum filtration. Do *not* wet the filter paper with water. Use ligroin. Put the filtrate into a ligroine-toluene recovery container. △△ Put enough dry, recrystallized caffeine in a melting point capillary to get a melting point.

Before using organic solvents for recrystallization, be sure no one nearby is using a burner.

Sublimation of crude caffeine. Put 0.05–0.10 g of caffeine in the sublimation apparatus and sublime it. Be careful not to decompose the caffeine by overheating it. Put enough sublimed caffeine in a melting point capillary to get a melting point. Submit the remainder to your instructor in a labeled vial.

Check for presence of stars or cracks in all glassware to be used with water aspiration or other evacuation equipment.

Use a water trap between the water aspirator and the sublimation apparatus so that if some loss of pressure causes cold water to enter the apparatus it will not fracture and implode.

Place a shield between yourself and evacuated equipment so that if it should be broken an implosion will not send glass fragments toward you.

Obtaining melting points of caffeine samples. Because caffeine sublimes appreciably at atmospheric pressure, it is advisable to obtain a sealed tube melting point (Technique 3). Use a Thiele tube or similar device to determine the melting points. Present them in tabular form in your notebook. △△ Obtain IR and NMR spectra as directed by your instructor.

Writing the discussion. Items worthy of discussion for this project should include your yield of crude caffeine relative to that of other students and your level of expertise in liquid-solid extraction, liquid-liquid extraction, and so on; rationalization of the melting points of the crude, recrystallized, and sublimed caffeine samples; and comparison of the melting points of the purified samples with literature values as helping to establish identity of the product. Compare your IR and NMR spectra with Figures E3.1 and E3.2.

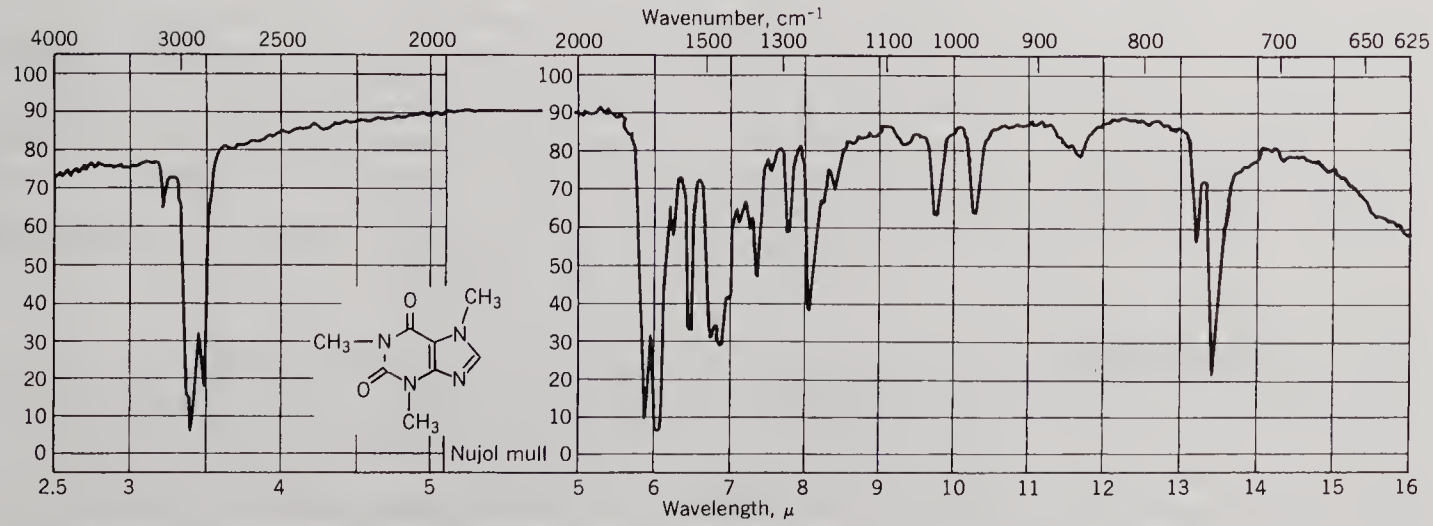


FIGURE E3.1 IR spectrum of caffeine. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

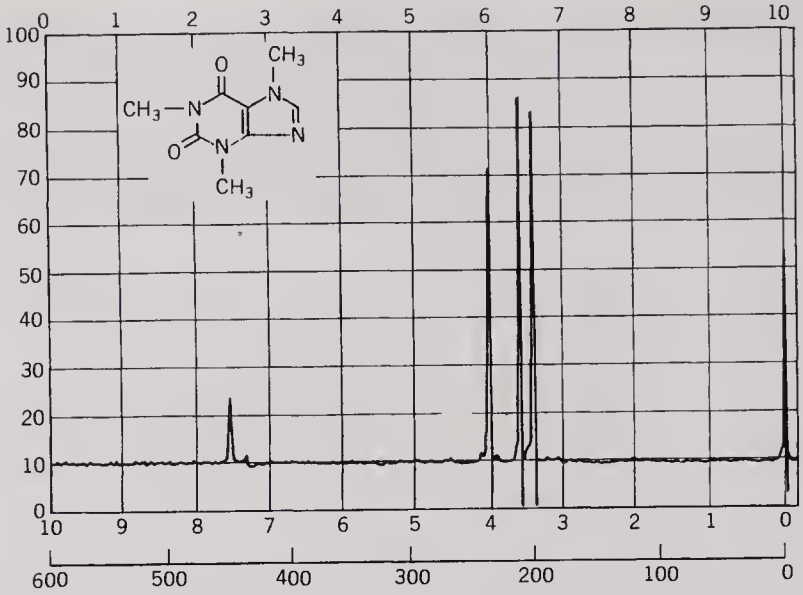


FIGURE E3.2 NMR spectrum of caffeine. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

E3.3 EXERCISES

Prelaboratory

1. Why is a filter aid used during filtration of the acid salts?
2. In the interest of time conservation, when is a good time to set up and prepare the Büchner funnel filtration system?
3. Paying particular attention to the routing of solutions to and from the separatory funnel, make a flow diagram of the steps in the extraction procedure.
4. What is the usual ratio of extracting solvent to product solution in the liquid-liquid extraction?
5. Your instructions call for preparation of 20 ml of a 10% lead (II) acetate solution. Note the use of one significant figure. Do you then think exact measurements are critical? Could you use 90 ml of water (assuming density of 1) and 10 g of lead (II) acetate to get 10%? What amounts of each will you use for this experiment?
6. Which layer will be on the bottom in the separatory funnel, the aqueous or trichloromethane layer?
7. Why is the trichloromethane extract washed with aqueous sodium hydroxide?
8. Why is the melting point capillary sealed before the melting point of caffeine is taken?
9. Make a list of the operations you will perform during this project in order of performance, including setting up and cleaning equipment. Try to plan and fit tasks in so that lab time will be best used. Show your instructor your plan at the beginning of the laboratory period.
10. For filtration of the recrystallized caffeine you were instructed to wet filter paper with ligroin rather than water. Why not use water?

Postlaboratory

1. Do you think gallic acid is present in a cup of coffee? Explain.
2. A cup of coffee contains about three to four times as much caffeine as a cup of tea even though the caffeine content of tea leaves is greater than that of roasted coffee beans. How do you account for this?
3. The partition coefficient for caffeine distributed between water and chloroform is 22. If 150 ml of coffee solution contains 0.80 g of caffeine and you extract once with 60 ml of chloroform, how much caffeine will remain in the aqueous layer?

4. If two successive extractions of 30 ml each are used, how much caffeine will remain in the aqueous layer of exercise 3?
5. Why can a 6% solution of copper (II) acetate be used, whereas it requires a 10% solution of lead (II) acetate? (think moles!)
6. If you wanted to obtain a more quantitative removal of caffeine from coffee than you did in this experiment, how could you alter the procedure?
7. For drying 20 ml of solution of caffeine in trichloromethane a student obtained a bottle of calcium sulfate dihydrate from the stockroom and added 0.5 g of it to the solution and stirred it for 10 min. Critique this procedure.

REFERENCES

1. Ault, A.; Kraig, R. *J. Chem. Educ.* **1969,** *46,* 767.
2. Durst, H. D.; Gokel, G. W. *Experimental Organic Chemistry,* 2nd ed.; McGraw-Hill: New York, 1987, p. 515.
3. Ritchie, J. M. "Central Nervous System Stimulants." In *The Pharmacological Basis of Therapeutics,* 4th ed.; Goodman, L. S.; Gilman, A., Eds.; MacMillan: New York, 1970, Chapter 17.

EXPERIMENT 4 ISOLATION OF CASEIN AND PREPARATION OF CASEIN GLUE

Time Required: 1 hr to isolate casein
3–4 hr total

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Vacuum filtration	(4.3)
Testing pH	(0.11)
Mortar and pestle	(0.10)
Storing chemicals	(0.12)
Labeling	(0.13)

New Technique:

Construction of an elevating block

INTRODUCTION

Casein, the main protein found in milk, is actually a mixture of several related proteins designated as *alpha-, beta-, gamma-,* and *kappa*-caseins. Although casein is nutritionally a very important protein because it contains calcium, phosphate, and an abundance of all essential amino acids, our current interest in it is as a raw material from which to make glue.

Crude casein glues have been used since the days of ancient Egypt, Greece, Rome, and China. Some of the finest paintings of the Medieval and Renaissance periods were set in frames put together with casein glues made from "lean cheese" and lime. These frames are still in good condition despite their having been made several hundred years ago.

Casein glues are used primarily on wood and paper, but, because of the water resistance of some casein glue, are also commonly used to secure labels to bottles, especially when a beverage such as champagne or beer is expected to be cooled in cold water or ice.

E4.1 INTRODUCTION TO ADHESION THEORY

Adhesion is the state in which two surfaces are held together by interfacial forces. Adhesion scientists recognize two kinds of adhesion: **mechanical adhesion,** which involves a physical interlocking of parts; and **specific adhesion,** which involves intermolecular interactions like ion-dipole, dipole-dipole, and van der Waals forces. An **adhesive** is a material capable of holding two bodies, called **adherends,** together by surface attachment.

We should expect that two polar surfaces are attracted to each other simply because of their polarities, in the same way that organic molecules are attracted to each other. Likewise, we anticipate that nonpolar surfaces should be attracted to each other by van der Waals forces. However, large surfaces like those on wood or metal blocks have little attraction for each other because as depicted in Figure E4.1, the *real* area of contact is a very small fraction of the apparent area. That is, since a submicroscopic view of what appears to us to be a smooth surface is in reality very rough, most of the atoms and molecules at surfaces cannot approach each other closely enough to set up attractive forces. Recall that van der Waals forces act appreciably only at distances of less than 1 or 2 Å and are approximately inversely proportional to the sixth power of the interatomic distance.

The purpose of the adhesive is to provide the right kind of intermolecular attractions at an effective interatomic distance. The adhesive acts as a bridge between two adherends, its molecules interacting with both. In order to make a sufficiently intimate contact with both adherend surfaces, the adhesive must initially be a liquid so that it can flow into all subatomic crevices and pores and displace air from them.

Any liquid which is sufficiently attracted to a surface that it *wets the surface* and which is subsequently converted to a tenacious solid or semisolid by evaporation, cooling, or chemical reaction is an adhesive for that surface. The three fundamental properties required of a successful adhesive are first, that it *wet the surface;* second, that it *solidify;* and finally, that it *possess enough deformability* to reduce buildup of stresses within the joint.

Surface Forces

Surface forces determine whether an adhesive will wet an adherend. Recall that surface forces are governed by the forces operating within the body of a material. A molecule within the body is attracted equally from all sides whereas one at the surface is more attracted to the bulk phase than to the air above it. Therefore, the molecule at the surface is pulled toward the interior, causing the surface to shrink to the smallest possible area. The *work* that is required to expand the surface by 1 cm^2 is a free energy and is referred to in various ways: **surface energy, interfacial energy, surface free energy** or **interfacial free energy.** It is given the symbol γ and has units of ergs/cm^2. Because it can also be thought of as the *force* that is required to expand the surface, it is also called a **surface tension** or **interfacial tension** and has units of dynes/cm (tension is the opposite of pressure).

When a drop of liquid adhesive (L) is put on a solid adherend (S), as depicted in Figure E4.2, a contact angle, θ, is produced and interfacial energies or tensions exist at the phase boundaries: γ_{SL} between the solid and liquid, γ_{SV} between the solid and the

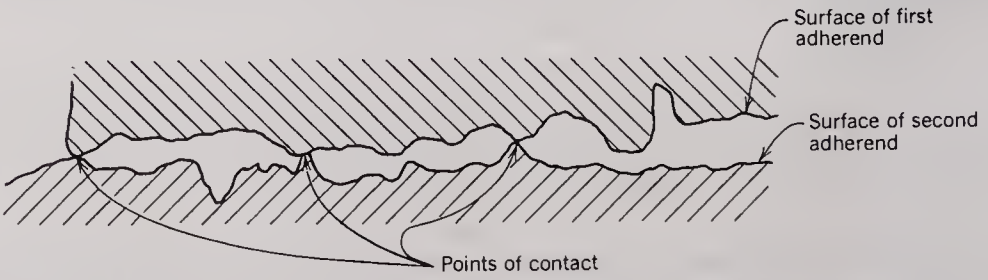


FIGURE E4.1 Real area of contact between adherends is a small fraction of apparent area.

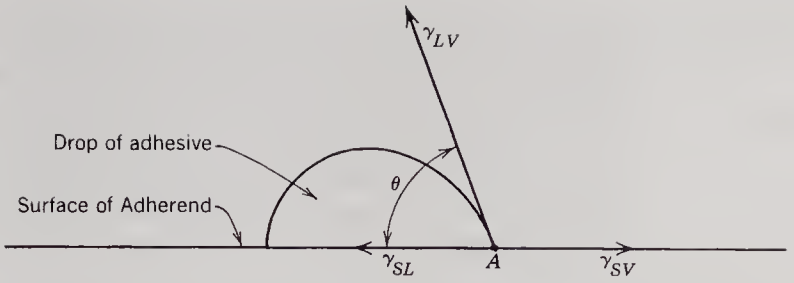


FIGURE E4.2 Adhesive drop on adherend surface. From *Encyclopedia of Polymer Sci. & Technol.*, Vol. 1; Bikales, N. M., Ed.; Wiley: New York, 1964. Reprinted by permission.

adsorbed vapor of the liquid, and γ_{LV} between the liquid and its vapor. The arrows represent the tensions that exist at the point, *A*, where the edge of the drop of adhesive touches the surface of the adherend: γ_{SV} is acting to spread the drop, γ_{SL} is acting to keep the drop from spreading, and γ_{LV} is acting to maintain a minimum liquid-vapor surface area. These three interfacial tensions are related by the Young-Dupre equation,

$$\gamma_{SV} - \gamma_{SL} = \gamma_{LV} \cos \theta \qquad \text{(E4-1)}$$

wherein θ is the contact angle of the drop with the solid surface. Rearrangement gives

$$\cos \theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}} \qquad \text{(E4-2)}$$

Equation E4-2 teaches that if the difference $\gamma_{SV} - \gamma_{SL}$ is the same as γ_{LV}, then $\cos \theta = 1$, and the contact angle θ is zero. This condition is possible when the attractive forces between molecules of adhesive and adherend are equal to or greater than those within the adhesive. When this condition prevails, the adhesive spreads freely over the surface at a rate that depends on the viscosity of the adhesive and the roughness of the adherend surface. That is, when the contact angle is zero, the adhesive is a very good one: It is strongly attracted to the surface and wets it well.

On the other hand, if γ_{SV} is the same as γ_{SL}, then the difference $\gamma_{SV} - \gamma_{SL}$ is zero, $\cos \theta$ also is zero, and θ is 90°. In other words, a contact angle of 90° means that the liquid adhesive beads up on the adherend surface and does not spread well. This situation results when the forces of attraction between molecules of adhesive and adherend are much less than those among molecules of adhesive alone. There are theoretically an infinite number of possibilities between a contact angle of 0° (complete wetability) and 180° (zero wetability). Actually, every liquid wets every solid to *some* extent, that is, θ is never 180°. Since the contact angle is inversely related to the tendency for an adhesive to spread, it is a useful inverse measure of adhesion.

Energy of Mixing

Mixing of adhesive and adherend molecules occurs at the interface between the two. If the attraction between adhesive and adherend is to be a strong one, there must be a decrease in free energy of mixing, that is, the mixing must be spontaneous. The free energy change of mixing is given by

$$\Delta G_{mix} = \Delta H_{mix} - T \Delta S_{mix} \qquad \text{(E4-3)}$$

wherein *G* is free energy, *H* is enthalpy, *S* is entropy, and *T* is Kelvin temperature. Remember that for mixing to be spontaneous, ΔG_{mix} must be negative. In general, entropy increases when two materials are mixed; that is, at the interface, where adhesive contacts adherend, the distribution of molecules is more random than in the adhesive itself. Because entropy increases, ΔS_{mix} is positive and the $T \Delta S$ term contributes to a negative free energy and spontaneous process. Notice that increasing the temperature increases the $T \Delta S$ term, making ΔG more negative.

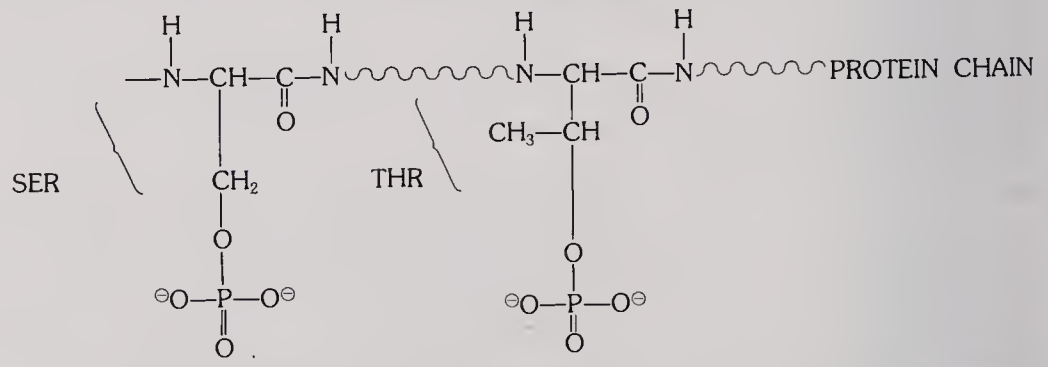
The enthalpy of mixing, ΔH_{mix}, depends on the intermolecular attractions between adhesive and adherend. If the intermolecular attractions within the adhesive and within the adherend are of a like magnitude, the conditions found for an ideal solution (Technique 7) prevail at the interface, and ΔH_{mix} will be 0; hence ΔG will be negative, and

the adhesive will spread and attract adherend. If the intermolecular attractions between molecules of adhesive and adherend are greater than those among molecules of adhesive or among molecules of adherend, energy will be released upon combination and ΔH_{mix} will be negative, making ΔG_{mix} considerably negative, and spreading and adhesion will surely occur. Notice that this latter case is reminiscent of a negative deviation from Raoult's law (Technique 7). Similarly, if ΔH_{mix} is quite positive as the result of lacking intermolecular attractions, ΔG might also be positive, and spreading and adhesion will not take place. (Imagine trying to spread water on a brick of lard or on polyethylene.)

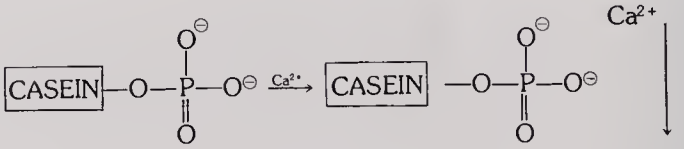
E4.2 CASEIN AND ITS ISOLATION

Each giant casein molecule is composed of hundreds of amino acids with side chains containing many functional groups like hydroxyl, amino, amido, and carboxyl.

Casein contains about 0.9% phosphorus by weight in the form of phosphate groups attached to hydroxyls in the side chains of threonine and serine:



The phosphate groups combine with calcium to form an insoluble precipitate in aqueous solution



(E4-5)

Therefore, casein exists in milk as calcium caseinate, which would be an insoluble precipitate were it not for *kappa*-casein, which is low in phosphate and includes carbohydrate as part of its structure. The many hydroxyls of the carbohydrate, as well as those of its serine and threonine side chains render *kappa*-casein more water soluble than the other forms of casein. Scientists believe that *kappa*-casein molecules with their hydroxyls directed outward into the water surround calcium caseinate molecule ions to form micelles (Experiment 24), which constitute the dispersed phase of the colloid, milk.

Milk has a pH of about 6.6. At this pH, amine type side chains (lysine, arginine, hydroxylysine) are largely protonated and carboxyl type side chains (aspartic acid, glutamic acid) are for the most part in the form of carboxylate. Therefore, there are both positive and negative charges along the protein chain. However, negative charges predominate, and if electrodes were put into milk, casein would migrate to the anode (positive electrode). The pH at which no migration takes place (positive charges equal negative charges) is called the **isoelectric point,** which for casein is 4.6. Minimum solubility of a protein occurs at its isoelectric point. Therefore, if you add acid to milk until a pH of 4.6 is reached, casein will precipitate. You must be careful not to go far below pH 4.6 for two reasons: First, the solubility increases somewhat again; and second, as the pH gets lower the likelihood of hydrolyzing the protein increases. You must also be careful not to increase the temperature much above 40 °C because high temperature

also promotes hydrolysis. Some literature sources suggest using acetic acid rather than hydrochloric acid, presumably because of the buffering action of acetate ion and the somewhat lesser likelihood of adding too much acid.

The acetone washes are to remove water and the small amount of milk fat on the casein.

E4.3 CASEIN GLUE

There are many formulations for making casein glues: methods, ingredients, and properties can be varied. However, the basic principles are the same, and we shall discuss the adhesive based on the formulation described in the experimental section.

There are two general classifications of casein glues: wet mix glues, and prepared glues. **Wet mix glues** are made as required from ground casein, water, and the additional chemicals specified in the formula. They have some advantages over prepared glues: a wider variety of ingredients, mixing in the most advantageous order, and often a somewhat lower cost. **Prepared glues** contain all of the necessary chemicals and require of the user only the addition of water. This saves time for the user because there is no necessity of carefully weighing each ingredient.

Your formulation consists of casein, calcium hydroxide, and sodium carbonate all ground together as a fine powder. The proportions of inorganic chemicals is such that the glue will have a working time of 2–3 hr and will give a water-resistant glue line. The working time of the glue can be increased by adding more water and/or more sodium carbonate.

The function of sodium carbonate is to react with calcium hydroxide, producing sodium hydroxide.

$$Ca(OH)_2 + Na_2CO_3 \longrightarrow CaCO_3\downarrow + 2NaOH \qquad \text{(E4-6)}$$

The sodium hydroxide reacts with casein, producing sodium caseinate, which is sufficiently water soluble to form a well dispersed **sol,** a solid dispersed in a liquid:

$$\text{casein}\text{—}\underset{\underset{O}{\|}}{C}\text{—}O\text{—}H + NaOH \rightleftharpoons \text{casein}\text{—}\underset{\underset{O}{\|}}{C}\text{—}\overset{\ominus}{O}\ \overset{\oplus}{Na} + H_2O \qquad \text{(E4-7)}$$

The function of calcium ion is to react with sodium carbonate to release sodium hydroxide and to react with the sodium caseinate to form enough calcium caseinate to bring about formation of a **gel,** a liquid dispersed within a solid network.

When you spread this adhesive gel on the surfaces of adherends, the gel wets their surfaces, squeezes out adsorbed air, and adheres to them. The conclusion of the process occurs by removal of water from the gel and consequent solidification of the adhesive, now bound to both adherends. Water can leave the gel in two ways: by soaking into the adherend and by evaporation.

E4.4 EXPERIMENTAL PART

Isolation of casein. Pour 100 ml of skimmed milk into a large beaker and heat it to about 40 °C. Stirring constantly, add to the mixture 1.25 ml of 3*M* hydrochloric acid; then with rapid constant stirring add dropwise enough additional 3*M* hydrochloric acid to produce an obvious coagulation of casein. When coagulation is complete, the pH of the mixture should be about 4.6 and the curds will have settled to the bottom, leaving a nearly clear supernatant solution. Avoid adding excess acid. Decant as much of the supernatant liquid as possible. Using a coarse filter paper, filter the casein in a Büchner funnel; then empty the suction flask. If filtration becomes too slow, change to a new

filter disc. Scrape the casein into a small beaker, add 10 ml of clean wash grade propanone (acetone), and mash the curds thoroughly. Filter the casein with suction again, return the casein to the small beaker, add 10 ml of wash grade acetone, mash the curds, and filter again. Put the filtrate into the propanone recovery bottle and the wet casein into a mortar, grinding it occasionally while it is drying until the granules are very fine. Then set the casein aside to dry thoroughly.

Do not dry the casein in an oven before the acetone has evaporated. The flash point of acetone is too low.

Weigh the dry casein and determine the yield. Put the dry casein in a mortar and **triturate** (grind to a fine powder) it thoroughly. Store it in a labeled vial. Obtain the melting point behavior of the powder. Casein does not melt, but begins to char and decompose at about 200 °C. Prepare an IR spectrum of casein (Nujol mull).

Compounding casein glue. Put 5.0 g of ground casein, 1.5 g of calcium hydroxide, and 0.7 g of anhydrous sodium carbonate in a mortar and thoroughly triturate it with a pestle. Store the prepared glue in a vial with a tight cap.

Do not inhale the caustic powder which might arise during grinding. Work in a hood.

Preparing the glue. For each 1.0 g of prepared casein glue put 2.5 g of water in a small beaker. Sprinkle the powder into the water while stirring, and stir it until the glue dissolves.

Cut a label-size piece of paper and glue it to the vial in which you store your prepared glue.

Construction of an elevating block. Obtain a piece of corrugated cardboard 31 × 42 cm or larger and draw on it the pattern shown in Figure E4.3. So that it will fold easily and more precisely, score the cardboard lightly along the dashed lines. Fold the cardboard upward along all scored lines. Prepare some casein glue, using about 2 g of powder. Smear a generous amount of your casein glue on the tabs labeled G, making sure that you are gluing the correct side of the tab. Fold the box together as shown in Figure E4.4 and set upon it a weight equal to a variac or several books until the glue is dry. Alternatively, fold the top of the box across to the top tab and glue it; then secure it with a couple of staples. Next fold the remainder of the glued tabs into place.

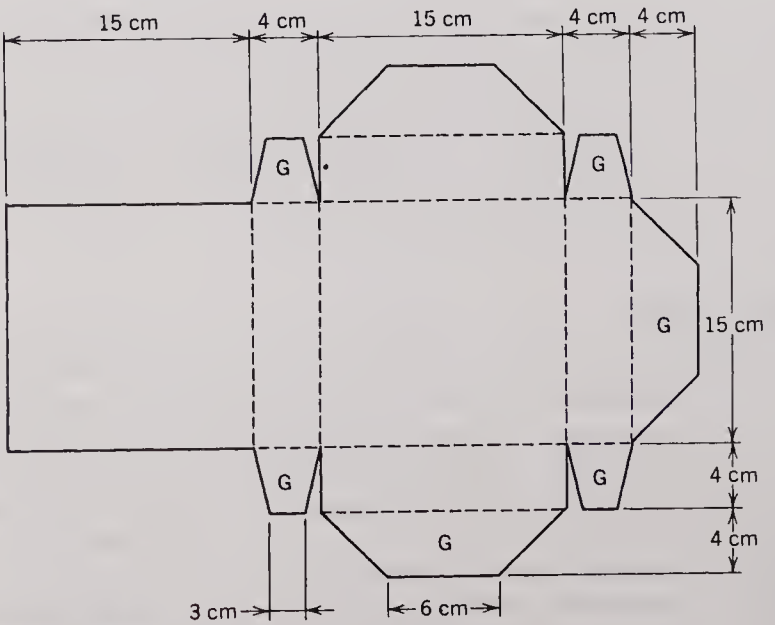


FIGURE E4.3 Laboratory elevating block pattern.

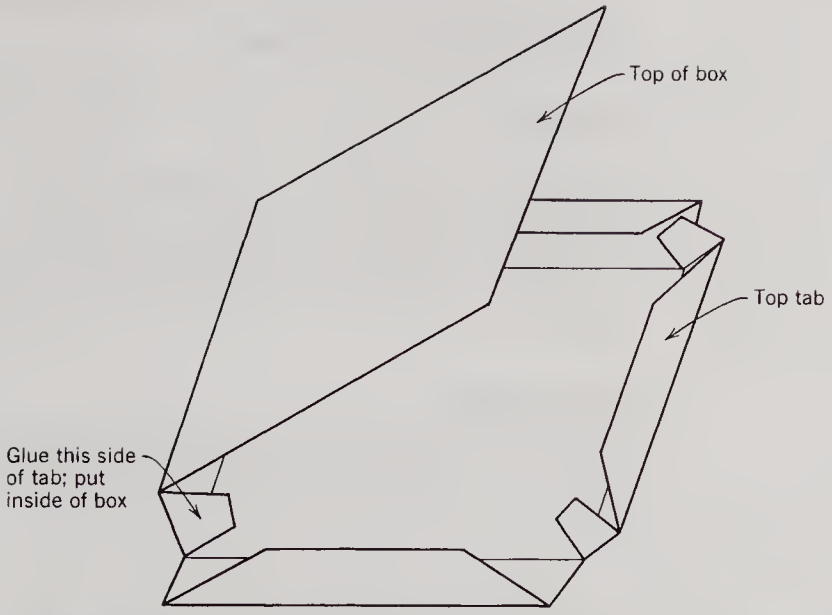


FIGURE E4.4 Folding the laboratory elevating block.

Use a brush or rubber-gloved finger to apply the glue. Remember that it is a caustic cement.

After the glue has dried for one day or more, you can paint the box with varnish or paint manufactured in Experiment 47.

Writing the discussion. Discuss the properties of casein and its identity as determined by melting point behavior and IR spectrum. Discuss the spreadability of the glue and its adhesive character on paper, glass, and cardboard. Report and discuss the percent recovery of casein.

E4.5 EXERCISES

Prelaboratory

1. Why must you not add too much hydrochloric acid to the milk?
2. Why must you keep the temperature of the milk at no more than 40 °C?
3. Why should you wash the casein with propanone?
4. What is the function of Na_2CO_3 in the prepared glue?
5. Why must you not breathe the prepared glue powder?

Postlaboratory

1. Using equation E4-3, explain why an adhesive might adhere and spread well on the surface of an adherend at an elevated temperature, but become loosened from it at a lower temperature.
2. Explain how ergs/cm^2 and dynes/cm are interchangeable units.
3. Using principles of the kinetic molecular theory, explain why surface tension should decrease as temperature increases.
4. Sketch a schematic drawing of a micelle that suggests how *kappa*-casein acts as a dispersing agent for insoluble calcium caseinate.
5. Using the Henderson-Hasselbalch equation (Experiment 42), calculate the ratio of charged to noncharged lysine side chains (pK_a = 10.5); of charged to noncharged glutamic acid side chains (pK_a = 4.2). Use the pH of milk.
6. *Kay Scene* made a prepared glue from casein, calcium chloride, and sodium hydroxide. If this powder were immediately mixed with water and used, would it make

a satisfactory adhesive? Explain. If it were set aside to use later, what might be the result in a humid environment?

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Acknowledgment
The writer thanks Carolyn Bye, Technical Director, Casein Dept., National Casein of New Jersey, for supplying and suggesting reference materials which were used in devising this experiment.

EXPERIMENT 5 ISOLATION OF PIGMENTS FROM SPINACH

Time Required: 3–4 hr

Review Techniques and Principles:

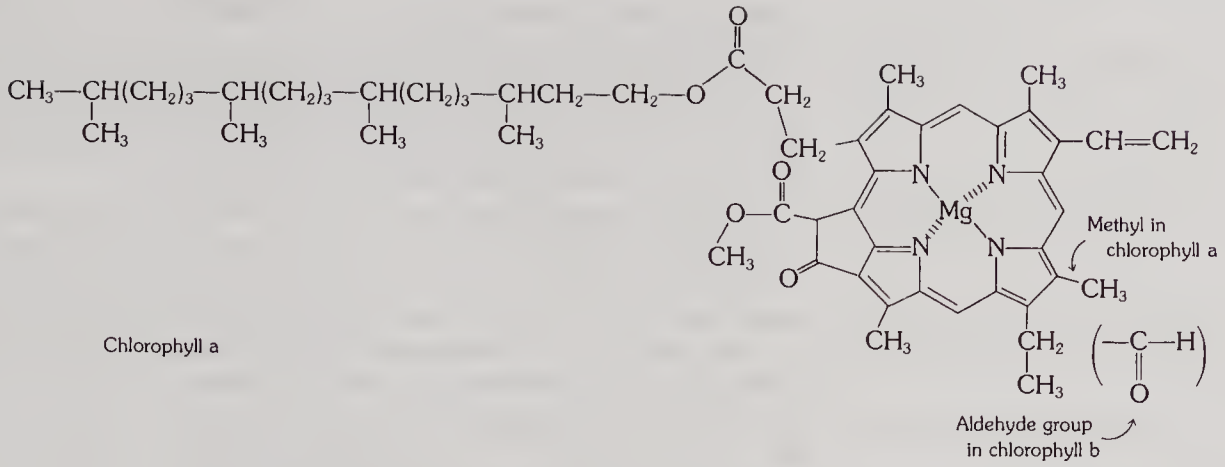
Lab notebook	(1)
Mortar and pestle	(0.10)
Solid-liquid extraction	(6.2)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Simple distillation	(7.2)
Vacuum filtration	(4.5)
TLC	(8.2)
Column chromatography	(10.2)
UV–VIS	(14.4)

INTRODUCTION

Growing plants usually contain a number of pigments. Leaves often have several colored compounds in them, but the compounds are masked by the large amount and intense green color of chlorophylls. In the fall when the days grow shorter, the equilibrium between production and destruction of chlorophyll becomes disturbed, and destruction exceeds production; then the other pigments become visible.

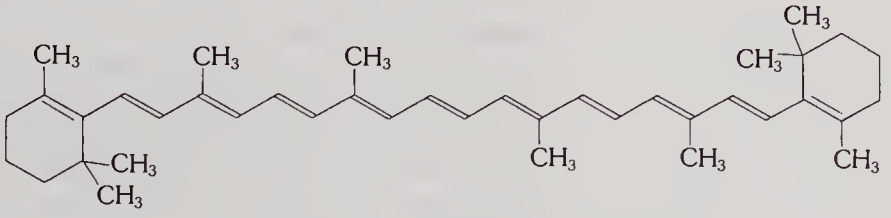
Spinach leaves contain chlorophylls (green), carotenes (yellow), and xanthophylls (yellow).

Chlorophyll a ($C_{55}H_{72}O_5N_4Mg$) and chlorophyll b ($C_{55}H_{70}O_6N_4Mg$) are both present in spinach. They are structurally similar, but chlorophyll b has an aldehyde function in place of the methyl group shown in the structure of chlorophyll a. In higher forms of plant life, chlorophyll a is usually found to be three times more abundant than chlorophyll b. In spite of the many polar functions, the chlorophylls have enough hydrocarbon character to make them soluble in relatively nonpolar solvents like ether and petroleum ether.



Chlorophyll a

The carotenes ($C_{40}H_{56}$) are alkenes with a long chain of conjugated double bonds. There are three intensely yellow isomers; *alpha, beta,* and *gamma*-carotene. Mature green leaves contain about 90% *beta* and 10% *alpha* carotene. Each beta-carotene molecule is converted in vivo to two molecules of vitamin A, whereas the alpha form yields one molecule of vitamin A. Notice that the carotenes are largely nonpolar, but are polarizable.



Beta-carotene

The xanthophylls ($C_{40}H_{56}O_2$) are hydroxylated forms of the carotenes. The quantity of xanthophylls in a green leaf is usually about twice that of the carotenes. The xanthophylls are more soluble in alcohol, and less soluble in petroleum ether than carotenes.

E5.1 DISCUSSION OF THE ISOLATION

To expose the pigments to the extracting solvent, the spinach leaves are first put into a mortar and crushed with a pestle. This breaks down the plant tissues and exposes the lipid-soluble pigments, but they cannot yet be extracted into a nonpolar solvent like hexane because they are surrounded by water. To remove water, the crushed leaves are extracted with methanol, leaving the pigments in a relatively anhydrous environment which a hexane-methanol mixture can penetrate.

E5.2 EXPERIMENTAL PART

Your instructor will tell you which of the following you should do after extraction of pigments: TLC, column chromatography, UV–VIS of TLC scrapings, UV–VIS of column elution fractions.

Pigment extraction. Crush about 20 g of chopped frozen spinach in a mortar with a pestle. Add 20 ml of methanol and grind the leaves thoroughly for a few minutes. Suck the leaves damp-dry using a fast filter paper and vacuum filtration. The filtering flask

should be in an ice-water bath to keep the filtrate from evaporating. Put the filtrate in a methanol-water recovery bottle.

Again using a mortar and pestle, mash and extract the leaves with 20 ml of 60/40 by volume hexane-methanol mixture. If the extract is not dark green, repeat with another 20 ml of the solvent mixture. Filter the mash each time using vacuum filtration and a filtering flask in an ice-water bath.

Put the combined filtrates in a separatory funnel and dispose of the mashed leaves in an assigned container. Wash the hexane-methanol filtrate twice with 10 ml of water, putting the first water wash in the methanol-water recovery. Pour the second washing down the drain. These washings will have removed almost all of the methanol. △

Dry the hexane solution over anhydrous sodium sulfate. Using a steam bath as a heat source, distill off the hexane until only about 1 ml is left. △ If steam cones are not available, use a boiling water bath on a hot plate. Remove the heat source before the volume gets down to 1 ml or the flask will distill to dryness. This is because hexane has a relatively low boiling point and will be distilled by the residual heat of the flask. Should this occur, a small amount of hexane can be satisfactorily added again if you were careful not to allow any pigment decomposition.

Be careful not to spill methanol or hexane onto a hot plate.

Check all glassware for stars or cracks; do not use thin-wall glassware for the system attached to the water aspirator.

Separating the pigments by TLC. Coat four microscope slides with silica gel. Oven dry them for ½ hr at 110 °C. Pipet onto each plate two spots equally spaced from each other and 1 cm from the bottom. Score the side of the plate to mark the spot positions.

Use hexane, toluene, trichloromethane (chloroform), and methanol as developers, running one plate in each system. Have two chambers ready for use so that when one is in use you can be getting the other ready. Watch the progress of the solvent front carefully so as to not let the solvent front travel to the end of the silica. Make a drawing of each developed plate, indicating distances and colors. △△ Calculate the R_f values for each spot, and identify the compounds associated with them as chlorophylls, carotenes, and xanthophylls.

If desired, you can scrape each separated spot into an individual test tube and add 3.0 ml of spectral grade methanol. Obtain a VIS spectrum for each spot.

Put all solvents in appropriate recovery containers.

Separating the pigments on a column. Prepare a silica or alumina column along with diatomaceous earth to help make the eluants run freely. Begin elution with hexane, change to toluene, and then to chloroform, and finally to methanol if necessary. (Remember, alumina adsorbs more strongly than silica.) Monitor the column and prepare an eluant plot. If desired, you can distill off solvents not suitable for VIS spectra and take up the pigments in spectral grade methanol. Obtain UV–VIS spectra of the various fractions.

Put all solvents in appropriate recovery containers.

Writing the discussion. Discuss your identification of the spots based on their colors, R_f values, and order of elution from the alumina column. Discuss the relationship of pigment polarities relative to silica and/or alumina, and the solvents used for developers and/or eluants. If UV–VIS spectra were obtained, discuss the colors of the pigments relative to their wavelength range of absorption and λ_{max}.

E5.3 EXERCISES

Prelaboratory

1. During the water wash of the hexane-methanol filtrates, in which layer of the separatory funnel will the pigments be found? Explain.

2. What do the aqueous washes of the hexane-methanol extract remove?
3. Why is an ice-water bath used around the filter flask during the vacuum filtration?
4. Which has more polar bonds: carotene or chlorophyll? Which would bind more strongly to silica or alumina?
5. List carotenes, chlorophyll a, chlorophyll b, and xanthophylls in the order in which you would expect to find them after development on a silica gel thin-layer plate.

Postlaboratory

1. Do you think pentane would be a usable solvent for extraction of the spinach pigments? Would methanol first have to be used to remove water? Might any problem arise when using pentane during vacuum filtration?
2. Discuss the colors of chlorophyll a and *beta*-carotene relative to the wavelengths of light they absorb.
3. Draw the structure of vitamin A and show how two molecules of it can be derived from one molecule of beta-carotene.

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EXPERIMENT 6 ISOLATION OF LIMONENE FROM ORANGES

Time Required: 3 hr

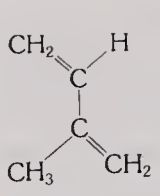
Review Techniques and Principles:

Lab notebook	(1)
Direct steam distillation	(7.15)
Drying liquids	(2.2)
Simple distillation	(7.2)
Qualitative tests for unsaturation	(Q8.1)
Polarimetry	(12.2)
Refractometry	(13.3)
IR	(15.4)
Boiling points	(8.4)
GLC	(11.3)
Labeling	(0.13)
Chemical literature	(18)

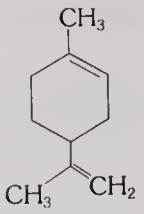
INTRODUCTION

Many chemicals of industrial, medicinal, or biological interest are of natural origin. The characteristic flavors and odors of fruits are largely associated with organic chemicals.

Limonene belongs to a class of natural substances known as **terpenes,** compounds with carbon skeletons composed of isoprene units joined together in a regular head to tail fashion. Isoprene is the naturally occurring diene, 2-methyl-1,3-butadiene. Limonene is the main terpene found in many oils, including those of lemon, orange, caraway, dill, and bergamot. No terpene, with the possible exception of *alpha*-pinene, is present in a greater variety of plants.



Isoprene



Limonene

Limonene has a chiral carbon and is optically active, both (+) and (−) forms occurring naturally. However, the orange tree produces only one of the enantiomers. In this experiment you will not only isolate limonene but will also determine which enantiomer the orange tree manufactures.

6.1 EXPERIMENTAL PART

You will either be supplied with three large navel oranges or be asked to bring them from home.

Orange peel puree. Using a sharp knife, remove the outer portion of the orange peel, leaving the heavy white pulp on the orange (If you do this at home, or at least not in the laboratory, you can eat the oranges.) Put the peels and 250 ml of water in a food blender. Over a 5-min period prepare a very finely ground puree (a fine, soupy slurry). Put the puree in a sealed jar and bring it to the laboratory. Or bring the orange peels to the laboratory in a sealed jar or sandwich bag to be pureed there. If it is not possible to make a puree, chop the peel into very small pieces.

Keep hands out of the blender; keep the lid on tight.
Do not eat oranges in the laboratory.

Steam distillation. Put the puree in a 500- or 1000-ml round-bottom flask and assemble an apparatus for direct steam distillation, using a Claisen distillation head for takeoff and a dropping funnel or separatory funnel for water addition. Use an Erlenmeyer flask for collection of the distillate. If a Claisen head is not available, you can use a two- or three-neck flask, one neck for the dropping funnel and one for a condenser of about 15-cm length. Mark the side of the flask at the level of the puree so you will know what level to maintain as the distillation proceeds. Insulate the Claisen head and column. Bring the mixture to a steady boil with a heating mantle or Bunsen burner. To avoid excessive frothing and bumping of the slurry over into the condenser, do not allow the mixture to boil too violently. If any of the slurry bumps over into the receiver, return the contents of the receiver to the boiling flask, clean the equipment with fresh water, and begin again. Allow water to drip in from the dropping funnel so as to maintain a constant liquid level in the boiling flask, or periodically add small amounts of water from the separatory funnel. From time to time record the boiling point at the sidearm. In order to save time, distill as rapidly as you can until about 150 ml of distillate has been collected and two phases are no longer apparent in the condenser. You should be able to see an oily layer on the surface of the distillate. Discard the remainder of the puree down the drain, and allow the distillate to cool.

Workup. Transfer the distillate to a separatory funnel. Add 5–10 ml of pentane to the Erlenmeyer flask, stopper it, shake it well, then pour the contents into the separatory

funnel. Shake the funnel well and then let the layers separate. Put the pentane solution into a small beaker and dry it over anhydrous magnesium sulfate. Filter or decant the solution into a tared vial and evaporate the pentane by holding the vial with a test tube clamp in a bath of hot water from the tap. No additional heat will be required. To speed up the process by entraining pentane vapors, use a gentle stream of air from a hose with an eyedropper tip extending well into the vial but not into the liquid. Evaporate until the volume no longer appears to be changing. A GLC analysis with a column near the temperature of the pentane boiling point will tell you whether the pentane is all evaporated. Weigh the product and calculate the percent recovery.

Analysis. Test a few drops of your product for unsaturation with bromine in CCl_4 and/or with $KMnO_4$ solution as described in the characterization tests for alkenes in Part III.

Obtain a neat IR spectrum, and identify the bands for C—H stretching, C=C stretching, and vinyl hydrogen in- and out-of-plane bending. Refer to a catalog of standard spectra or to an atlas of spectral data to see if your spectrum appears to be that of limonene.

Determine the refractive index, using the average of three measurements. Check a handbook of chemistry and physics or atlas of spectral data for a literature value. Be sure to correct your value for temperature variation if necessary.

Determine the specific rotation of neat limonene or prepare a solution of about 0.5 g of limonene in absolute ethanol to make a total of 10 ml, using three significant figures in all measurements. If larger amounts are required for your polarimeter, use a similar ratio. It might be necessary to pool your product with that of several other students in order to get enough for either neat or solution determinations. When finished, put the solution or neat limonene in its specified recovery container. The literature value is $+125.6°\cdot ml/g\cdot dm$.

Writing the discussion. At least include a discussion of the characterization tests, of IR and refractometry identifications of limonene, and of the purity of the limonene as shown by refractometry.

E6.2 EXERCISES

Prelaboratory

1. Will you expect the temperature at which the steam distillate comes over to change as the distillation proceeds?
2. In collecting data for calculations of specific rotation, what quantities will you have to measure or record?
3. Make a flow diagram of the method you will use in conducting the steam distillation.
4. What piece of equipment will be used to keep the liquid level constant in the boiling flask? Considering the amount of liquid to be collected, what will be a convenient size for this piece of equipment?
5. During separation of product from water, which layer will be the upper layer in the separatory funnel, aqueous or organic? Why?
6. The boiling point of limonene is 177 °C. Do you think the limonene-water distillate will boil much below the boiling point of water?
7. Is a good temperature gradient necessary from the bottom to top of the distilling column during the steam distillation? Explain.
8. What GLC column in your laboratory would you use to test for pentane in your limonene?
9. What do you think is the purpose of putting pentane into a receiver flask and shaking it well before adding its contents to the separatory funnel?

10. Which would provide a greater surface area for boiling, 250 ml of liquid in a 500-ml flask or 250 ml in a 1000-ml flask? Which flask is likely to permit a more rapid distillation?

Postlaboratory

1. There are 14 possible isomers having the limonene skeleton but which differ in the positions of the double bonds in and out of the ring. Draw the structures.
2. Give an IUPAC name to limonene.
3. From your recorded boiling point for the limonene-water codistillate, determine the molar and gram ratios of the two components. Use equation 7-13 and the table of vapor pressures of water at given temperatures in a handbook of chemistry and physics.
4. Show how limonene can be considered to be composed of two isoprene units.
5. Identify the chiral center of limonene.

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III NONBONDED INTERACTIONS

Most often when we think of chemistry we tend to center our attention on chemical transformations, the making and breaking of bonds. However, much important organic chemistry focuses on interactions *between* molecules, the **nonbonded interactions.** Many of the processes and products that we use daily and the effects that they produce depend on the chemistry of nonbonded interactions: solvents effects, extractions, distillations, chromatography, adhesives, cosmetics, antifoams, latex paints, waxes, protective coatings, and a host of others.

In this section, we shall investigate two pharmaceutical preparations, both of which form protective skin coatings: an appropriate mixture of oils and waxes to make an antichap lipstick (Experiment 7), and the formation of a stable emulsion to make a hand cream (Experiment 8).

A chemical bond results when attraction between atoms is great enough that a distinct and independent species composed of those atoms is produced. All three of the major types of bonds (ionic, covalent, and metallic) form because of the attraction that the electrically positive nucleus of one atom has for the electrically negative electrons of another.

In addition to the three major types of bonding, there are several classifications of lesser attractions which come into play when molecules, ions, and atoms approach one another. These attractions, referred to as **nonbonded interactions** or **intermolecular interactions,** include ion-dipole (5–15 kcal/mole), dipole-dipole (1–5 kcal/mole), ion-induced dipole (ca. 1 kcal/mole), dipole-induced dipole (0.5–1 kcal/mole), and van der

Waals forces (ca. 0.5 kcal/mole). Nonbonded interactions occur for the same basic reason that bonding does, that is, the attraction of electrically positive centers of one compound for electrically negative centers of another. Note that the rule-of-thumb strengths of these nonbonded interactions are quite small when compared to the strengths of bonds (35–150 kcal/mole). But it is important to realize that although the intermolecular interactions are relatively weaker than bonds, many weak interactions working together produce an overall effect of strength. An analogy is that in *Gulliver's Travels* the combined strength of the many threads used by the diminutive people of Lilliput who bound Gulliver were just as effective as if one large rope had been used.

SKIN PROTECTION

Probably the most important function of human skin is protection against adverse environmental effects. It must, among other things, provide a barrier against foreign materials. The most important barrier is a layer of tissue lying at the base of the hornified outer covering known as the **stratum corneum.** The most obvious examples of this hornified covering are palm callouses and the thick pads on the heels of one's feet. An auxiliary protection is afforded by the complex layer of **lipid** (fatty) materials which are secreted by the body and cover the surface of the skin. The lipids not only make the skin more impermeable to waterborne materials but also permit the skin to remain pliable by retaining moisture. It is important to realize that the flexibility of the skin is primarily a function of its own water content and not due to softening by oils.

Because lipids are very much less polar than water, water and lipids are not particularly attracted to each other. The attraction is one of water for water and lipid for lipid, very little of water for lipid. The rule of thumb is that "like dissolves like," meaning that polar liquids will dissolve ions and other polar compounds, and that nonpolar liquids dissolve nonpolar compounds. Because water does not dissolve appreciably in lipids and cannot pass through them readily, an important lipid function is to occlusively prevent excess water loss from the skin. If too much moisture is removed, the skin loses its flexibility and becomes dry, brittle, and superficially cracked. Such a condition, known as **chapping,** is not only uncomfortable or painful but can be unattractive as well (see Figure E7.1).

The lips, along with the hands, are particularly susceptible to chapping because of constant exposure to wind, heat, cold, foods, water, soap, detergent, and sunlight, all of which lead to loss of normal skin lipids. Application of an artificial lipid-like layer is often beneficial, helping to protect the lips or hands by maintaining a higher water content while allowing damaged tissues to repair themselves. Figure E7.2 is a schematic drawing of a lipid layer applied to skin either by glandular secretions or by artificial application. The zig-zag path of water illustrates its diffusion through the stratum corneum. Where there is no hydrocarbon coating, water can diffuse to the surface and escape by evaporation. But wherever the highly polar water encounters the nonpolar hydrocarbon layer it can only diffuse back deeper into the stratum corneum because it cannot permeate the layer that is chemically so different from itself. **Permeation** consists of three steps:

FIGURE E7.1 Girl lips to boy lips: "You're o.k., but there's no such thing as a good looking chap."

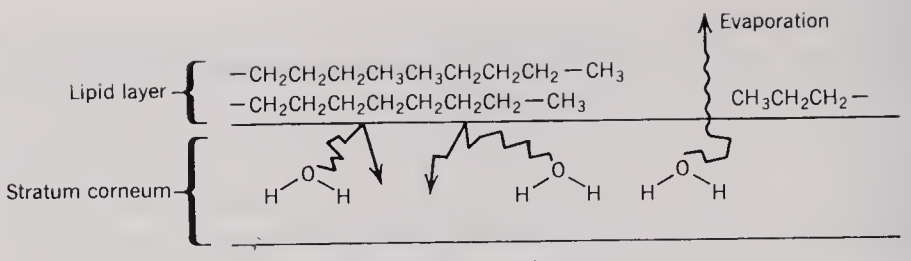


FIGURE E7.2 Impermeability of lipid layer on skin.

dissolution, diffusion, and desorption. The first step, the dissolving of water in the hydrocarbon, is so highly improbable that it precludes the remainder of the permeation process.

Because pharmaceutical and cosmetic preparations are designed for use on or within the human body, it is imperative that they be prepared using pharmaceutically approved chemicals and in an environment that will not contaminate the ingredients or the final product. Chemicals suitable for such use are designated **U.S.P.** or **N.F.**, meaning that they have been manufactured and tested in accord with documented procedures and standards of purity as set forth by the *United States Pharmacopoea* or *National Formulary*.

EXPERIMENT 7 ANTICHAP LIPSTICK

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook (1)
Heating (0.5)

New Principles and Techniques:

Thixotropy

E7.1 DISCUSSION OF THE PREPARATION

In this experiment you will compound an antichap lipstick. In pharmacology, **compound** simply means to combine and mix according to direction.

A chap-preventive lipstick is composed largely of combinations of fatlike materials which are blended in proportions such that a stick is formed which is sufficiently hard and holds together well, but which applies easily. Its composition permits some degree of **thixotropy,** the property of liquefying when agitated and returning to the solid state upon standing. Thixotropy results when a multitude of minute intermolecular forces are very readily set up but which are also quite easily disturbed. A thixotropic composition is desirable since thixotropy allows the surface of the stick to be fluid while the friction of application supplies enough energy to keep molecules in motion, but allows the stick to remain solidified when at rest.

The lipstick you will prepare contains beeswax, carnauba wax, cetyl alcohol, castor oil, and lanolin. These materials permit production of a lipstick consisting of a complex mixture of largely hydrophobic compounds held to each other or to skin by mutually similar attractive forces. The stick also contains butyl *p*-hydroxy benzoate which acts as a preservative by disturbing the reproductive functions of microorganisms, and menthol, used for its cooling, soothing effect.

E7.2 EXPERIMENTAL PART

Before beginning work or measuring out any materials for preparation of the antichap lipstick, clean the entire bench top at the lab bench where you work by wiping it with

a wet sponge. Next, thoroughly scrub the area where you work as far as you can reach in any direction with a suitable cleaner or scouring powder and water; then rinse your work area twice with fresh water. Similarly clean all laboratory equipment you will need to use. Do not commence formulation of your lipstick until your work area has been inspected by the lab instructor. As you work, confine your activities to your lab bench area. Do not remove U.S.P. or N.F. chemicals from their containers with any utensil other than that provided for each container.

Observe the lipstick ingredients, noting which are sticky, or greasy, or slippery, or hard.

The lipstick tube. If you do not have a ready-made container, you can quite easily make a serviceable tube. Cut from a sheet of aluminum foil a section 10 cm square. Make a 2-cm fold at each of two opposite sides, and smooth the foil so that there are no wrinkles. With the folded edges up, put the foil on a hard, flat surface. Place a number 6 cork borer or a 15-cm piece of a $\frac{1}{2}$-in. smooth wood dowel at one end of the foil at right angles across the width of the foil (please see Figure E7.3). Rolling the borer on the flat surface, wrap the foil tightly around the borer, but not so tightly that you can not slip the borer out of the finished tube. Hold the foil in position with a strip of cellophane tape. Slip the borer out of the tube, using care not to dent the tube. If you are going to label the tube, put the label on before removing the borer. Insert a number 2 cork into the bottom of the tube so that the large end of the stopper is farthest into the tube (see Figure E7.4). Then put the bottom of the tube over the number 4 cork and tape it securely. After the lipstick is made, remove the number 4 cork and use the number 2 cork to push the lipstick up out of the tube as needed. Support the tube in a vertical position.

Compounding the lipstick. Thoroughly scour an 8-cm-diameter evaporating dish and rinse it with acetone (a 50-ml beaker can be used but it is more difficult to clean up afterward). Carefully weigh into the dish U.S.P. or N.F. chemicals as follows: 1.0 g carnauba wax, 1.6 g beeswax, 0.6 g lanolin, 0.6 g cetyl alcohol, 6.2 g of castor oil, and optionally 5 mg of butyl *p*-hydroxybenzoate. Heat the evaporating dish and its contents on a steam bath until all ingredients have melted. Optionally add about 20 mg of *d,l*-menthol. Stir the mixture, immediately pick up the dish with tongs, and pour the molten mixture into the lipstick tube. Allow the stick to harden. If convenient, you can put the filled lipstick mold into a refrigerator to hasten solidification. A conical indentation will

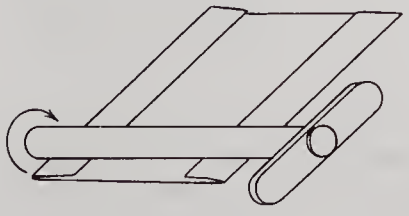


FIGURE E7.3 Rolling the tube.

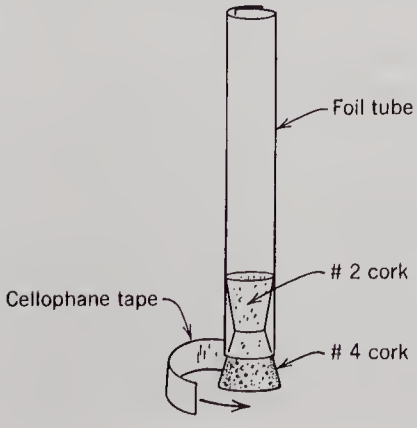


FIGURE E7.4 Arrangement of corks in the tube.

form at the top of the stick as a result of shrinkage; so after the stick has hardened, pour an additional amount of the molten materials into the tube until the stick becomes smoothly convex at the top. After the newly added material has become solid you can pass the tip briefly through a flame to impart a smooth glossy finish, a process known in the cosmetics industry as "flaming."

Writing the discussion. Report on the appearance, feel, and ease of application of your product. Suggest modifications in formulation that would improve it if necessary.

E7.3 EXERCISES

Prelaboratory

1. Prepare a flow diagram for the preparation of the tube and lipstick.
2. What precautions must you take when formulating a pharmaceutical product?

Postlaboratory

1. Would a lipid layer on your lips help to prevent percutaneous absorption of water-borne irritants? Explain.
2. Explain why water can permeate protein-like tissues.

EXPERIMENT 8 PHARMACEUTICAL EMULSIONS

Time Required: 1 hr

Review Techniques and Principles:

Lab notebook	(1)
Mixing	(0.4)
Storing	(0.12)
Labeling	(0.13)
Cleaning work area	(E7.2)

New Principles:

Emulsions

INTRODUCTION

Skin is normally an elastic membrane covering the entire body except for the body's various openings. Elasticity varies genetically, with age, and its state of health. Skin varies in thickness on different parts of the body, being 0.4 mm on the eyelids and 3 to 4 mm on the back, palms, and soles. The outer layer of the epidermis consists of dead cells composed of keratin, a type of protein, which sloughs off completely about every three weeks. The skin is richly supplied with three kinds of glands, one of which is called sebaceous. **Sebaceous glands,** found in all parts of the body except the palms, fingers, and toes, secrete an oily, semiliquid substance called **sebum.** The sebum assists in maintaining pliability of skin, partly because of its oily nature but primarily by providing a barrier that is impermeable to water. (see the discussion preceding Experiment 7). People possessing highly active sebaceous glands are sometimes referred to as having oily skin, whereas those having less active glands might be said to have dry skin.

The primary function of a hand cream is to replace sebum that has been removed by exposure to weather, water, soaps, and detergents. The raw materials for various types of cream vary considerably, but generally they all contain (1) oils, greases, or waxes to form the protective coating on the skin and to help control consistency; (2) **humec-**

tants, which are water-attracting and retaining substances like glycerine, propylene glycol, and sorbitol; (3) **emollients** (skin conditioners), which are substances like lanolin, lecithin, or cetyl alcohol, that soften and smooth the skin; (4) **emulsifiers,** substances that create a suspension of one immiscible phase in another; (5) emulsion stabilizers to help make the suspension long lasting; (6) preservatives; and (7) perfumes. Hand creams are usually prepared as emulsions because they are cosmetically appealing, being smooth and easy to apply as a thin coating.

E8.1 EMULSIONS

An **emulsion** is a suspension of minute droplets of one liquid in a second immiscible liquid. The droplets in general are larger than colloidal sizes, that is, larger than 0.5 μ. Except in very dilute and highly dispersed systems, a stable suspension does not result unless an emulsifier is present to form a film around the droplets to prevent their coalescence (fusing together) when they collide with each other.

Figure E8.1 illustrates the two possible types of emulsions: First, there are **water-in-oil emulsions** in which minute droplets of water are suspended in oil as in butter; and second, there are **oil-in-water emulsions** like milk. The term "oil" as applied to emulsions refers to any organic phase. The preparation of a stable emulsion requires an **emulsifier,** a substance that keeps the emulsion from breaking down. Generally, emulsifiers that are satisfactory for preparing water-in-oil emulsions are unsatisfactory for oil-in-water emulsions. For example, alkali metal soaps are good emulsifiers for preparing suspensions of oils in water but are not useful for suspending water droplets in organic phases.

There is no theory that explains all aspects of emulsification, but the type of emulsion can usually be explained on the basis of surface tension at the interfaces between oil and emulsifier and emulsifier and water. Please refer to Figure E8.2. The emulsifier has a polar end oriented toward water and a nonpolar end directed toward oil. If the force

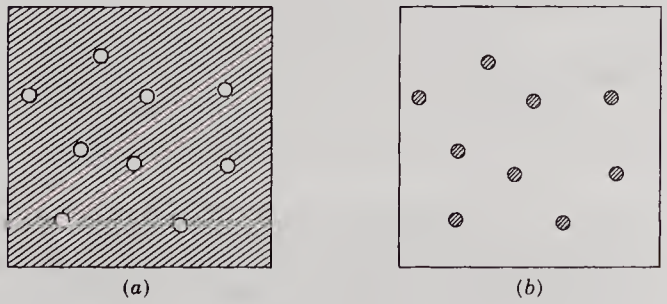


FIGURE E8.1 Types of emulsions. (*a*) Water-in-oil. (*b*) Oil-in-water.

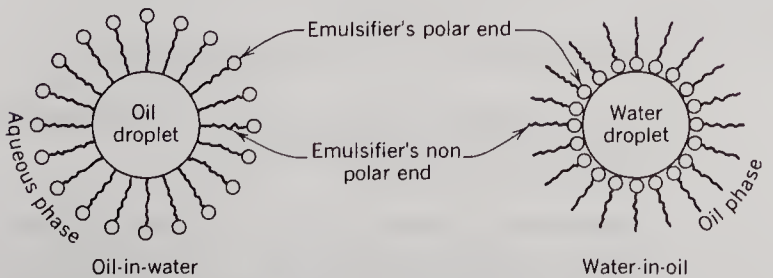


FIGURE E8.2 Molecular orientations of emulsifiers in the two types of emulsions.

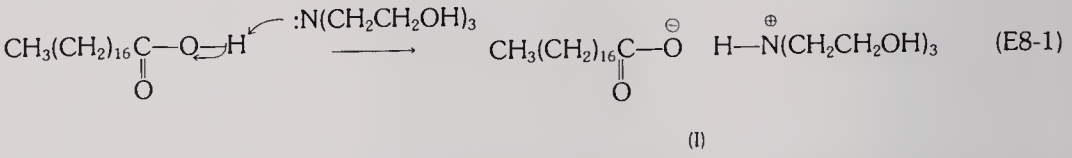
that opposes expansion of the surface, the surface tension, at the interface between oil and emulsifier is greater than that at the interface between water and emulsifier, the oil-emulsifier interface will require the smaller surface area; hence a droplet of oil will be formed inside the protective coating of emulsifier. On the other hand, if the surface tension at the interface between water and emulsifier is greater than at the interface between oil and emulsifier, the water-emulsifier interface must contract and produce a droplet of water inside the emulsifier. Apparently, then, the emulsifying agent determines which type of emulsion will be produced. Usually, alkali metal soaps, albumin, casein, gelatin, and other emulsifiers with polar ends strongly attracted to water, will interact with water strongly, reduce its surface tension, and produce oil-in-water emulsions. Conversely, alkaline earth metal soaps, other multivalent metal soaps, rosin, cellulose nitrate, and other emulsifiers which have polar ends less strongly attracted to water, will reduce its surface tension less and yield water-in-oil emulsions.

To form very stable emulsions, it is necessary during their formation to agitate the mixture so as to break up the dispersed liquid into very fine droplets. Emulsion stability also depends on the purity of the water because dissolved salts tend to break up an emulsion.

When an oil-in-water emulsion is applied to skin, the water evaporates, leaving behind the oils and emulsifiers as a protective layer.

E8.2 LIQUID EMOLLIENT CREAM PREPARATION

In the experimental section, you will be directed to prepare an oil-in-water liquid emollient cream. The *stearic acid* used in this cream (lotion) serves several functions: First, the nonionized acid acts as a skin protectant; it improves the appearance of the product if it is left standing undisturbed for about 1–2 weeks, during which time the acid crystallizes to impart to the product a pearly sheen; it helps to make the applied lotion feel dry; and finally, it reacts with the triethanolamine, $N(CH_2CH_2OH)_3$, to form the emulsifier triethanolammonium stearate (I):



(E8-1)

(I)

Lanolin, a very sticky semisolid, is derived from the wool fat of sheep. It serves as the emollient, helps to stabilize the emulsion, and gives very good protection against wind and weather. The *mineral oil* helps to form a protective coating on the skin and make the preparation apply smoothly. If you are going to keep the hand cream for very long, you should also add a small amount of preservative (ca. 0.01 g). An optional ingredient is perfume.

E8.3 EXPERIMENTAL PART

Prior to beginning work on this experiment you must clean up your equipment and work area as described in Section E7.2.

Preparation of hand cream. Weigh into a 250-ml Erlenmeyer flask 2.0 g of stearic acid, 0.5 g of lanolin, and 3.0 g of mineral oil. Weigh into a beaker 0.5 g of triethanolamine and 44.0 g of distilled water. Test the pH of a solution consisting of five drops of triethanolamine in 1 ml of water. Heat the ingredients of both containers to 85 °C on a

hot plate or steam bath. Pour the aqueous mixture into the Erlenmeyer flask, stopper the flask with a clean one-hole stopper, and stir the mixture *vigorously*, creating a vortex with a 2-cm or larger stirring bar and magnetic stirrer. Because the stirrer generates heat, you can complete the stirring by setting the flask in a cold water bath on the stirrer. Alternatively, you can shake the flask *very vigorously* until the mixture has cooled to room temperature. Observe the product, noting in particular the presence of any globules of unemulsified oils. Test the pH of the emulsion with pH paper. The pH should be neutral. Pour a small amount (about the size of a quarter) of the hand cream on your palm and spread it over both hands, noting ease of application and feel. Check the feel of the preparation again after a few minutes and run some water on one of your hands, observing its appearance.

Do not use a solid stopper. Vapor pressure of the hot, shaken materials will violently blow out the stopper.

Use an insulating pad of cloth or paper to ameliorate the 85 °C temperature of the flask if you are shaking it.

Actually, the emulsion is best prepared by using a stirring motor and propeller type stirring rod to actively agitate the mixture of oils while the aqueous mixture is added, then continuing to stir rapidly until the emulsion is cool. However, the Erlenmeyer flask method works reasonably well.

Writing the discussion. Discuss the extent of emulsification of your product, its appearance, and feel relative to the method and ingredients used. Suggest alterations you would make to improve the product.

E8.4 EXERCISES

Prelaboratory

1. Make a flow diagram of the procedure you will use in making the hand cream.
2. Explain with use of chemical equations why it could be unsatisfactory to use hard water to prepare an oil-in-water emulsion with sodium stearate as the emulsifier.
3. A student incorporated into her formulation of an oil-in-water liquid hand cream a fat-soluble perfume. Explain why the finished cream had no odor.

Postlaboratory

1. A painter allowed an emulsified water-base latex paint to freeze. When he opened the can to use it he found the emulsion had separated into two distinct phases. Explain.
2. Explain, on the basis of a kinetic-molecular approach, why heating an emulsion could cause it to break.
3. Trucks that transport food product emulsions like mayonnaise have sometimes been equipped with special springs to reduce jarring and road shock. Explain on a kinetic-molecular basis how road shock and vibration could affect the product.
4. Explain the difference in pH between triethanolamine in water and the pH of the product emulsion.
5. Give triethanolamine an IUPAC name.

REFERENCES

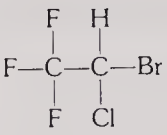
1. Keithler, W. R. *The Formulation of Cosmetics and Cosmetic Specialties;* Drug and Cosmetic Industry: New York, 1956.
2. Weiser, H. B. *A Textbook of Colloid Chemistry,* 2nd ed.; Wiley: New York, 1949.

IV

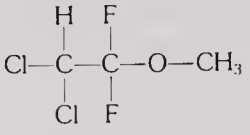
HALOALKANES

Haloalkanes (alkyl halides) are important synthetic intermediates. Even a cursory look in your lecture textbook at the chapter on alkyl halides will show you that there are a great many useful reactions using these intermediates.

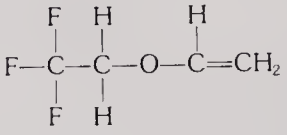
Haloalkanes have a long history of medicinal or medically related uses. Chloroform, $CHCl_3$, was introduced as a general anesthetic late in 1847 as a substitute for diethyl ether which had been used clinically as early as 1842 in the United States. Although chloroform is more potent than ether, it is easier to give an overdose and, in addition, it is far too toxic, especially to hepatic tissues. As a matter of fact, all halogenated compounds have to be held suspect as being toxic. In general, the higher the relative halogen content of a compound, the greater is its toxicity. Chloroform is no longer used as an inhalation anesthetic, but because of its sweet taste and odor has been used in recent years to make toothpaste taste sweet. Because halogenation reduces flammability and increases potency, halogens are found in several of the more modern inhalation anesthetics like halothane (I), methoxyflurane (II), fluroxene (III), and halopropane (IV).



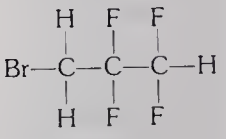
(I)



(II)

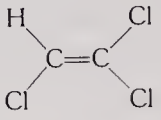


(III)

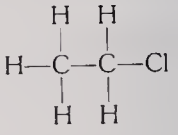


(IV)

Trichloroethylene (V) has been used as an inhalation analgesic (pain killer), and ethyl chloride (VI) has been used as a local anesthetic because it has a boiling point of 12 °C and when applied as a fine-liquid spray evaporates rapidly and freezes tissue.

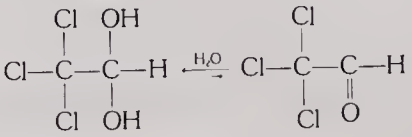


(V)



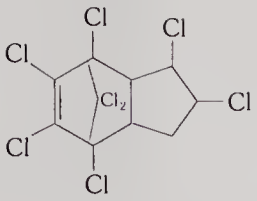
(VI)

The biochemical metabolites of trichloroethylene are trichloroacetic acid and trichloroethanol, both of which also are metabolites of chloral hydrate (VII), a compound used as a sedative and hypnotic (sleep inducer) since 1869. Although chloral hydrate itself has some efficacy as a hypnotic, it is believed that the effect is principally due to its metabolite, trichlorethanol. The precursor to chloral hydrate, chloral (VIII), when mixed with alcohol, is known as a Mickey Finn and can produce poisoning similar to that of acute barbiturate poisoning.

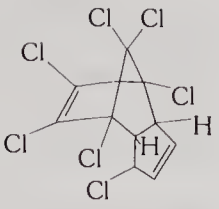


(VII) (VIII)

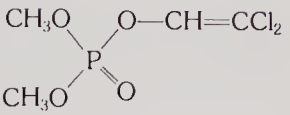
Outside of medically related products, there are many halogenated compounds in use. You can even tell by their names that the insecticides chlordane (IX), heptachlor (X), and dichlorvos (XI) contain chlorine.



(IX)



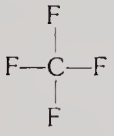
(X)



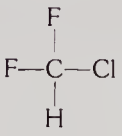
(XI)

The bicyclo compounds can be easily synthesized by Diels-Alder reactions using hexachlorocyclopentadiene as the diene. Large differences in biological activity result from such spatial differences as *exo* and *endo* configurations. Notice that heptachlor has the *endo* configuration.

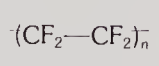
There are a number of commercially important fluorine-containing compounds like the freon refrigerants and aerosal propellants (XII) and (XIII), and the polymer Teflon (XIV).



(XII)



(XIII)



(XIV)

There are two experiments in this section: the S_N1 preparation of a haloalkane and the preparation of a bicyclo compound via dichloromethylene. Other haloalkanes are involved in Experiments 9, 11, 16, 32, 39, and 40; haloalkanes are also discussed in Organic Qualitative Analysis in Part III.

In this section you will be introduced to the preparation of 2-chloro-2-methylpropane, an intermediate that can be used in the kinetics study of Experiment 42.

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2. Goodman, L. S.; Gilman, A.; *The Pharmacological Basis of Therapeutics,* 4th ed.; Goodman, L. S.; Gilman, A., Eds.; MacMillan: New York, 1970.

EXPERIMENT 9 SYNTHESIS OF 7,7-DICHLOROBICYCLO [4.1.0] HEPTANE

Time Required: 6–7 hr
3–4 hr if commercial sodium methoxide is used
3–4 hr by phase transfer catalysis

Review Techniques and Principles:

Lab notebook	(1)
Flaming an apparatus	(E32)
Simple distillation	(7.2)
Glassware	(0.3)
Adding chemicals to reaction vessels	(0.8)
Heating and reflux	(0.5)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)

Vacuum distillation	(7.11)
Cooling	(0.5)
Boiling points	(3.5)
GLC	(11.3)
Refractive index	(13.3)
IR	(15.3, 15.4)
Wet analysis for halogen	(Q7.1, Q7.2)

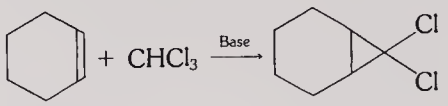
New Techniques and Principles:

Phase-transfer catalysis

In this experiment you will have opportunity to prepare a bicyclo compound by either a classical dichlorocarbene process or by phase-transfer catalysis.

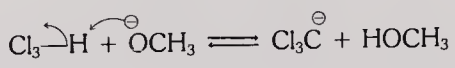
E9.1 DISCUSSION OF THE SYNTHESIS

To make 7,7-dichlorobicyclo [4.1.0] heptane, (I), also called 7,7-dichloronorcarane, you will generate dichlorocarbene from trichloromethane (chloroform), (II), and let it react with cyclohexene (III):



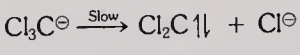
(III) (II) (I) (E9-1)

The first step in the process is a Brønsted acid-base reaction, the removal of a proton from trichloromethane by a base like alkoxide or hydroxide:



(IV) (E9-2)

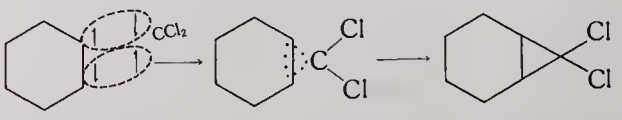
(The acid-base step occurs much more readily than an S_N2 attack on carbon.) Trichloromethyl anion (IV) is to some extent stabilized by inductive withdrawal of electrons from carbon by the three chlorine atoms. Nevertheless, the carbanion is not well stabilized and loses chloride ion in a slow, rate-controlling step to form the highly reactive, neutral singlet, dichlorocarbene (V):



(V) (E9-3)

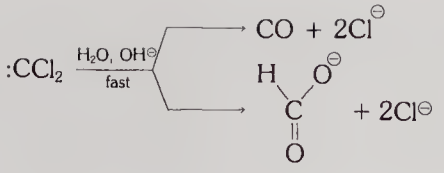
The formation of dichlorocarbene results from elimination of proton and chloride both from the same carbon. This sort of elimination is not uncommon, and is referred to as an *alpha* elimination because both atoms are eliminated from the *alpha* carbon (the carbon bearing the functional group).

When dichlorocarbene collides with cyclohexene, in a sufficiently forceful, properly oriented collision (see Section IX), cycloaddition occurs, with the electrons of the two species forming two new electron pair bonds:



(E9-4)

The dichlorocarbene singlet is more stable than methylene or a dialkylcarbene and does not undergo insertion reactions. However, it does rapidly react with water, forming carbon monoxide or methanoate (formate), (VI):



(E9-5)

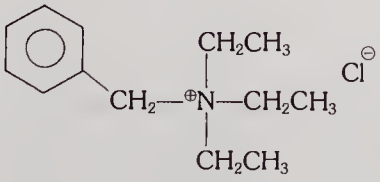
(VI)

Therefore, it is important to have anhydrous conditions during the reaction.

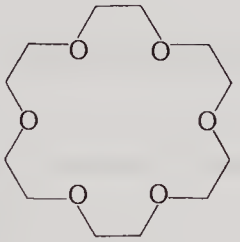
Because we must exclude water from the reaction mixture, our classical synthesis employs sodium methoxide as base. The more readily available sodium hydroxide is not satisfactory because it is not sufficiently soluble in a mixture of hexane, chloroform, and cyclohexene. However, by employing a two-phase system and a hydroxide carrier we can make hydroxide transfer from the aqueous layer into the organic layer where it can react with chloroform to generate dichlorocarbene.

E9.2 PHASE-TRANSFER CATALYSIS

Since the 1960s many reactions have been adapted to the use of phase-transfer catalysis. A **phase-transfer catalyst** is a substance that changes the rate of product formation by transferring a reactant from one phase into another. The catalyst must have solubility in both phases, usually an aqueous phase and an organic phase. To possess such a property, the substance must have both polar and nonpolar characteristics as do quaternary ammonium salts and crown ethers. Examples are benzyltriethylammonium chloride (VII) and 18-Crown-6 (VIII), systematically called 1,4,7,10,13,16-hexaoxacyclooctadecane.



(VII)



(VIII)

Crown ethers are not as widely used as quaternary salts because they are considerably more expensive.

For the preparation of our bicyclo compound, cyclohexene and chloroform form the organic phase, and aqueous sodium hydroxide and benzyltriethylammonium chloride make up the second phase. For a sufficiently energetic, properly oriented collision (see Section IX discussion) between hydroxide and chloroform to generate the dichlorocarbene, they must both be in the same phase. It is the function of benzyltriethylammonium chloride to transport hydroxide into the organic phase. Figure E9.1 illustrates the sequence of events. A catalytic amount of the quaternary salt is present at (A) and reacts with hydroxide, yielding the quaternary ammonium hydroxide at (B). Because of its considerable hydrocarbon character, the quarternary ammonium hydroxide is soluble in the organic layer and diffuses into it. After being transported into the organic phase, hydroxide ion is vastly more nucleophilic than it was in the aqueous layer because it is not as strongly solvated; so, a properly oriented collision with chloroform is very effective in yielding the benzyltriethylammonium trichloromethyl anion at (C). Subsequent α-elimination generates dichlorocarbene which reacts largely with cyclohexene but also with water. Collision between two dichlorocarbenes is relatively unlikely, but careful analysis of the reaction mixture would undoubtedly indicate the presence of some tetrachloroethene. The quaternary ammonium chloride at (D) is free to cross into the aqueous phase and repeat the cycle.

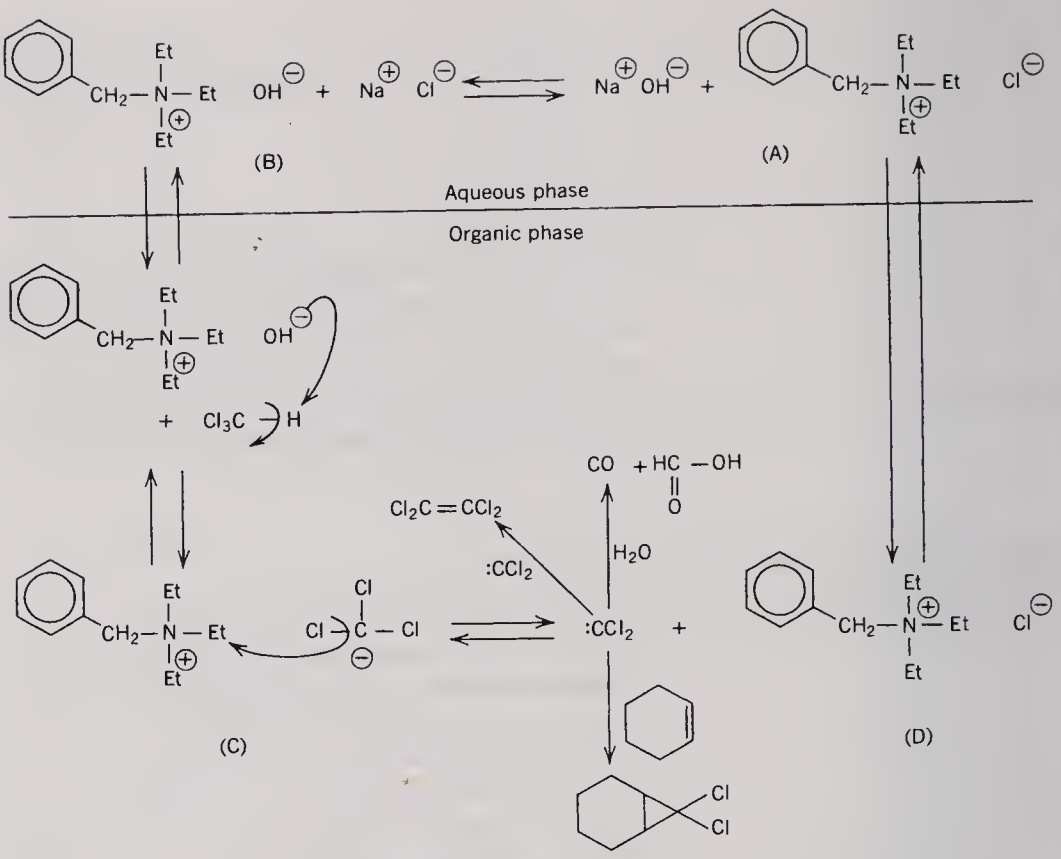


FIGURE E9.1 7,7-Dichlorobicyclo[4.1.0] heptane by phase-transfer catalysis.

E9.3 EXPERIMENTAL PART

A. The Classical Synthesis

Preparation of sodium methoxide. Beginning with 15 ml of dry methanol (methyl alcohol), 1.7 g of sodium metal, and no toluene, follow the instructions given in Section E32.2 for the preparation of potassium isopentoxide, but instead of cooling the final mixture to room temperature, cool it to just below its boiling point. Then remove the reflux condenser and reassemble the apparatus for simple distillation. Distill off the excess methanol nearly to dryness. Put the recovered methanol into a recovery container. Remove the distillation head from the flask and replace it with a drying tube. Allow the contents of the flask to cool to room temperature. △ To remove the remaining methanol, add 10 ml of dry hexane to the product and shake the flask to mix it well; then pour off the hexane. Repeat with another 10 ml of hexane. Immediately put the drying tube back on the flask, and put the hexane into a recovery container. △△

Review all of the precautions for preparing and handling of alkoxides given in Experiment 32, Section E32.2.

Preparation of 7,7-dichlorobicyclo [4.1.0] heptane. To one side neck of a 250-ml three-neck, round-bottom flask attach a reflux condenser. Put a drying tube at the top of the condenser and place a stopper in the other side neck. In the center, put a dropping funnel or separatory funnel with drying tube. The apparatus will look like that of Figure E9.2 (see as an alternative prelab exercise 7). Put a stirring bar in the flask and flame the apparatus, being careful not to heat strongly in the region around the bar or at ground glass joints. Set the apparatus over a magnetic stirrer.

Put the sodium methoxide into the three-neck flask. (Or if commercial sodium methoxide is to be used in order to save time, put 4.0 g of it into the three-neck flask.) Rinse the methoxide flask twice with 10 ml of dry hexane and pour the rinses into the

three-neck flask. Use a pipet or measure into a graduated cylinder 7.5 ml of dry cyclohexene and add it to the three-neck flask. Rinse the graduated cylinder with hexane and add the rinse to the three-neck flask. Put 10 ml of dry hexane and 5.9 ml of dry trichloromethane (chloroform) in the dropping funnel and mix them well. Over a period of about 15 min add the trichloromethane solution dropwise to the constantly stirred mixture in the flask. After addition is complete, reflux the mixture on a steam bath or hot water bath for 30 min.

Pour the reaction mixture into a separatory funnel containing 25 ml of water and shake the mixture thoroughly. Drain off the aqueous layer and decant the hexane layer into a beaker. Put the aqueous layer back into the separatory funnel and wash it with 10 ml of hexane. Combine in the drained separatory funnel the hexane wash with the original hexane solution. Wash the combined hexane solution with two successive 10-ml portions of water; then dry it over anhydrous sodium sulfate. △△

Using an ice-cooled receiver and steam or water bath, distill off the hexane and put it into a hexane recovery container. Transfer the residue to a small-scale simple distillation apparatus and distill it in vacuo (under vacuum), collecting as product the fraction coming over at 75–80 °C and 15 torr. You can distill it with only slight decomposition at atmospheric pressure and 198 °C. Weigh the product and calculate its percent yield.

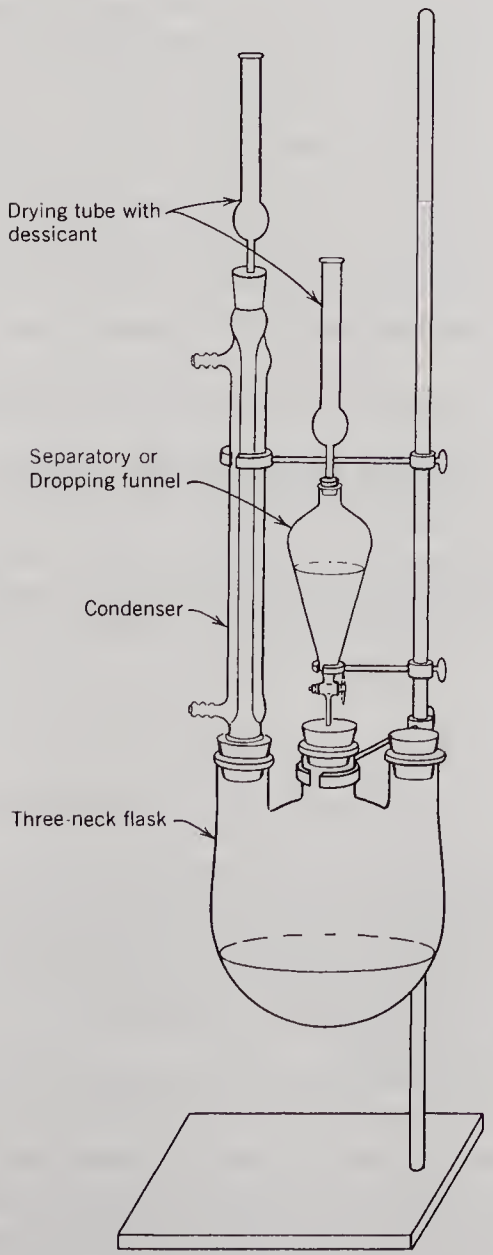


FIGURE E9.2 Apparatus for preparing 7,7-dichlorobicyclo[4.1.0] heptane.

Work in a hood. Chloroform is a suspected carcinogen.

The carbene reaction is exothermic. Do not add the trichloromethane solution so rapidly that the boiling becomes violent and overpowers the ability of the condenser to maintain reflux.

Analysis. As directed by your instructor, obtain GLC, refractive index, IR analyses, and wet analysis for halogen. Turn in your product in a labeled vial. △△

B. The Phase-Transfer Catalyzed Synthesis

Preparation of 7,7-dichlorobicyclo [4.1.0] heptane. Use the same apparatus as described in part A, but omit the drying tubes and flaming.

Put 7.5 ml of cyclohexene, 30 ml of chloroform, and 0.75 g of benzyltriethylammonium chloride into the 250-ml flask; and put 25 ml of 50% aq NaOH into the addition funnel. Start the magnetic stirring motor and stir the reaction mixture rapidly. Drain into the flask 2 or 3 ml of the base and, if necessary, warm the reaction vessel with a hot water bath until it begins to reflux. Continue to add the NaOH solution over a period of 15–20 min, maintaining a gentle reflux with the exotherm of the reaction. Do not be concerned if there is no reflux during addition. After addition is complete, reflux the constantly stirred mixture for 45 min. Allow the mixture to cool; then add 25 ml of water followed by 25 ml of hexane. Put the reaction mixture in a separatory funnel and discard the aqueous phase. If the density of the organic phase is too near that of the aqueous phase to permit separation in the separatory funnel, add either additional hexane (to decrease the density) or additional chloroform (to increase the density). Wash the organic phase twice with 25 ml of water; then dry it over anhydrous magnesium sulfate. Using an ice-cooled receiver and steam or hot water bath, distill off the organic solvents and put them into a hexane recovery container. Transfer the pot residue to a small-scale still and distill it in vacuo, collecting as product the fraction coming over at 75–80 °C and 15 torr. You can distill it with only slight decomposition at atmospheric pressure and 198 °C. Weigh the product and calculate its percent yield.

Do not add the chloroform solution so rapidly that boiling is violent and overpowers the ability of the condenser to maintain reflux.

Work in a hood. Chloroform is a suspected carcinogen.

Analysis. As directed by your instructor, obtain GLC, refractive index, IR, and wet analysis for halogen. Turn in your product in a labeled vial. △△

Writing the discussion. Discuss the method of preparation you used, comparing it to the other described method. Speculate on how your yield would compare with that of the other method. Discuss the identity and purity of the product as based on the analyses performed.

E9.4 EXERCISES

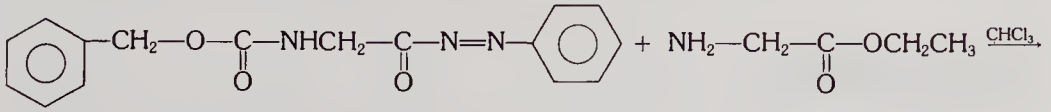
Prelaboratory

1. Having started with 1.7 g of sodium and assuming complete conversion to sodium methoxide, with what gram amount of sodium methoxide are you starting?
2. What is the limiting reagent in the preparation of 7,7-dichlorobicyclo[4.1.0]heptane?
3. Why is it necessary to use dry reagents and a dry apparatus for these reactions in the classical synthesis?
4. Why is sodium kept under hexane while cutting it and waiting to use it?
5. What is the density of sodium? About how many milliliters of sodium will have to be cut from the stockroom supply to make up 1.7 g?
6. Does the wash with hexane in the separatory funnel require dry hexane?
7. Using a Claisen head, make a drawing of an apparatus that could substitute for the one requiring a three-neck flask as described in Section E9.3.

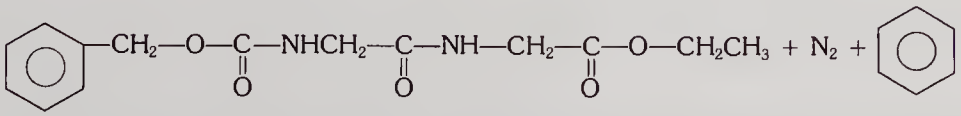
8. How can you tell which is the aqueous phase in the separatory funnel? See Technique 6, Section 6.2.
9. If during drying the reaction mixture over anhydrous salt a second liquid phase develops, how should you proceed? See Technique 2, Section 2.2.
10. Write an equation showing how the presence of water destroys the sodium methoxide reagent.
11. Review all of the precautions for preparation and handling of alkoxides given in Experiment 32, Section E32.2.

Postlaboratory

1. *Ethel Esther* generated singlet methylphenylcarbene ($C_6H_5—\ddot{C}—CH_3$) in presence of *cis*-2-butene. She not only obtained 1,2,3-trimethyl-1-phenylcyclopropane but also a considerable amount of ethenylbenzene (styrene). Propose a mechanism to show how the latter product was formed.
2. In the first step to make the dipeptide glycylglycine, a graduate student mixed benzyloxcarbonylglycinephenyldiimide (A) with glycine ethyl ester (B) in the solvent chloroform to get this reaction:



(A) (B)



He was surprised to find considerable amounts of glycine ethyl ester hydrochloride ($Et—O—\overset{O}{\overset{\|}{C}}CH_2—\overset{\oplus}{N}H_3\ Cl^{\ominus}$) in the product mixture. Propose a mechanism showing how this byproduct was formed.

3. Draw resonance structures showing why dichlorocarbene is more stable than methylene (CH_2:) or alkylcarbenes (:CR_2).
4. What is the product if dichlorocarbene reacts with *trans*-2-pentene?
5. When diazomethane (CH_2N_2) is photolyzed in the gas phase, triplet methylene is produced. Write an equation that shows the photolysis reaction of diazomethane with *cis*-1,2-dichloroethene.
6. What would be the structure of the product if 2 moles of dichlorocarbene reacted with 2-butyne?
7. Draw the structure of benzyltriethylammonium chloride and label on it the nonpolar and polar parts.
8. To have "reasonable" solubility in both water and an organic phase, a quaternary ammonium salt must possess somewhere around 10 to 16 carbons. Draw examples of two of these salts other than benzyltriethylammonium chloride.
9. Describe how the methanoic acid in Figure E9.1 is changed to methanoate ion.
10. Which of the two procedures, classical or phase-transfer, is more likely to yield methanoate ion? Explain.
11. Propose a mechanism for the formation of formic acid from dichlorocarbene and water.

REFERENCES

1. Gokel, G. W.; Weber, W. P. *J. Chem. Educ.* **1978,** *55,* 350.
2. Durst, H. D.; Gokel, G. W. *Experimental Organic Chemistry,* 2nd ed.; McGraw-Hill: New York, 1978, p 255.

EXPERIMENT 10 PREPARATION OF 2-CHLORO-2-METHYLPROPANE

Time Required: 2½ hr

Review Techniques and Principles:

Lab notebook	(1)
Liquid-liquid extraction	(6.2)
Simple distillation	(7.2)
Drying liquids	(2.2)
Ice bath	(0.5)
Boiling points	(3.5)
Refractometry	(13.3)
GLC	(11.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Characterization tests	(Part III)
Labeling	(0.13)

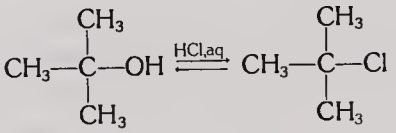
INTRODUCTION

In this experiment you will synthesize 2-chloro-2-methylpropane (*t*-butyl chloride) not only as a demonstration of an S_N1 reaction but also to prepare a chemical intermediate which can be used in the kinetics studies of Experiments 39 and 40. This same procedure can be used to prepare 2-chloro-2-methylbutane (*t*-amyl chloride).

Because tertiary alcohols are quite reactive, hydrochloric acid is sufficient to convert the alcohol to the haloalkane. To best understand this experiment, you should review the section on S_N and E1 reactions in your lecture textbook.

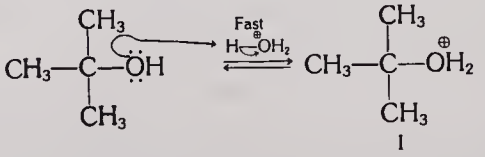
E10.1 DISCUSSION OF THE PREPARATION

The synthesis of 2-chloro-2-methylpropane proceeds according to the reaction



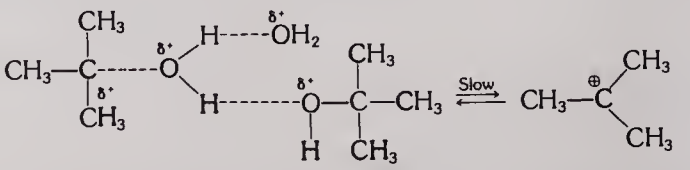
(E10-1)

The first step is formation of an oxonium ion (I) by protonation *via* hydronium ion:



(E10-2)

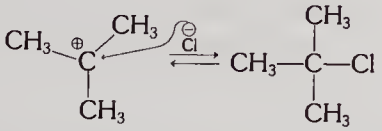
Next, in the rate-determining step, solvent molecules of water and alcohol help to remove the leaving group from the substrate oxonium ion:



(E10-3)

It is the hydrogen-bonding capability of protic solvents in S_N1 reactions that so aptly aids in removing a leaving group and in stabilizing it afterward. Solvent molecules also help

to stabilize the carbocation (carbonium ion) by donating nonbonding electrons into the ion's empty *p* orbital and in a more general way by clustering about it, as idealized in Figure E10.1. In reality, of course, the arrangement of molecules is three-dimensional, and there is a greater randomness. We refer to the solvent molecules next to the ion as the primary solvation sphere. Because of attraction to the ion, electron density is drawn from oxygen, thereby making the solvent hydrogens more partially positive than normal. Therefore, these hydrogens in turn attract electrons from neighboring solvent molecules more strongly than usual and create a secondary solvation sphere. The effect is repeated with diminishing intensity, as is usual in inductive effects, again and again. So, you see that the ion is stabilized not only by one or two solvent molecules but by a whole army of them. (Perhaps there is an analogy here to the religious experience of having one's soul saved: The removal of the leaving group bares the "soul" of the substrate, which is "saved" for the nucleophile by the *Solvation Army.*) Of course, the carbocation (carbonium ion) is also stabilized by hyperconjugation. (See postlaboratory exercise 5 in Section E10.4). In the final step, chloride ion, the nucleophile, pushes solvent molecules out of the way, and in a correctly oriented, sufficiently energetic collision (see Section IX) with carbon, forms the product



(E10-4)

The concentrated hydrochloric acid has a threefold function in this reaction: First, as you have already seen in equation E10-2, it supplies the protons to catalyze the reaction; second, it supplies the chloride ion; and third, it helps to shift the equilibrium in the forward direction by protonating water and forming non-nucleophilic hydronium ions which are incapable of reversing the reaction.

The equilibrium is also directed forward because alkyl halides are insoluble in water; so, as fast as the product is formed it is removed from the reaction arena, thereby shifting the equilibrium in the direction of making more product. As the reaction progresses, you will observe development of a second phase in the reaction mixture.

In this reaction you can expect a small amount of alkene in accord with the general

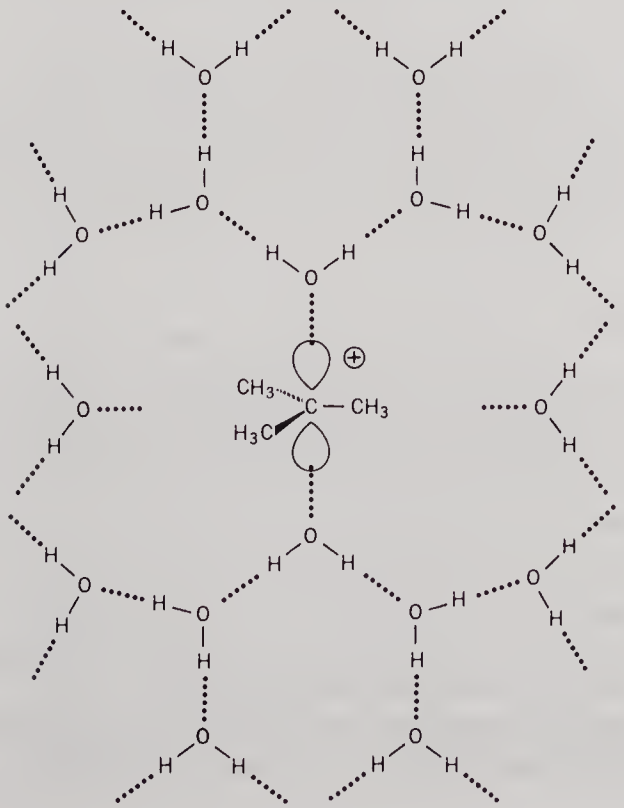
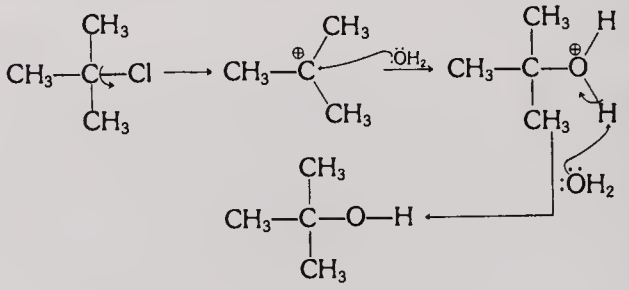


FIGURE E10.1 Solvation spheres around a carbocation.

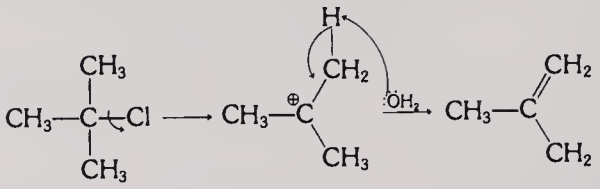
principle that any S_N reaction is in competition with elimination. Concentrated hydrochloric acid is used as the catalyst rather than concentrated sulfuric acid along with chloride ion because elimination is minimized by such a choice of reagent. This is because bisulfate, the conjugate base of sulfuric acid, is a stronger base than chloride and would be more likely to lead to formation of alkene.

E10.2 DISCUSSION OF 3° HALOALKANE WORKUP

It is necessary to wash the crude haloalkane in a separatory funnel to remove excess chloride, acid, alcohol, and water. Most of these components of the reaction mixture are removed in the initial wash, which is particularly important for removing acid so that in the subsequent wash with bicarbonate a violent foaming will not occur. The bicarbonate wash is for the purpose of neutralizing last traces of acid and must be approached with caution so that pressure does not build up inside the separatory funnel. It is important to obtain good contact of the nonaqueous phase with the bicarbonate; therefore you must shake the funnel vigorously and intermittently release gas. You then remove traces of bicarbonate with a final wash with water. During the aqueous workup of a tertiary alkyl halide you must proceed as rapidly as possible because it will react slowly with water to produce the corresponding alcohol and possibly form small amounts of alkene:



(E10-5)



(E10-6)

Drying the alkyl halide prior to distillation is an important step because any residual water in the final product can lead to some reversion to alcohol and/or formation of alkene, such reactions being encouraged by the higher temperature of the distillation. Furthermore, the formation of an azeotrope is possible, and water would be distilled along with product.

E10.3 EXPERIMENTAL PART

Preparation of 2-chloro-2-methylpropane. Put 0.10 mole of 2-methyl-2-propanol (*t*-butyl alcohol) and 20 ml of concentrated hydrochloric acid into a 125-ml Erlenmeyer flask. (If the alcohol is solid (mp 25.6 °C), heat the container under a warm (not hot) tap.) Gently swirl the mixture for about 1 min; then shake it more vigorously for another 3 min.

Examine your glassware for cracks or stars, which might lead to breakage during heating.

Be sure to release pressure due to carbon dioxide formation during neutralization of the acid in the separatory funnel.

Preferably work with rubber gloves in a hood while working with concentrated hydrochloric acid.

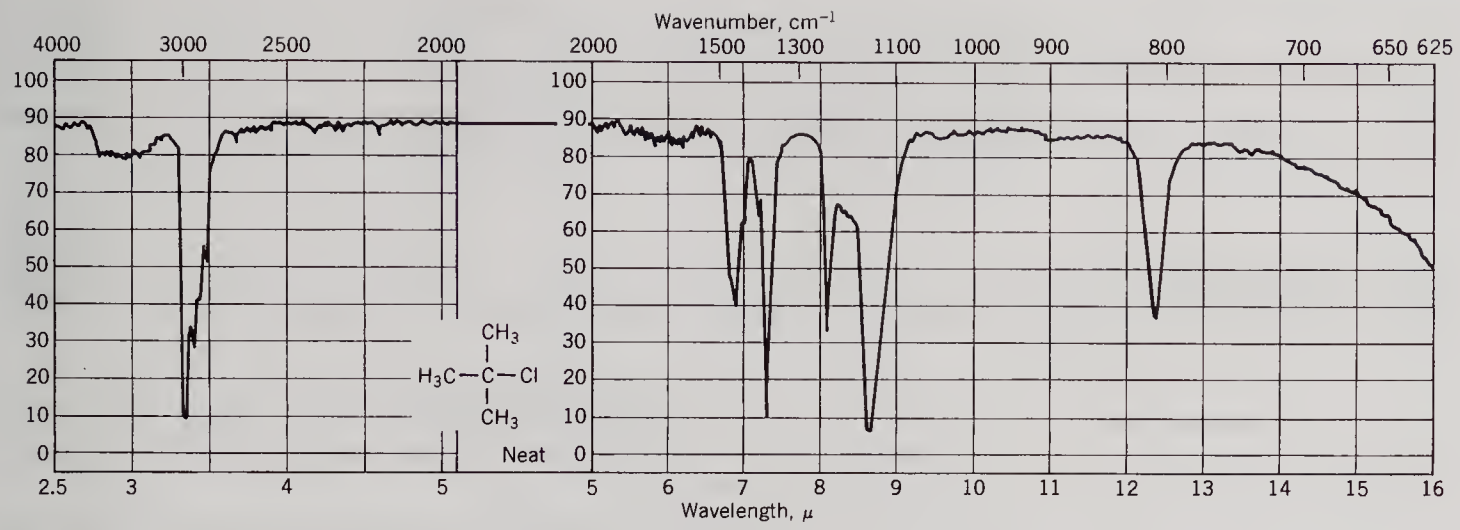


FIGURE E10.2 IR spectrum of 2-chloro-2-methylpropane. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

Workup. Decant the mixture into a 110-ml separatory funnel. Rinse the Erlenmeyer flask with a small amount of water and put the rinse also into the separatory funnel. Allow the two layers to separate and drain off the aqueous layer. Working calmly but rapidly, wash the organic layer in the separatory funnel successively with 10 ml of water, 10 ml of 5% aqueous sodium bicarbonate, and 10 ml of water. Shake the funnel well in each case, but shake it vigorously for about 1 min during the bicarbonate wash. Discard the aqueous layers down the drain. Decant the organic layer into a small Erlenmeyer flask, and dry the 2-chloro-2-methylpropane over anhydrous calcium chloride until it is clear.

Decant the clear product into a small, dry, distilling flask. Discard the wet drying agent into a container located in a hood. Add a boiling chip and distill the product into a dry, tared receiver, collecting the fraction that boils at 79 to 84 °C. Use a steam or hot water bath as the source of heat, and cool the receiver in an ice bath. △△ If the initial distillate is cloudy, stop and redry the product before continuing the distillation. Calculate the percent yield.

Analysis. As directed by your instructor, obtain IR and NMR spectra, GLC chromatogram, and refractive index of the product and substrate, and wet analysis tests of

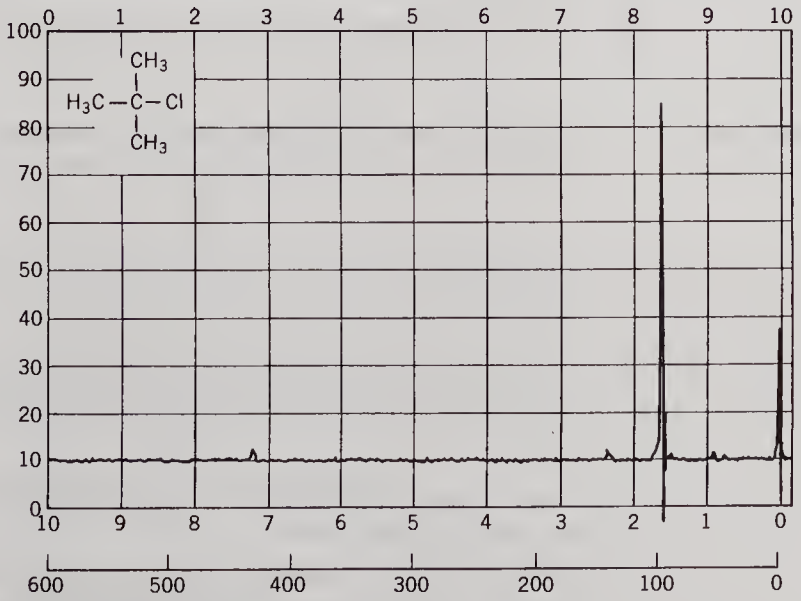


FIGURE E10.3 NMR spectrum of 2-chloro-2-methylpropane. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

the product (Q7.1 and Q7.2 in Part III). Turn in your product in a labeled vial or save it for Experiments 39 and 40.

Writing the discussion. Discuss the proof of identity and purity of the product based on analyses performed.

E10.4 EXERCISES

Prelaboratory

1. Calculate the number of grams and milliliters of the alcohol to use. (Find the densities in a handbook.) Which will be more convenient to use, grams or milliliters? Calculate the amounts of the other reagents to use.
2. Make a step-by-step outline or flowchart of the procedure you will use from charging of the reaction vessel through workup.
3. What does the term "wash" mean?
4. Why do two layers form during synthesis of the haloalkanes?
5. Why must heating during drying with anhydrous salt be gentle?
6. How can you test to see which is the aqueous phase in the separatory funnel?
7. Calculate the number of moles of HCl used, obtaining the density and percent HCl in concentrated hydrochloric acid from a handbook or the label on the container. Does the HCl/2-methyl-2-propanol ratio seem reasonable considering what you want for product?
8. Explain the functions of the two water washes and the aqueous bicarbonate wash.
9. Why is the crude haloalkane washed with a basic solution?
10. Why must one work rapidly during the basic washes?
11. Considering the reactivity of 2-chloro-2-methylpropane and possible S_N1, S_N2, E1, or E2 byproducts, why is the wash of crude product with aqueous sodium bicarbonate rather than aqueous sodium hydroxide?
12. Why is frequent release of pressure in the separatory funnel required during the bicarbonate wash? Write an equation showing the reaction that makes pressure release necessary.
13. Why is it necessary that the crude product be completely dry before distillation?

Postlaboratory

1. Explain on the basis of intermolecular attractions why unreacted *t*-butyl alcohol is extracted from the reaction mixture by the aqueous washes, but *t*-butyl chloride is not.
2. Draw the structure of the alkene byproduct that is most likely to form during the bicarbonate wash of 2-chloro-2-methylpropane. Write mechanisms showing its production.
3. Draw an energy curve for the preparation of *t*-butyl chloride from *t*-butyl alcohol and anhydrous HCl, including the Brønsted catalytic step and using the following information: kcal/mole bond energies—HCl, 334; C—O, 208; C—Cl, 157; O—H, 390.
4. Draw a hyperconjugation hybrid of the *t*-butyl cation, showing how solvent molecules are attracted to the cation.
5. Aqueous NaOH is used to neutralize acids in the 1-bromopropane workup. Even though $NaHCO_3$ is more difficult to work with, you were instructed to use it in the 2-chloro-2-methyl propane workup. Explain.

REFERENCES

1. Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry*, 4th ed.; Saunders: Philadelphia, 1985; p 452.
2. Durst, H. D.; Gokel, G. W. *Experimental Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1987, p 273.

V

ALKENES

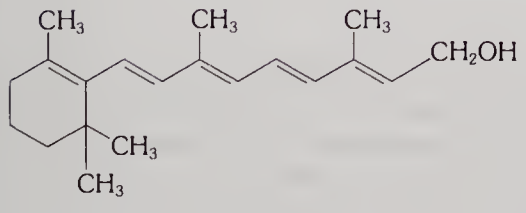
Alkenes are hydrocarbons with carbon-carbon double bonds. They are also occasionally referred to as **ethylenes** after the common name of the smallest member of the series, ethylene (I); or sometimes they are called **olefins,** also named for ethylene, which was once called **olefiant gas** (oil-forming gas, because the reaction with chlorine produces the water-insoluble liquid 1,2-dichloroethane). When the ethylene group, $CH_2{=}CH{-}$, is a substituent, it is called ethenyl, or vinyl, as in vinylbenzene (II)

Ethene (ethylene) (I)

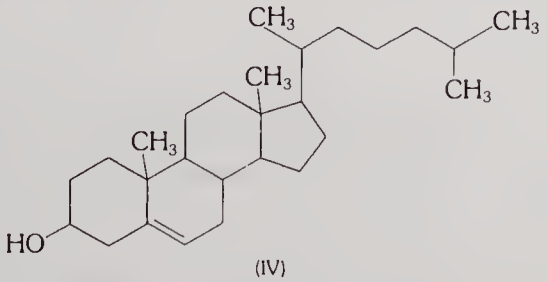
Ethenylbenzene (vinylbenzene) (styrene) (II)

Because alkenes contain less than the maximum possible number of hydrogen atoms, they are often referred to as one of the classes of **unsaturated** hydrocarbons.

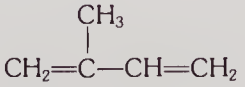
Unsaturation is a very common phenomenon among natural products. Among the hundreds of such alkenes are the following familiar compounds; vitamin A (III), cholesterol (IV), and isoprene (V), the precursor to natural rubber.



(III)



(IV)



(V)

Alkenes are produced commercially by cracking of natural gas and petroleum. The most important of the alkenes is ethylene, which is used as a chemical intermediate.

In Section V there are two methods of preparing alkenes: dehydrohalogenation and dehydration. Other experiments involving alkenes are Experiments 5, 6, and 9. There is also a section in Part III on qualitative organic analysis of alkenes.

EXPERIMENT 11 DEHYDROHALOGENATION

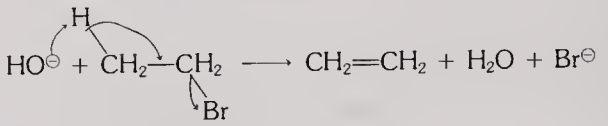
Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Cooling	(0.5)
Fractional distillation	(7.7)
Reflux	(0.5)
Ground glass joints	(0.3)
Tests for unsaturation	(Q8.1)
GLC	(11.3)

E11.1 DISCUSSION OF DEHYDROHALOGENATION

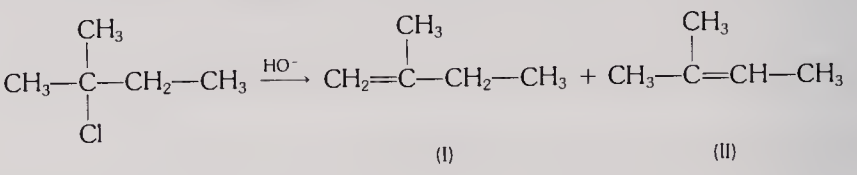
Dehydrohalogenation is an elimination reaction in which hydrogen and halogen are both removed from the substrate:



(E11-1)

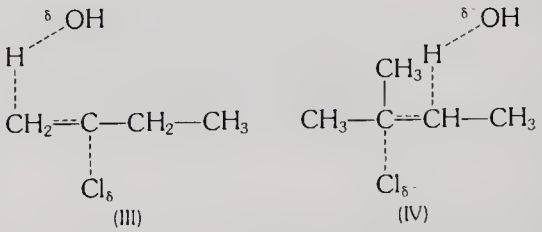
The transition state includes both base and substrate alkyl halide; hence the reaction is a bimolecular elimination and is referred to as E2.

In this experiment, you will use 2-chloro-2-methylbutane as a substrate. Because of its structure, both Hofmann (product I) and Saytzeff (product II) products are possible:



(E11-2)

Possible transition states for formation of the two products (I) and (II) are (III) and (IV), respectively.



Recall that the rate of product formation depends on three factors: collision frequency, collision orientation, and collision energy. The orientation, or probability factor, involves the numbers of abstractable protons and steric considerations; the energy factor relates to the transition state stability. Statistically, it is more probable that hydroxide will collide with and abstract one of the methyl hydrogens of the substrate to give transition state (III) than for hydroxide to abstract one of the two methylene hydrogens and produce transition state (IV). On steric grounds also we should expect transition state (III) to be favored. On the other hand, the incipient double bond in (IV) is better stabilized by sacrificial hyperconjugation. Product analysis by GLC will help you decide or confirm whether the orientation factor or the energy factor is more important in this reaction.

Although the elimination reaction in this experiment takes place in ethanol, a hydroxylic solvent generally associated with E1 and S_N1 reactions, the E2 process prevails because of the high concentration and considerable strength of the base, hydroxide. The elimination is also a competition with bimolecular substitution, S_N2. But here also elimination is favored by base strength and concentration, high temperature, and the steric effect associated with a branched substrate.

t-Butoxide is a larger, more bulky, and stronger base than hydroxide. Because of its steric effect, it should be more difficult for *t*-butoxide to attack a secondary hydrogen

on C-3 of 2-chloro-2-methylbutane than a primary hydrogen on C-1. Therefore, we might expect the reaction with *t*-butoxide as base to give a different proportion of isomeric 2-methylbutenes than the reaction with hydroxide.

E11.2 EXPERIMENTAL PART

Your instructor will tell you whether you should use potassium hydroxide or potassium *t*-butoxide as base, and if you are to use the latter, whether you or the chemistry stockroom personnel will prepare it.

Preparation of alcoholic potassium hydroxide. Put 25 ml of anhydrous ethanol in a 100-ml round-bottom flask (95% ethanol can be substituted if necessary). Working rapidly because potassium hydroxide pellets are hygroscopic, weigh 3 g of pellets and add them immediately to the alcohol. Attach a drying tube to the flask and, swirling it continually, warm the mixture on a steam or water bath until the potassium hydroxide dissolves. A small insoluble residue of potassium carbonate might remain. Cool the mixture to room temperature, using an ice-water bath if desired.

Do not use flames for any heating during this project. The products, in particular, are highly flammable.

The basic reagent solutions are very caustic and readily cause chemical burns. Wearing rubber gloves is a good precaution.

Remember that potassium reacts violently with water to produce hydrogen gas which is likely to burst into flame. Review the precautions for preparation of potassium isopentoxide in Experiment 32.

Dehydrohalogenation and distillation. Assemble the round-bottom flask into a system set up for fractional distillation as shown in Figure E11.1, using a packed Hempel column so that the reflux efficiency will be high. Run cooling water into the bottom of

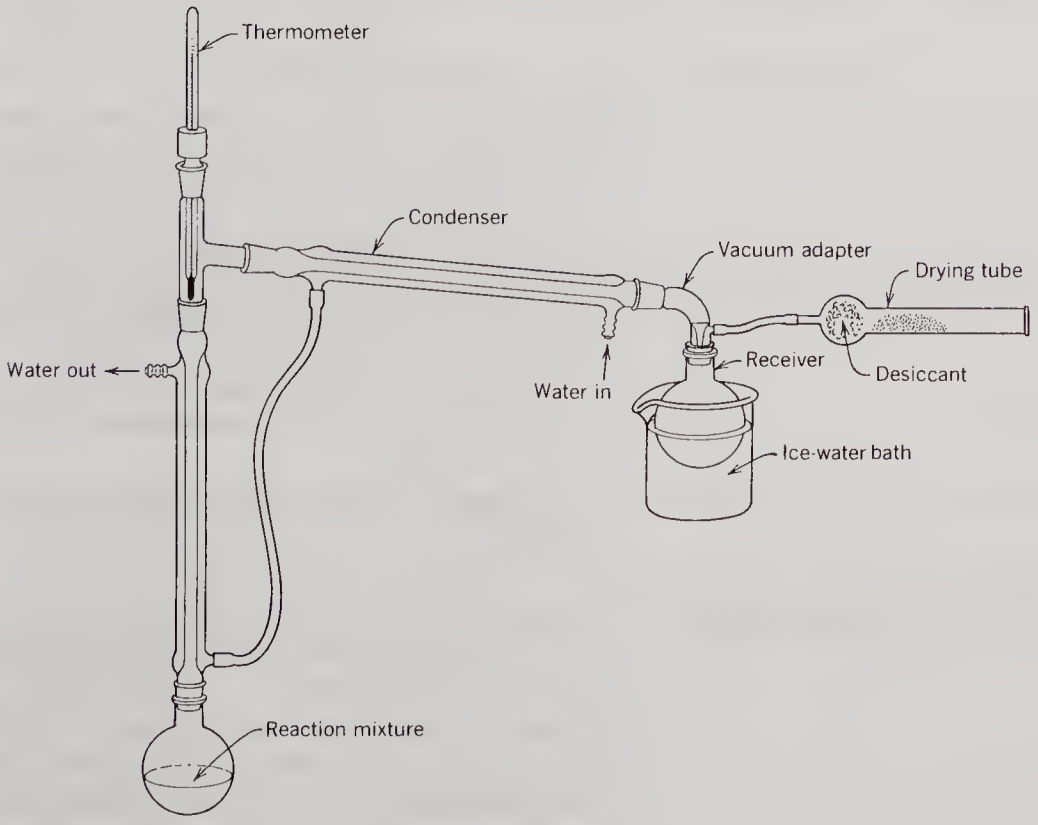


FIGURE E11.1 Dehydrochalogenation apparatus.

the condenser, out the top of the condenser into the bottom of the column, and out the top of the column. Tare a receiver and cool it in an ice bath, being sure to grease ground glass joints. Add 0.025 mole of 2-chloro-2-methylbutane and reflux the mixture for 2 hr. △

At the end of the reflux period, disconnect the cooling water from the distillation column, but not from the condenser. Distill the product mixture, collecting all distillate that comes over at less than 45 °C. Some product might have already collected in the receiver during reflux. Pour the liquid remaining in the pot into a recover container.

Analysis. Cap the receiver tightly, and weigh it while it is cold. Be sure to take into account the weight of the cap. Calculate the percent yield. Keep the flask in an ice bath or refrigerator until all tests have been performed; then pour the remainder into a refrigerated recovery container.

Perform the bromine and potassium permanganate characterization tests for alkenes as described in Part III on qualitative analysis. Run a qualitative and quantitative GLC analysis and determine the relative amounts of the isomers present.

Dehydrohalogenation using potassium t-butoxide. You can proceed in the same way as for the dehydrohalogenation using potassium hydroxide. If you need to prepare the alcoholic solution of base, proceed as described in Experiment 9.

Writing the discussion. You should answer these questions: What did the characterization tests reveal? How did you establish identity of the compounds? How do you account for the overall yield of product? What did the experiment teach in terms of the ratio of position isomers? If you have results for the *t*-butoxide elimination as well as for the hydroxide elimination, what was observed in terms of change in position isomer ratio?

E11.3 EXERCISES

Prelaboratory

1. Why is it important to grease ground glass joints for this reaction?
2. Why should the receiver be cooled in an ice bath?
3. Why is cooling water run through the distillation column and condenser during reflux, but only through the condenser during distillation?
4. As the reaction progresses a precipitate forms. What is the precipitate? Check a handbook to see if the subject of your answer is soluble in ethanol.
5. What GLC stationary phase and temperature do you suggest for analysis of the 2-methyl-1-butene/2-methyl-2-butene mixture?
6. With the right stationary phase and proper control settings, the GLC peaks are symmetrical and reasonably well separated. What quantitative GLC method of analysis do you suggest?
7. Review hazards associated with heating reaction mixtures (Section 0.5) and distillation (Section 7.7).

Postlaboratory

1. 2-Chloro-2-methylbutane was the starting material for this project rather than 2-chloro-2-methylpropane. What experimental difficulty would have arisen if the latter compound had been used?
2. If *t*-butoxide is used in place of hydroxide in the dehydrohalogenation of 2-chloro-2-methylbutane, which isomeric product should dominate? Explain.
3. What effect would nonanhydrous conditions have on the reaction employing *t*-butoxide as base?

4. Does transition state (I) or (II) in Section E11.1 have a lower activation energy? Explain.
5. What conditions in this reaction (a) with hydroxide and (b) with *t*-butoxide favor elimination over substitution?
6. Draw an energy curve for the production of 2-methyl-2-butene; partly superimposed on this curve draw the energy curve for formation of 2-methyl-1-butene.

REFERENCES TO SIMILAR PROCEDURES

1. Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry,* 4th ed.; Saunders: Philadelphia, 1985; pp 337–345.
2. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; p 302.

EXPERIMENT 12 DEHYDRATION OF CYCLOHEXANOL

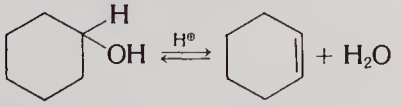
Time Required: 4 hr

Review Techniques and Principles:

Lab notebook	(1)
Simple distillation	(7.2)
Mixing	(0.4)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Fractional distillation	(7.7)
GLC	(11.3)
IR	(15.3, 15.4)
Refractometry	(13.3)
Storing products	(0.12)
Tests for unsaturation	(Q8.1)
Labeling	(0.13)

E12.1 DISCUSSION OF DEHYDRATION

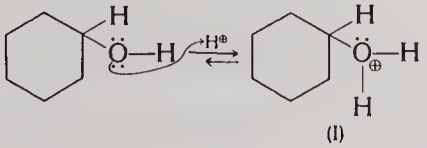
The acid-catalyzed dehydration of alcohols is an important means for preparation of alkenes, and is accomplished by heating the alcohol in the presence of a Brønsted acid like sulfuric acid, phosphoric acid, or a hydrogen halide:



(E12-1)

Because use of sulfuric acid is often accompanied by oxidation to yield tars and char, we shall use phosphoric acid in this reaction.

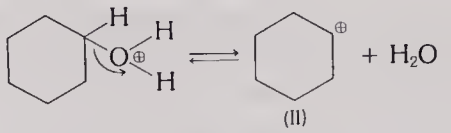
If, among other things, the alcohol used in the dehydration is secondary, tertiary, allylic, or benzylic, the reaction is likely to be an E1 process in which a carbocation (carbonium ion) is an intermediate. The first step in the mechanism is the formation of the oxonium ion (I):



(I)

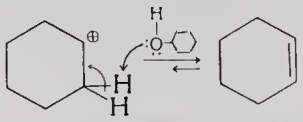
(E12-2)

This is an important step because it transforms the alcohol's hydroxide, a very poor leaving group, into water, a very good leaving group. Subsequent loss of water produces the carbocation (II):



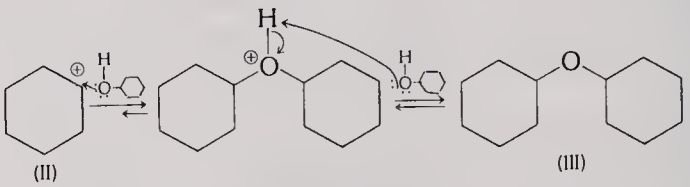
(E12-3)

Finally, one of the Brønsted bases in solution abstracts one of the protons on carbon adjacent to the positive center, thereby producing the alkene



(E12-4)

A reaction competing with formation of cyclohexene is the S_N reaction that forms dicyclohexyl ether (III):



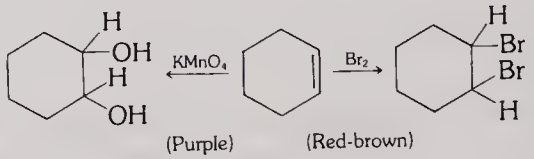
(E12-5)

Although this sort of S_N1-E1 competition is a common one, we should not expect much ether to be produced in the cyclohexanol dehydration reaction because the temperature of the reaction and the method of alkene preparation shift the equilibrium in favor of the alkene.

Notice that all of the steps in the dehydration mechanism represent equilibria. Therefore, product distribution is equilibrium controlled, and the amount of alkene that can be produced is limited. However, the equilibrium is shifted in accord with Le Chatelier's principle by distilling the alkene from the reaction mixture as fast as it is produced. This selective distillation is possible because the alkene has a lower boiling point than the other substances present in the pot.

It is inevitable that small amounts of water and phosphoric acid will distill along with cyclohexene during simple distillation. So you must remove the phosphoric acid by a sodium carbonate wash, and remove water by drying the product over anhydrous magnesium sulfate. It is important to remove water because cyclohexene forms a minimum-boiling azeotrope with water and little or no separation of the two would occur during purification of cyclohexene by fractional distillation.

You can characterize the cyclohexene as an alkene by testing it with bromine or potassium permanganate solutions:



(E12-6)

E12.2 EXPERIMENTAL PART

Preparation of cyclohexene. Using a distilling flask as small as possible (25–50 ml), assemble a simple distillation apparatus. Use as a receiver a 25–50 ml Erlenmeyer flask or round-bottom flask clamped in position so it is immersed to its neck in an ice-water bath.

Put 10.0 g of cyclohexanol into the pot along with 2 ml of 85% phosphoric acid

and one or two boiling chips. Thoroughly mix the contents of the flask by swirling. (Cyclohexanol freezes at 24 °C, so it might be necessary to warm it before use.)

85% phosphoric acid can cause severe chemical burns.

Using an oil bath or heating mantle, heat the mixture to boiling and distill the contents of the flask *at no more than 90* °C at the sidearm until only 2–3 ml remains in the pot. The head temperature will remain around 85 °C if the pot is not heated too strongly. The temperature and rate of boiling is most easily and safely controlled with an oil bath.

Avoid use of flames. Cyclohexene is very flammable.

Avoid turning on or off electrical switches in the vicinity of cyclohexene vapors.

Workup. Pour the distillate into a separatory funnel of appropriate size and wash it with about 5 ml of 3*M* aqueous sodium hydroxide which has been saturated with sodium chloride. Drain off the lower layer and test it with litmus paper. Repeat the wash until the lower, aqueous layer tests basic to litmus. Discard the aqueous washes and decant the organic layer into a 50-ml Erlenmeyer flask and, with occasional swirling, dry the liquid for about 10 min, or until it is clear, over about 0.5–1 g of anhydrous magnesium sulfate (do not use more than necessary). △△ If you are going to store the organic layer at this time, it is best kept refrigerated in a lightly greased, stoppered, standard taper flask or screw-top vial. Cyclohexene evaporates easily, diffuses through cork, and dissolves in rubber.

While waiting for the crude cyclohexene to dry, clean and dry the distillation apparatus. Clean and dry the condenser by rinsing the condensing surface with wash acetone (IUPAC propanone) from your squeeze bottle, and then passing a gentle stream of air through the inside of the condenser to dry it. Put the wash acetone in a recovery bottle. Using a small, tared receiver immersed in an ice-water bath, reassemble the apparatus for distillation. Filter the crude, dry product into a 25-ml round-bottom flask and distill it at no more than 5 C° above the boiling point of cyclohexene. Weigh the distillate and calculate the percent yield. Store the product in a labeled, screw cap vial. △△

Analysis. As directed by your instructor, obtain unsaturation tests (organic qual for alkenes, Section IV), IR and NMR spectra of starting material and product, a GLC analysis of the dried crude and fractionated cyclohexene, and refractive index of both the dried crude and fractionated cyclohexene, and refractive index of both the dried crude and fractionated cyclohexene. For GLC, choose a column temperature that is in the neighborhood of the boiling point of the anticipated highest boiler. Put the product in a labeled, tightly capped vial and turn it in to your instructor.

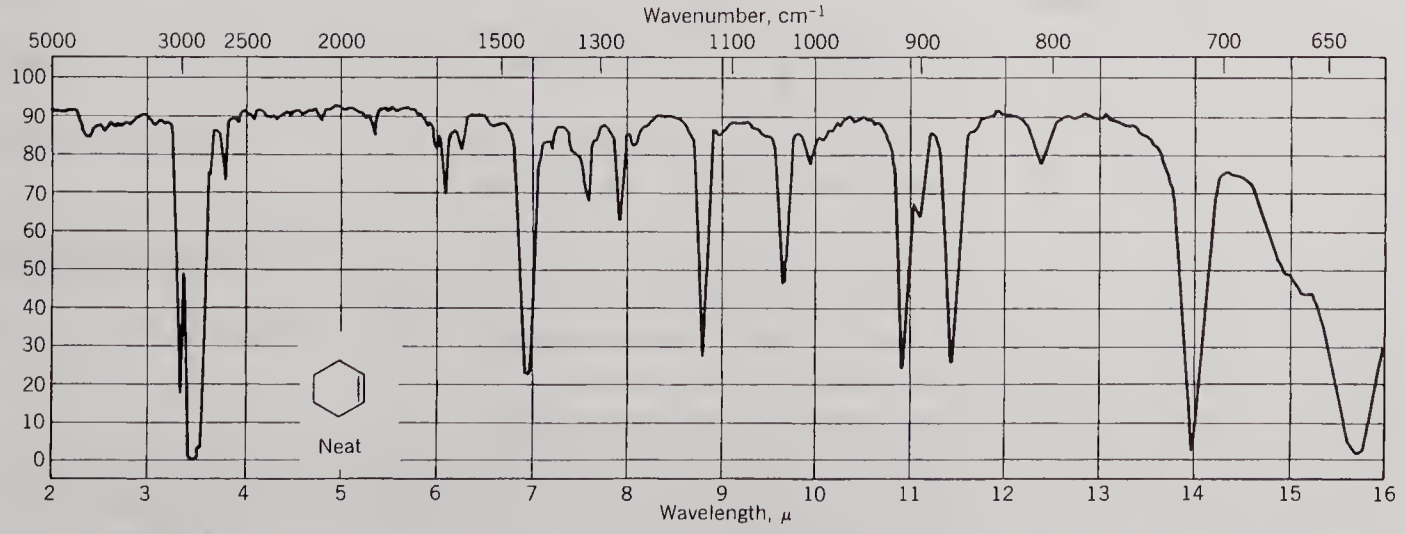


FIGURE E12.1 IR spectrum of cyclohexene. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

Wash your glassware in a hood! Pour cyclohexene washings down a drain that is enclosed in a hood.

Writing the discussion. Based on your results and observations, do you think drawing conclusions about your percent yield would be appropriate? Should you discuss the results of the characterization tests? Do you think you should discuss the formation of cyclohexene via the carbocation mechanism, or would this be something other than what *you* discovered? Do the boiling points of your final distillation products indicate anything worth discussing? Should you discuss the identification of GLC peaks? What about IR data relative to identification?

E12.3 EXERCISES

Prelaboratory

1. What is the catalyst for this reaction?
2. The amount of phosphoric acid to use is given as 2 ml (one significant figure). How critical do you think it is to take time to measure very carefully?
3. Why is the sodium hydroxide wash saturated with sodium chloride?
4. What would be an "appropriate size" separatory funnel for the washing of the first distillate?
5. Which layer will be in the bottom of the separatory funnel, the aqueous or cyclohexene layer?
6. Which end of the separatory funnel will be used to remove the aqueous layer? The organic layer?
7. Approximately what size boiling flask will be appropriate for the final distillation? Base the size on the theoretical yield and density of cyclohexene.
8. What other item needs to be added to the boiling flask of the final distillation besides the crude cyclohexene?
9. What stationary phase would you suggest for GLC analysis of the cyclohexene samples?
10. Make a flow diagram of the procedures you will use in the laboratory for this project.
11. Review the procedural hazards for distillation (Sections 7.2 and 7.7) and for extraction (Section 6.2).

Postlaboratory

1. Draw the hyperconjugation resonance hybrid that illustrates how the positive charge in cation (II) of equation 12-3 is distributed over five centers.
2. Explain why cyclohexene has a lower boiling point than either cyclohexanol or dicyclohexyl ether.
3. Draw the product structure of cold, dilute, aqueous permanganate oxidation of cyclohexene. What is the IUPAC name?
4. *Stu Dent*, noting that cyclohexene boils at 83 °C and that the crude product mixture should be distilled at no more than 90 °C, set up his reaction on a steam bath. After 7 hr, he had still collected no product. Explain.
5. Show the likely products that would result from dehydration of 3-phenyl-2-butanol.

REFERENCES TO RELATED PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 243.
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VI ALCOHOLS

Alcohols are characterized by the presence of a hydroxyl (—OH). The hydroxyl is a very important functional group and one of the most widespread functions found in natural products. Sugars, starch, cellulose, nucleic acids, some amino acids, most steroids, and many other compounds possess hydroxyls.

Industrially, alcohols are important as intermediates and as solvents.

The word "hydroxy" as the name for —OH was first proposed by the renowned Sicilian chemist Stanislau Cannizzaro. It is a combination of *hydro*gen and oxygen.

The word "alcohol" comes from the Arabian *al kuhl,* a very fine powder used for painting eyelids. Because the fineness of the powder was thought to be parallel to the highly purified spirit obtained by distillation, the distillate became known as alcohol. A spirit was originally any liquid produced by distillation; later it came to mean the flammable liquid composed primarily of ethanol and water. In pharmacology, a spirit, or essence, is an alcoholic solution of a voltaile substance, viz, spirits of ammonia or essence of peppermint.

In this section we shall discuss the preparation of ethanol by fermentation. Other experiments involving alcohols are Experiments 10, 12, 15, 16, 17, 20, 21, 32, 34, 36, 38, and 39; also Technique 7 and the section in Part III on organic qualitative analysis.

EXPERIMENT 13 ALCOHOL BY FERMENTATION

Time Required: To set up fermentation: $\frac{1}{2}$ hr
Preparation of 95% alcohol: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Vacuum filtration	(4.3)
Filter aid	(4.5)
Simple distillation	(7.2)
Fractional distillation	(7.7)
Refractive index	(13.3)
GLC	(11.3)
Organic qualitatives tests	(Q8.2, Q9.1)

New Techniques and Principles:

Fermentation

INTRODUCTION

Ethanol, commonly named ethyl alcohol or simply, alcohol, is the alcohol used in beverages. Other alcohols are too toxic. That is not to say that ethanol does not have some toxic effects: Excess ethanol consumption can lead to **alcoholism,** a chronic physiological and behavioral disorder manifested by repeated drinking to an extent that interferes with the drinker's health and/or social and economic functioning. Alcoholism can easily come about because ethanol is an addictive drug, exhibiting to a considerable extent all three components of drug addiction: tolerance, psychic craving, and physical

dependence. The classic form in which chronic alcoholism is usually observed is cirrhosis of the liver, a disease marked by progressive destruction of liver tissue. However, the liver is not the only organ affected by chronic alcoholism. The circulatory system and central nervous system are also affected. The brain of an alcoholic can be so damaged that it loses a considerable amount of its usual form and possesses many clotlike pools of bloody tissue. Some medical studies have indicated that a small degree of brain damage occurs even with low doses of alcohol. A very significant problem associated with alcoholism is poor nutrition. Because alcohol has a caloric equivalent of 7 kcal/g, its continual consumption provides many calories but little else.

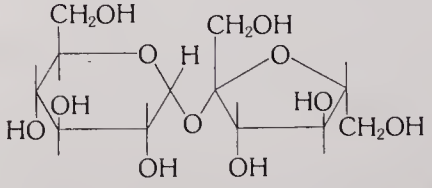
The effects of drinking alcohol in lesser quantities than those involved in alcoholism can be beneficial in terms of relaxation. However, the same factors that produce relaxation also produce decreased motor and mental capabilities. It is a complete fallacy that mental and physical ability are increased during intoxication, although the drinker often has the feeling that they have been. Ethanol is rapidly absorbed from the stomach, small intestine, and colon. After absorption it is quite uniformly distributed throughout all body tissues and fluids. Because the brain has an excellent blood supply, the concentration of alcohol in the brain very quickly approaches that of the blood, and in general, the effects on the brain and central nervous system are proportional to the alcohol concentration in the blood. The apparent stimulation that a drinker receives arises from unrestrained activity of the parts of the cerebral cortex that have been freed from various socially derived inhibitions. The cerebral cortex, however, is apparently not the most alcohol-sensitive part of the brain. Alcohol seems to exert its first depressant action on the reticular formation, the system that is responsible for much of the integration of various activities throughout the central nervous system. So, the cerebral cortex is released from control by the reticular formation, with the result that thought and motor processes become disorganized and jumbled. The first mental processes that are affected are those related to *previous training* and *experience*. The obvious conclusion is that drinking alcohol and then operating chemical or mechanical equipment, including automobiles, is dangerous, not only for the drinker but for others nearby. Drinkers should be aware that the impairment of judgment and muscular coordination that attends even moderate alcoholic consumption is aggravated by concurrent use of many medicinal agents, in particular the ataractic drugs (sedatives and tranquilizers).

Ethanol is important in industry as a solvent and as a chemical intermediate. Most alcohol for laboratory use is denatured, that is, it contains a poisonous additive like methanol or benzene which renders it unfit for drinking. The purpose of denaturing is the ensure that the high taxes associated with alcoholic beverages will be paid.

A recently developed use for ethanol is as a fuel for internal combustion engines. Some nations already require that gasoline be diluted with ethanol to help conserve fossil fuels.

E13.1 DISCUSSION OF SYNTHESIZING ETHANOL BY FERMENTATION

The balanced chemical equation for the conversion of sucrose (I) to ethanol is



$$+ H_2O \xrightarrow[4\ ADP + iP\ \ 4\ ATP]{Enzymes} 4CO_2 + 4CH_3CH_2OH \qquad \text{(E13-1)}$$

It is the same equation that pertains to wine-making, and depends on consumption of sugar by yeast organisms. Yeast is the common name for the genus *saccharomyces*, a type of fungus. Actually, fermentation does not require living yeast cells, but only an

extract from them, since fermentation is the result of the catalytic activity of enzymes manufactured by yeast. In actual fermentation practice, however, living yeast cells are used to produce the necessary enzymes, which are collectively known as *zymase*. There are many steps in the fermentation process, and a special enzyme is used at each step, as shown in Figure E13.1.

Enzymes are organic catalysts, generally proteins along with vitamins and inorganic ions as cofactors. These catalysts are very specific and interact only with compounds of the certain sizes, shapes, and polarities for which they were biologically designed.

There are many varieties of yeasts, many of which are found in nature and are referred to as wild yeasts. The most common wild yeast is *Kloeckera apiculata,* whose activity becomes inhibited after producing a solution that contains only 4% alcohol. Baker's yeast is *Saccharomyces cerevisiae,* which produces 12–14% ethanol. The most commonly used wine yeast is also a species of the same genus and is known as *Saccharomyces ellipsoideus.*

Although the yeast obtains its metabolic energy by anaerobic (without oxygen) fermentation of sugars, the growth of a yeast colony requires certain other substances which are essential for its growth and reproduction. In the wine industry they are referred to as *yeast nutrients,* and include potassium, magnesium, phosphate, and sulfate ions, and nitrogenous compounds like ammonium ions or urea; also copper, iron, cobalt, zinc, and iodide ions in trace amounts. Vitamins, especially thiamine, are also important. Even though the major fermentation is anaerobic, an initial, rapid establishment of the yeast colony requires oxygen which can be supplied from the air by vigorous shaking of the reaction flask.

You can see from Figure E13.1 that the biochemical pathway from sugar to alcohol requires many biochemical transformations. The benefit of these transformations to the yeast microorganism is that there is an overall gain in energy. From the energy stored in sucrose, four molecules of adenosine diphosphate (ADP) can be converted to four molecules of energy-rich adenosine triphosphate (ATP). The first step in this pathway is enzymatic hydrolysis of sucrose (I), yielding the simple sugars, glucose (II) and fructose (III). Although the ultimate consequence of the pathway is to make ATP, this process commences with utilization of ATP in the hexokinase reactions to make glucose-6-phosphate (IV) and fructose-6-phosphate (V). These reactions are essentially irreversible because of the large exotherm associated with them. Because the sequence proceeds only through fructose-6-phosphate, utilization of glucose-6-phosphate requires its isomerization by the enzyme phosphohexose isomerase. At this point, another molecule of ATP irreversibly contributes a phosphate to make fructose-1,6-diphosphate (VI), which subsequently cleaves in the presence of the enzyme aldolase, forming D-glyceraldehyde phosphate (VII) and dihydroxyacetone phosphate (VIII). These two phosphates, like the glucose- and fructose-6-phosphates, are biochemically interconvertible in the presence of triose phosphate isomerase. The next step proceeds through glyceraldehyde-3-phosphate (VII), which is oxidized by nicotinamide adenine dinucleotide (NAD^+), a hydrogen acceptor molecule, in the presence of phosphoglyceraldehyde dehyrogenase. At this step the substrate loses its aldehydic hydrogen, and gains inorganic phosphate in its place. The resulting 1,3-diphosphoglyceric acid (IX) is an energy-rich acid anhydride of phosphoric acid, having derived its energy from the oxidation of the aldehydic function. Because of this stored energy, hydrolysis of this phosphate ester ($\Delta G = ' -10$ kcal/mole) yields enough energy to permit transfer of phosphate back to ADP, yielding ATP and 3-phosphoglyceric acid (X). Intramolecular transfer of phosphate to yield phosphoglyceric acid (XI) is followed by formation of a phosphorylated enol of pyruvic acid (XII). Because the keto form of pyruvic acid (XIV) is far more stable than the enol form (XIII) and because hydrolysis of the phosphate ester therefore is very exothermic, sufficient free energy is available ($\Delta G = -12$ kcal/mole) to transfer another phosphate back to ADP, yielding ATP and the enol of pyruvic acid (XIII). In an essentially irreversible step, pyruvic acid is then decarboxylated, yielding carbon dioxide and ethanal (acetaldehyde) (XV). The final step that yields ethanol comes about by a reduction of ethanal (XV), catalyzed

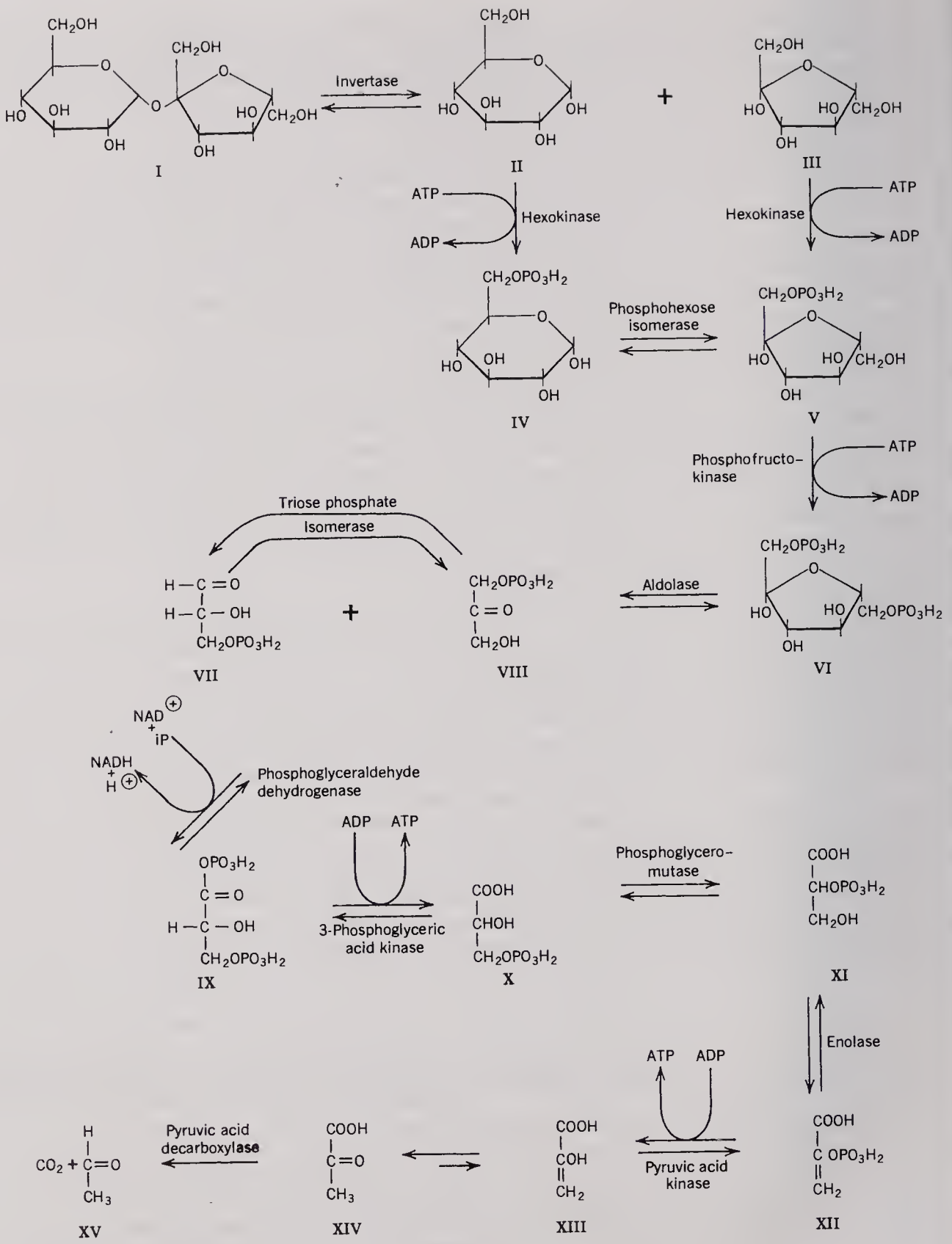
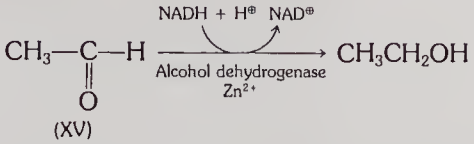


FIGURE E13.1 Fementation pathway.

by alcohol dehydrogenase and involving the reduced form of nicotinamide adenine dinucleotide, NADH:

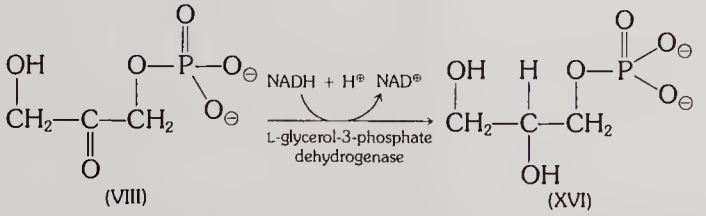


(XV) (E13-2)

The reverse of this reaction is the first step in metabolism of alcohol after it has been consumed as a beverage.

Fermentation produces a number of other products besides ethanol. The most obvious byproduct, which appears in equation E13-1, is carbon dioxide, which in commercial wine-making processes is sold to make dry ice. Ethanal (acetaldehyde) is produced near the end of the biochemical pathway shown in Figure E13.1, and some residual amount of it is left unconverted to ethanol by alcohol dehydrogenase at the end of the reaction period.

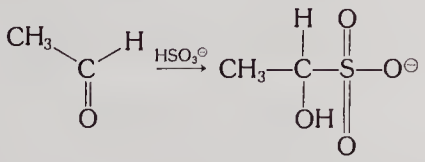
Another byproduct is glycerol (glycerine), usually produced to the extent of 1 or 2%. Most of the glycerol is produced from dihydroxyacetone phosphate (VIII) which can also accept hydrogen from NADH:



(VIII) (XVI) (E13-3)

The product of this reaction, *alpha*-glyceryl phosphate (XVI), then undergoes hydrolysis to yield the glycerol.

An interesting variation of this process was used by the German chemist Neuberg to commercially produce glycerol. If sodium bisulfite is added to the fermentation vessel, it combines with ethanal, producing its bisulfite addition compound (XVII):



(XVII) (E13-4)

The addition compound is unable to attach to the enzyme, alcohol dehydrogenase, and be reduced by NADH. Therefore, all of the NADH is available to reduce dihydroxyacetone phosphate (VIII), as it does in equation E13-3. This reduction continually shifts the triose phosphate isomerase reaction equilibrium toward dihydroxyacetone phosphate.

Another byproduct is *fusel oil,* a mixture of mostly isomeric amyl (pentyl) alcohols. Most of these arise from deamination of amino acids. They are responsible for the headaches associated with lower quality wines.

Another product often found along with alcohol is acetic acid. The acid is not produced as a byproduct of the fermentation but from the aerobic oxidation of ethanol by the enzyme system found in *Acetobacter,* an organism that is widely distributed in air. It is to keep out *Acetobacter* that a water seal or cotton plug is used during fermentation.

To obtain the final product free of most impurities and most of the water, you will fractionally distill the product mixture. However, you will not be able to collect anything more than a 95.6% alcohol/water mixture because alcohol and water form a binary, minimum-boiling azeotrope.

E13.2 EXPERIMENTAL PART

Ethanol by fermentation. Put 25 g of cane or beet sugar (sucrose) in a 500-ml flask along with 25 ml of a solution prepared from 0.3 g of calcium phosphate, 0.3 g of magnesium sulfate, and 1.6 g of ammonium tartrate, ammonium sulfate, or urea in 100 ml of water, along with a tablespoon of concentrated orange juice to supply vitamins and trace minerals. Add 225 ml of water and agitate it to dissolve the sugar. Add 1 g of dried baker's yeast; then shake the mixture vigorously, so that air is mixed with the solution. Put a loose plug of cotton in the top of the flask or construct a water seal by bending a piece of glass tubing so that it can be put into a one-hole stopper in the top of the flask and extended down into a small beaker of water sitting beside it, as in Figure E13.2. Set the solution aside to ferment for one or two weeks at no more than 37 °C (it will be satisfactory to use ambient temperatures of 25–30 °C). If a water seal is used, check the water level in the small beaker from time to time to ensure that the water is deep enough to immerse the end of the glass tube. It takes longer to prepare the water seal, but it is more certain to prevent formation of mold.

Separation of liquid from the sediment. At the end of the fermentation period, carefully move the fermentation flask to the bench top so as to disturb the sediment at the bottom of the flask as little as possible. Set the flask on a piece of wire gauze on a ring stand ring about 10 cm above the bench top. Set a 1000-ml beaker beside it. Select a section of rubber tubing long enough to reach from about 1 cm above the sediment in the flask, out of the flask, and back down to the bench top. Completely fill the tube with water, pinch one end shut with a screw clamp, insert the other end into the liquid to about 1 cm above the sediment, place the pinched end in the bottom of the beaker, and release the constriction. The liquid in the flask will siphon into the beaker. As the level of the liquid approaches the sediment, it might be necessary to tighten the screw somewhat in order to decrease the flow rate and prevent sucking sediment into the beaker. Filter the liquid by vacuum filtration using a filter aid (2–4 ml). Put the filtrate in a distilling flask of appropriate size. Now, filter the remainder of the liquid which was left in the fermentation flask, decanting the less sedimentatious material first. When the filtration becomes impractically slow, desist and discard the remainder down the drain. If the filtrate is reasonably clear, add it to the first filtrate in the distillation flask, otherwise put it in a recovery container. △△

Fractional distillation. Fractionally distill the filtrate through a Hempel column using an appropriate takeoff. The first fraction might consist of a small ethanal (acetaldehyde, bp 21 °C) forerun. Save as one sample all the fractions coming over at the boiling point of the azeotrope. Use a 5 C° interval for other fractions. As you work, prepare a table of data as described in Technique 7 on fractional distillation. △△ Plot a distillation curve and determine the throughput for each section of the curve.

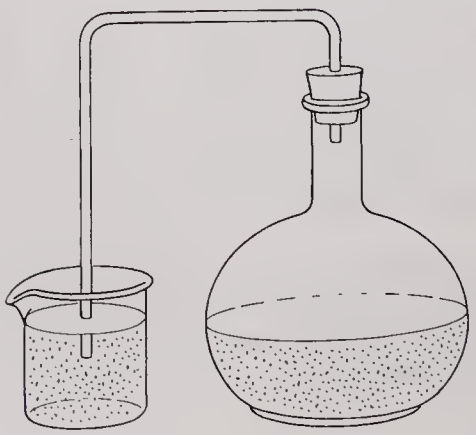


FIGURE E13.2 Flask with water seal.

Analysis. Perform organic qual characterization (Section III) and/or identification test for the distillate, obtain the refractive index, and make a quantitative GLC analysis using the cut and weigh technique. Select the column available in your laboratory which best fits the criteria outlined in Technique 11. You will probably want the column temperature at about 60–70 °C.

Prepare a set of standard curves, using the following ethanol/water mole or weight ratios: 95/5, 75/25, 50/50, 25/75, 0/100. Or, in the interest of saving laboratory time, your instructor might have prepared a set of standard peaks for all to use.

After analyses are completed, submit the product, in a labeled vial, to your instructor. Calculate the percent error as compared to the known azeotropic composition of 95.6% ethanol/4.4% water; calculate the percent yield.

Writing the discussion. Include discussions of the following: results of the characterization and identification tests; what refractive index indicated, why the percent yield was (or was not) as expected and where losses occurred in the experimental procedure; which GLC peak belongs to ethanol and which to water, and why you draw that conclusion; why the GLC curves have the shapes they do; why GLC resolution was complete or incomplete, and the efficiency of your fractionation as indicated by GLC analysis.

13.3 EXERCISES

Prelaboratory

1. Why is a plug of cotton or water seal put at the top of the fermentation flask?
2. In the interest of conserving time, when is a good time to prepare the filter?
3. Where is the most likely place during the process where considerable ethanol might be lost?
4. The alcohol-water GLC peaks might not be completely separated. What quantitative method of GLC analysis is indicated?
5. Will the holdup in the column reduce the amount of 95% ethanol obtained? Explain.
6. What GLC column available in your laboratory do you suggest using for analysis of the ethanol-water samples?
7. Make a flow diagram for the experimental section.
8. Make an outline for the GLC quantitative analysis of the ethanol/water mixture.
9. Review the procedural hazards for vacuum filtration (Section 4.3) and distillation (Sections 7.2 and 7.7).

Postlaboratory

1. If, instead of making ethanol, you wanted to prepare 1,2,3-propanetriol, how would you alter the experimental procedure?
2. Using the information in Figure E13.1, calculate the maximum amount of glycerol you could obtain from 25 g of cane or beet sugar.
3. The importance of Neuberg's discovery to Germany during World War II was that large amounts of glycerol were needed to make explosives. Write a balanced equation showing how glycerol can be converted to nitroglycerine.
4. Using a table of bond dissociation energies, show that the keto form of pyruvic acid (XIV) is more stable than the enol form (XIII).

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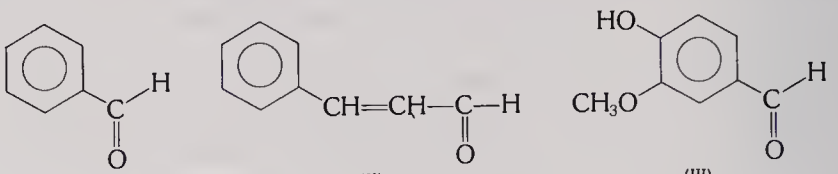
2. Duncan, R.; Acton, B. *Progressive Winemaking;* Standard Press, Ltd.: Andover, Hants, 1971.
3. White, A.; Handler, P.; Smith, E. L. *Principles of Biochemistry;* McGraw-Hill: New York, 1964.

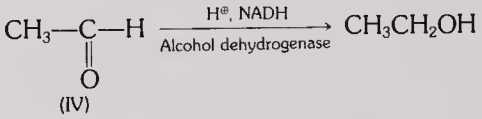
VII ALDEHYDES

Aldehydes are widely distributed in nature. For example, benzaldehyde (I) is found in bitter almonds, cinnamaldehyde (II) in cinnamon, and vanillin (III) in vanilla beans.



(I) (II) (III)

A number of sugars are aldehydes, and acetaldehyde (IV) is an important intermediate in the biosynthesis of ethanol by yeast:

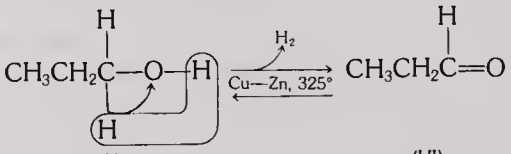


(IV) (VII-1)

Both naturally occurring and synthetic aldehydes with their variety of fruity, citrus-like, sharp floral, spicy sage, coconut, peach, strawberry, and other odors are incorporated into perfume blends to create muguet, lilac, jasmine, violet, orange, and gardenia scents.

As you can see from the above examples of aldehyde structure, the distinguishing characteristic is C=O, the carbonyl, attached to hydrogen on one side and carbon on the other. The carbonyl bond tends to be reactive because of its polar nature and pi electrons. Aldehydes represent an intermediate oxidative stage between alcohols and carboxylic acids, and can therefore be either reduced or oxidized.

The word *aldehyde* is derived from two words and a prefix: *al*cohol *de-hyd*rogen-atum, employing the old Latin word *alcohol,* the new Latin word *hydrogenatum* meaning hydrogen, and the prefix *de-* meaning without. Hence, aldehyde literally means "alcohol without hydrogen" or "dehydrogenated alcohol," and we can see that dehydrogenation of *n*-propyl alcohol (V) does indeed produce propionaldehyde (VI):



(V) (VI) (VII-2)

In this section, you will find one preparation and one reaction of aldehydes. Experiment 14 is an oxidation of an alcohol and Experiment 15 involves reduction of an aldehyde. Experiment 34, the Cannizzaro reaction, includes both oxidation and reduction. Experiments 36, 37, and 38 and Technique 8 also relate to aldehydes, as does the section on qualitative analysis of aldehydes in Part III.

EXPERIMENT 14 PREPARATION OF PROPANAL

Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Simple distillation	(7.2)
Addition of liquids	(0.8)
Drying liquids	(2.2)
Fractional distillation	(7.7)
Storing products	(0.12)
Labeling	(0.13)
GLC	(11.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Aldehyde characterization and identification	(Q8.4, Q9.2)
Boiling points	(3.5)

New Principal:

Design of alternate permanganate oxidation	(postlab exercise 5)

E14.1 OXIDIZING PRIMARY ALCOHOLS TO ALDEHYDES

Although chromium (VI) reactions might be more complicated than shown below, the following pathways are commonly proposed and/or reasonably explain formation of products.

Primary alcohols are easily oxidized to aldehydes by oxidizers like chromic acid (I):

$$3CH_3CH_2CH_2OH + 2H_2CrO_4 + 3H_2SO_4 \longrightarrow 3CH_3CH_2\underset{\underset{O}{\|}}{C}H + Cr_2(SO_4)_3 + 8H_2O \qquad \text{(E14-1)}$$

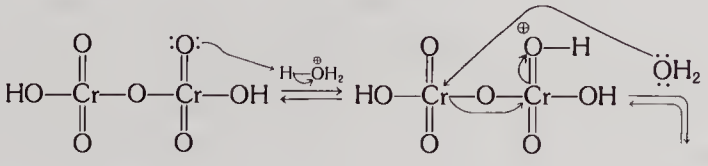
(I)

Chromic acid can be prepared by a Brønsted acid-base reaction in which dichromate ion (II) abstracts protons from sulfuric acid or hydronium ion and is transformed into dichromic acid (III):

$$2Na^{1+} + Cr_2O_7^{2-} + 2H_2SO_4 \rightleftharpoons H_2Cr_2O_7 + 2NaHSO_4 \qquad \text{(E14-2)}$$

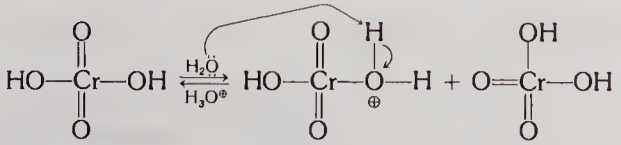
(II) (III)

In a second equilibrium reaction, dichromic acid becomes protonated, then dissociates upon properly oriented, sufficiently forceful collision with water, yielding chromic acid (I):



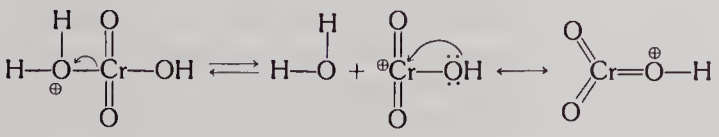
(E14-3)

(III)



(I) (IV) (I)

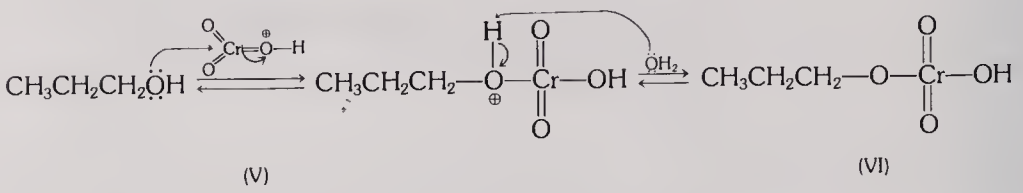
Protonated chromic acid (IV) can dissociate, producing cation (V), which is stabilized by resonance:



(E14-4)

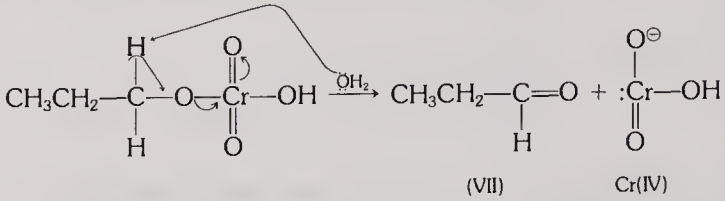
(IV) (V)

Then, when 1-propanol collides with sufficient force and correct orientation with cation (V) and gives up a proton to some nearby base like water or alcohol, the chromate ester (VI) is produced:



(V) (VI) (E14-5)

The next step is the oxidation-reduction step:



(VII) Cr(IV) (E14-6)

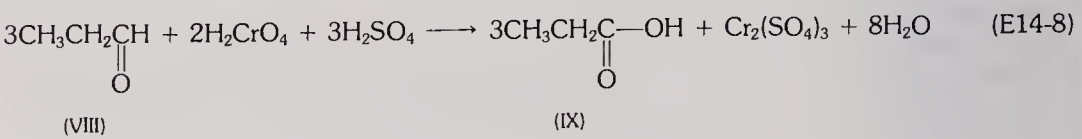
Notice that this formation of product aldehyde (VII) is an elimination similar to that which forms alkenes in a dehydrohalogenation reaction. Even though this step occurs quite readily because of its being driven by reduction of Cr(VI) to Cr(IV), it is the rate-controlling step.

The chromium(IV) ion is unstable; so it accepts a proton and then undergoes **disproportionation,** (auto oxidation-reduction), yielding Cr(VI) and Cr(III) compounds:

$$3H_2CrO_3 + 3H_2SO_4 \longrightarrow \underset{\text{Cr(VI)}}{H_2CrO_4} + \underset{\text{Cr(III)}}{Cr_2(SO_4)_3} + 5H_2O \qquad \text{(E14-7)}$$

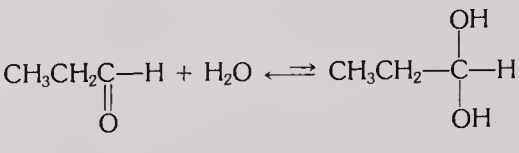
It is the Cr(III) ion that gives the product mixture a green color.

Unfortunately, the aldehyde oxidizes more readily than the alcohol! The consequence is that the final product is propanoic acid (IX) rather than propanal (VII):



(VIII) (IX) (E14-8)

The aldehyde is oxidized by the same mechanism as is the alcohol. However, the oxidation is preceded by hydration to form a low concentration of 1,1-propanediol (X):



(X) (E14-9)

Once formed, the diol can react with cation (V) in the same way as shown in equation E14-5. Because the diol is in equilibrium with aldehyde, all of the aldehyde will eventually be oxidized unless steps are taken to prevent it.

You can reduce the amount of carboxylic acid produced in this experiment by carrying out the oxidation at a temperature above the boiling point of the aldehyde but below that of the alcohol. If you keep the amount of oxidizer in the reaction mixture relatively low, you can distill a large proportion of aldehyde before it oxidizes. It is therefore important that you do not add too much oxidizer at any one time and that you distill off the aldehyde before adding more oxidizer. The initial distillate will consist of propanal, along with some 1-propanol and water. Smaller amounts of propanoic acid and propyl propanoate might be present also.

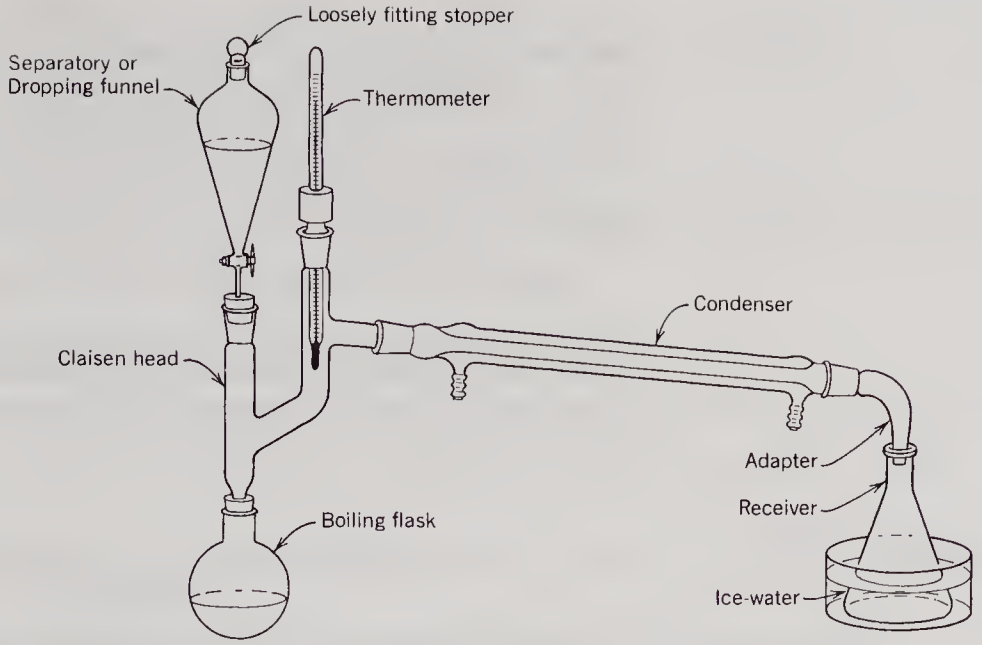


FIGURE E14.1 Apparatus for preparation of aldehyde.

E14.2 EXPERIMENTAL PART

Apparatus. Assemble a simple distillation apparatus using a Claisen flask or 200-ml round-bottom flask and a Claisen head. Attach a dropping funnel to the neck of the Claisen head which is directly over the flask, as shown in Figure E14.1. Insert a thermometer into the offset neck at the proper height for measuring the temperature of the distillate. Thoroughly insulate the sidearm and thermometer branch of the Claisen head with fiberglass and/or aluminum foil. As a receiver, use an Erlenmeyer flask cooled in an ice-water bath. Use a heating mantle, an oil bath, sand bath, or a water bath for the heat source.

Preparation of propanal. Put 17 g of 1-propanol (*n*-propyl alcohol) into the flask and add a couple of boiling chips. If, instead of using boiling chips, you can use a magnetic stirrer, you can get a higher yield. The yield depends to a large extent on the efficiency of stirring.

Prepare a solution of 28 g of sodium dichromate dihydrate in 150 ml of water. Cautiously add 40 ml of concentrated sulfuric acid, slowly, and with swirling. Carefully pour the solution into the dropping funnel.

Cautiously add the concentrate sulfuric acid to the dichromate solution, not vice versa.

Be sure the stopcock of the addition funnel is closed during the filling of it with acidic dichromate.

It is advisable to wear rubber gloves and an apron when working with the powerfully corrosive chromic oxide.

Note that chromates are potential carcinogens. See postlab exercise 5.

Heat the 1-propanol near, but not quite to, its boiling point. Drop in the dichromate solution slowly, but at a rate which will cause distillation of aldehyde to occur. It will probably take about 20–30 min. Do not hurry through the addition! The reaction is exothermic but additional heating might be required to cause distillation. Allow the mixture to boil for about 10 min after addition of dichromate is complete in order to distill out all of the aldehyde. Discard the reaction vessel's acidic contents slowly down the drain along with plenty of water or into a disposal container. Ask your instructor

which to do. Put the cold distillate in a cold separatory funnel and drain off any aqueous layer that might be present. Dry the nonaqueous layer over anhydrous magnesium sulfate. △ Redistill the dried solution, using a small distillation flask with Hempel or Vigreux column. Collect the fraction boiling at 49 ± 3 C° in a tared, ice-cooled, screw top vial. Clean up your glassware with soap and water. △△

As directed by your instructor, perform the following analytical tests: GLC, IR, NMR, refractive index, iodoform, and 2,4-dinitrophenylhydrazone. (See organic qual in Part IV.)

Calculate the percent yield and turn in your sample in a labeled, screw-cap vial.

Writing the discussion. You should discuss your yield relative to your method. If others in your class obtained higher yields, try to ascertain why. Discuss the results of analytical procedures with respect to the purity and identity of your product. Compare your spectral data with Figures 16.7 and E14.2.

E14.3 EXERCISES

Prelaboratory

1. What is the boiling point of 1-propanol? Of propanal? Should it be possible to keep the reaction mixture at a temperature at which aldehyde distills but alcohol doesn't?
2. Why is a Claisen head used for this preparation?
3. Suggest why might it be possible to obtain a higher yield of aldehyde when a magnetic stirrer is used.
4. Why is the receiver cooled in an ice-water bath?
5. For what reason might it not be necessary to heat the reaction vessel during addition of chromic acid?
6. Review the procedural hazards for distillation (Sections 7.2 and 7.7).

Postlaboratory

1. What product would result from reaction of 2-propanol with sodium dichromate-sulfuric acid? To what class of compounds would the product belong? Write the oxidation mechanism.
2. Could 2-methyl-2-propanol be oxidized by chromic acid via the mechanism shown for oxidation of 1-propanol? Explain.
3. Considering the structure of cation (V) shown in equation E14-4, do you think a

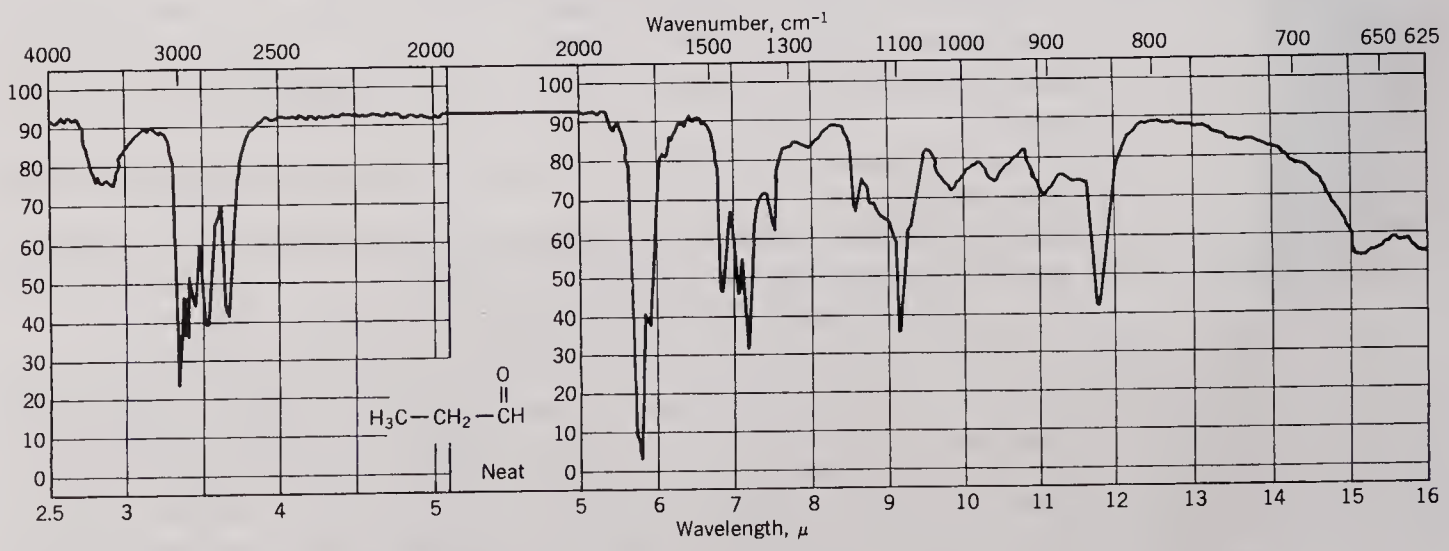


FIGURE E14.2 IR spectrum of propanal. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

chromium(VI) oxide-sulfuric acid system could just as well be used for 1° alcohol oxidations? Would the same oxidation mechanism apply? Explain.

4. Write a complete mechanism illustrating the conversion by chromic acid of ethanal to a carboxylic acid.
5. Chromates are carcinogens. Therefore, your instructor might prefer that you work with permanganate. Using Experiments E14 and E37 as models, outline a procedure (including amounts of chemicals) for conversion of 1-propanol to propanal using potassium permanganate as the oxidizer.

REFERENCES TO RELATED PROCEDURES

1. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; p 252.
2. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 320.

EXPERIMENT 15 ALDOL CONDENSATION OF PROPANAL

Time Required: 3 hr

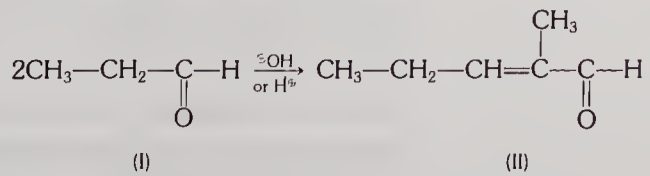
Review Techniques and Principles:

Lab notebook	(1)
Reflux	(0.5)
Stirring	(0.4)
Addition of liquids	(0.8)
Drying liquids	(2.2)
Fractional distillation	(7.7)
Boiling points	(3.5)
Storing products	(0.12)
Labeling	(0.13)
GLC	(11.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Alkene and aldehyde characterization	(Q8.1, Q8.4)
Refractive index	(13.3)

INTRODUCTION

Aldol condensations are fairly common organic reactions, their utility lying mainly in forming new carbon-carbon bonds.

An aldol condensation is the coupling of an *alpha*-carbon of a ketone or aldehyde molecule to the carbonyl carbon of a second ketone or aldehyde molecule. In the simplest aldol condensation the molecule with the alpha-carbon is the same kind as the molecule that supplies the carbonyl carbon, as shown in the condensation of propanal (propionaldehyde):



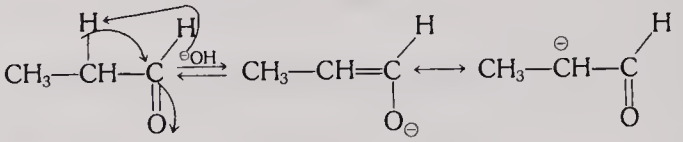
(I) (II) (E15-1)

The reaction is catalyzed by either acid or base.

In some cases the molecule with the *alpha*-hydrogen is different from another carbonyl molecule in the reaction mixture. Aldol condensations of this sort are referred to as *crossed* aldol condensations and often produce a mixture of products.

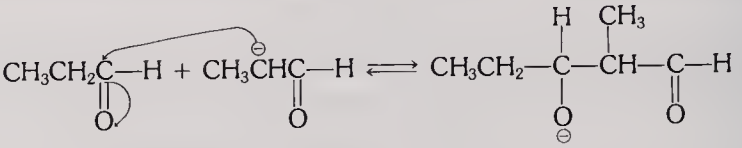
E15.1 DISCUSSION OF THE REACTION

The first step of the reaction involves removal of an *alpha*-hydrogen by hydroxide:



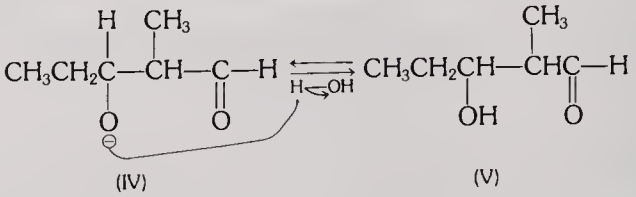
(I) (III) (E15-2)

The enolate (III) is stabilized by resonance. In a properly oriented collision of sufficient force the enolate ion (III) collides with the carbonyl of a second propanal molecule, making the new carbon-carbon bond:



(IV) (E15-3)

Because the negatively charged species (IV) is the salt of an alcohol ($pK_a \sim 18$), it is more basic than hydroxide, whose conjugate acid is water ($pK_a \sim 16$). Therefore the equilibrium of equation E15-4 lies to the right:



(IV) (V) (E15-4)

The 3-hydroxy-2-methylpentanal (V) is not isolable under these reaction conditions. It dehydrates readily in the presence of base to yield the product, 2-methyl-2-pentenal (II).

E15.2 EXPERIMENTAL PART

Aldol condensation of propanal. Attach a Claisen adapter to a 25-ml flask. Place a separatory funnel in the Claisen neck directly above the flask and a reflux condenser in the offset neck. Grease ground glass joints lightly. Cool the condenser with water.

Put a magnetic stirring bar in the flask along with 2 ml of 10% aqueous sodium hydroxide. Position the apparatus over a magnetic stirrer. Put 6.0 ml of freshly distilled propanal (distilled to remove contaminant propanoic acid) into the separatory funnel.

Start the stirring motor and run in the propanal over a period of about 5 min. Following addition, stir the mixture until it cools to room temperature; then stop the stirrer and remove the flask from the apparatus. With an eyedropper or Pasteur pipet, reach through the organic layer into the aqueous phase and remove as much of the aqueous layer as possible.

Workup and analysis. Assemble the 25-ml flask and its contents into a well-insulated fractional distillation apparatus. Add a boiling chip and distill, keeping the temperature at no more than 140 °C.

Dry the distillate over about 0.2 g of anhydrous calcium chloride. Swirl the flask occasionally, and over a period of about 10 min, remove with an eyedropper the water

that gathers around the calcium chloride. Repeat this calcium chloride treatment and water removal until no more liquid gathers and the salt appears to remain anhydrous. △△

Decant the liquid into a 25-ml distilling flask and distill it once more, collecting the fraction that boils between 133 and 137 °C. △△

Perform the following tests as directed by your instructor: GLC, IR, NMR, refractive index, and wet analysis characterization tests (Part III, this text). Turn in the product in a labeled vial. Calculate the percent yield.

Writing the discussion. Your discussion should include an analysis of your percent yield relative to the technique and equipment used, and of the identity and purity of the product based on the tests performed. Find spectral data from handbooks and compare your spectra to them (see Technique 18, Section 18.2) and/or to similar spectra in Techniques 15 and 16.

E15.3 EXERCISES

Prelaboratory

1. What is the molar ratio of propanal to hydroxide ion?
2. What piece of equipment in the apparatus leads you to believe the reaction is exothermic? Explain.
3. By what two means will water be removed from the product?
4. Draw and label an illustration of the apparatus you will use for the condensation.
5. Review the procedural hazards for distillation (Sections 7.2 and 7.7).

Postlaboratory

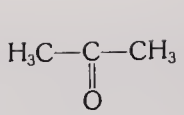
1. Write the equation for the crossed aldol condensation between ethanal (acetaldehyde) and 1-phenylethanone (acetophenone). Give IUPAC names to the four products.
2. Write an equation for an example of a crossed aldol condensation that yields only two products. Give IUPAC names to the products.
3. Write a mechanism showing how a properly oriented, sufficiently energetic collision of base with (V) in equation E15-4 ultimately results in formation of product (II) in equation E15-1.

REFERENCES TO RELATED PROCEDURES

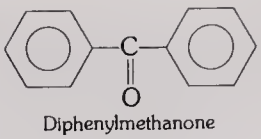
1. Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry,* 4th ed.; Sanders: Philadelphia, 1985; p 515.
2. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; p 174.

VIII KETONES

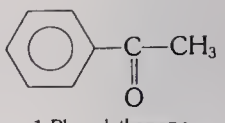
Ketones, like aldehydes (Section VII), are characterized by C=O, the carbonyl. However, whereas aldehydes have at least one hydrogen attached to the carbonyl, ketones have only carbons bound to the carbonyl. Ketones can be either aliphatic (I), aromatic (II), or combinations of the same (III).



Propanone
(Acetone)
(Dimethyl ketone)
(I)



Diphenylmethanone
(Benzophenone)
(Diphenyl ketone)
(II)

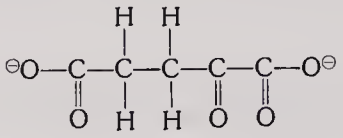


1-Phenylethanone
(Acetophenone)
(Methyl phenyl ketone)
(III)

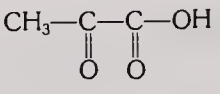
As in aldehydes, the keto carbonyl tends to be reactive because of its polar nature and pi electrons. Unlike aldehydes, however, ketones do not as readily oxidize.

The word *ketone* is derived from the German *Keton*. Keton is an abbreviated form of the German word *Aketon,* the smallest possible ketone, which we commonly call acetone.

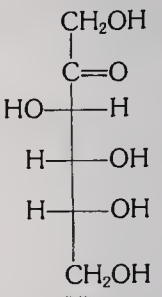
Ketones are widely occurring natural products, being found in fruits as flavors and scents. Keto functions are also biochemically important in metabolic intermediates such as α-ketoglutarate (IV), pyruvic acid (V), and the sugar, fructose (VI):



(IV)



(V)



(VI)

Ketones are also important as chemical intermediates and industrial solvents.

In this section, you will find one reaction and one preparation of ketones. Experiment 16 is an oxidation of a methyl ketone, and Experiment 17 is the oxidation of an alcohol. Experiments 27 and 33 also relate to ketones, as does the section in Part III on qualitative analysis of ketones.

EXPERIMENT 16 THE HALOFORM REACTION

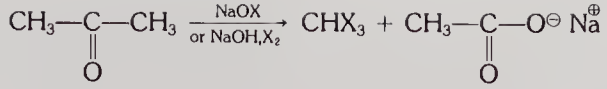
Time Required: 2 hr

Review Techniques and Principles:

Lab notebook	(1)
Reflux	(1.4)
Simple distillation	(7.2)
Boiling chips	(0.5)
Decolorizing	(5.2, 5.3)
Stirring	(0.4)
Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.3)
IR	(15.3, 15.4)
Test for halogen	(Q7.1, Q7.2)

INTRODUCTION

The haloform reaction is so-called because it produces as one of the products chloroform, bromoform, or iodoform with the generalized formula CHX_3:



(E16-1)

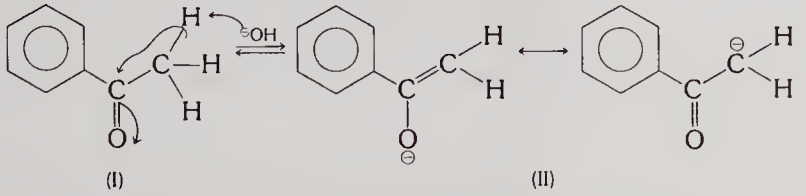
The second product is the salt of a carboxylic acid. Ordinarily, if a carboxylic acid is the desired product, chloroform is the chosen byproduct because of the ready availability and low cost of the hypochlorite. The haloform reaction is a very effective preparative method for carboxylic acids when a methyl ketone is more available or lower in cost than the acid itself.

The iodoform reaction is commonly used as a wet characterization test for certain classes of compounds discussed in Part III. Iodoform is a pale yellow, crystalline solid with a characteristically medicinal odor and melting point of 119 °C. At one time it was used as a mild iodine-releasing antiseptic.

E16.1 DISCUSSION OF THE REACTION

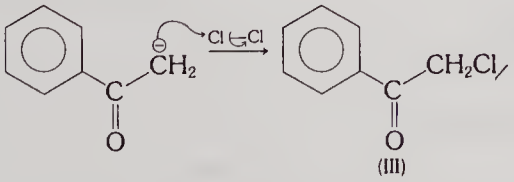
Methyl ketones are the only ketones that are useful for preparing carboxylic acids by the haloform reaction. It is essential that a methyl group be attached to the carbon that will become a carboxyl because it is the methyl group that becomes the haloform byproduct. The other group attached to the carbonyl becomes the alkyl or aryl portion of the carboxylic acid product. So, the obvious starting material for preparation of benzoic acid must be acetophenone (IUPAC 1-phenylethanone).

The first step in the reaction involves removal of one of the methyl protons:



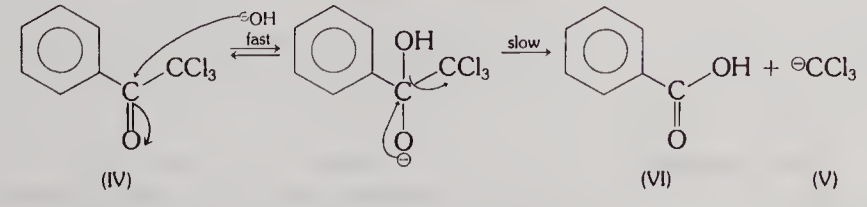
(E16-2)

The next step apparently involves transfer of chlorinium ion (Cl^+) to carbon by correctly oriented and sufficiently forceful collision of enolate (II) with a halogen-containing species, like Cl_2:



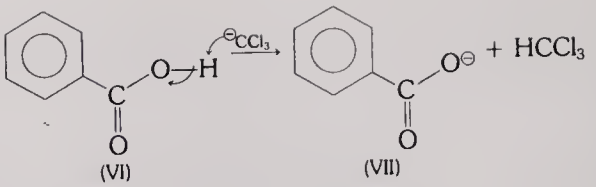
(E16-3)

Once the first proton has been removed, the second is easier to remove because of the increased acidity of a proton next to a halogen. The steps in equations E16-2 and E16-3 are therefore repeated twice more, the result being 1-phenyl-2,2,2-trichloroethanone (IV), the starting material for a carbon-carbon cleavage step which is exactly analogous to saponification of an ester:



(E16-4)

In this step, trichloromethyl anion (V) is formed. Being considerably more basic than benzoate ion (VII), it removes the carboxyl proton from benzoic acid (VI), forming the salt of the acid and chloroform (IUPAC trichloromethane):



(E16-5)

Acidification of the carboxylate with mineral acid produces the desired product acid, in this case benzoic acid.

E16.2 EXPERIMENTAL PART

Haloform reaction of acetophenone. Put 40 ml of 5.25% sodium hypochlorite (laundry bleach), 1.0 ml of acetophenone, and a boiling chip into a 100-ml round-bottom flask and swirl the mixture vigorously; then put the flask on a hot water or steam bath and reflux the mixture 15 min. Add 8–10 drops of acetone (IUPAC propanone) to destroy excess hypochlorite. Replace the reflux condenser with a still head and distill the mixture until the temperature at the still head rises to 70 °C. Use as a receiver a 10-ml graduated cylinder cooled in an ice-water bath. Record the apparent amount of chloroform distillate and put it in its assigned recovery container.

Constantly swirling the mixture, put a little decolorizing carbon in the flask and heat it to the boiling point. Gravity filter the mixture hot. To the hot solution add concentrated hydrochloric acid dropwise to pH 1. It will probably take 2–5 ml. Cool the mixture to room temperature; then cool it in an ice-water bath. Filter off the crystals in a Hirsch funnel, wash them, and dry them. Obtain a melting point and IR spectrum, as directed by your instructor. Put the product in a labeled vial and turn it in.

Concentrated HCl can cause serious chemical burns.

Writing the discussion. Discuss the percent yield of benzoic acid relative to your technique and the apparent amount of chloroform collected. Consider also the melting point and IR spectrum relative to proof of structure and purity. Compare the IR spectrum of your compound with that found in a handbook of spectral data (see Technique 18, Section 18.1).

E16.3 EXERCISES

Prelaboratory

1. What reagent is used to destroy excess hypochlorite? Write the equation that shows how it reacts. Does the product interfere with the separation of benzoic acid? Explain.
2. Make a simple, labeled drawing of the reflux apparatus you will use.
3. Calculate the molar amounts of reagents and determine from a balanced equation the theoretical yield. Which reagent is the limiting reagent?
4. Write an equation that illustrates the purpose of adding hydrochloric acid to the reaction mixture.
5. Make a flow diagram of reaction and workup for this experiment.
6. Review the hazards associated with vacuum filtration (Section 4.3) and with recrystallization (Section 5.3).

Postlaboratory

1. Write the formulas of products from the following reactions: (a) 2-butanone with sodium hypobromite; (b) benzophenone with sodium hypochlorite; (c) 1-cyclohexylpropanone with iodine and sodium hydroxide.
2. What would be the products when 1 mole of 2,4-pentanedione is heated with 6 moles of aqueous NaOH and I_2?

REFERENCES TO SIMILAR PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 299.
2. Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry;* Wiley: New York, 1980; p. 182.

EXPERIMENT 17 CYCLOHEXANONE FROM CYCLOHEXANOL

Time Required: 3–4 hr

Review Techniques and Principles:

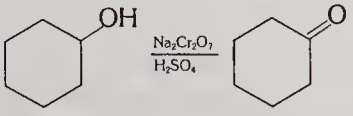
Lab notebook	(1)
Adding liquids and solids	(0.8)
Stirring	(0.4)
Heating and cooling	(0.5)
Direct steam distillation	(7.15)
Liquid-liquid extraction	(6.2)
Gravity filtration	(4.2)
Simple distillation	(7.2)
Drying liquids	(2.2)
IR	(15.3, 15.4)
GLC	(11.3)
Refractometry	(13.3)
Wet analysis	(Q8.4, Q9.3)
Storing	(0.12)
Labeling	(0.13)

New Principle:

Design of alternate permanganate oxidation	(postlab exercise 7)

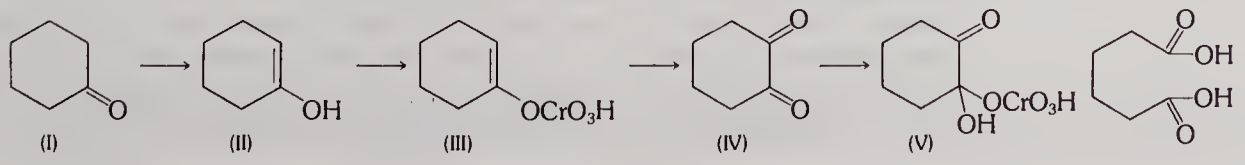
E17.1 CHROMIUM(VI) OXIDATION OF CYCLOHEXANOL

The sodium dichromate oxidation of cyclohexanol proceeds in the same manner as the oxidation of 1-propanol in Experiment 15:



(E17-1)

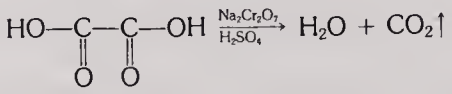
However, ketones do not oxidize as readily as aldehydes, and can be easily prepared in mildly acidic media of relatively low temperatures. Nevertheless, use of basic media, or of excess oxidizer, highly acidic conditions, and high temperatures can cause oxidation of enolizable ketones. In such a reaction, the ketone is broken down into two carbonyl- or carboxyl-bearing fragments. Even under mildly acidic conditions, you might expect that a small amount of such products will be produced. In the oxidation of cyclohexanol, the ketone forms by the same mechanism as was shown for the oxidation of 1-propanol in Experiment 14. Further oxidation apparently proceeds via the enol (II):



(E17-2)

The process must be considerably more difficult than for formation of the ketone (I) because two carbon-carbon bonds must be broken, first the pi bond of the enol, and second, the sigma bond between carbonyls of cyclohexandione (IV). You can imagine the mechanisms of the reaction to have many more steps than are shown in equation E17-2 and to perhaps involve a properly oriented and sufficiently forceful collision of water with the number two carbons of the chromate esters (III) and (V).

In this experiment, you will destroy excess dichromate in the reaction vessel by reducing it with oxalic acid, an ideal choice because its organic oxidation product escapes into the atmosphere:



(E17-3)

E17.2 EXPERIMENTAL PART

Apparatus. Assemble an apparatus consisting of a Claisen adapter, 100-ml round-bottom flask, thermometer, and separatory funnel. Set the Claisen adapter in the neck of the round-bottom flask. Suspend a thermometer in the neck of the Claisen adaptor centered over the flask, using a piece of wire hooked over the rim of the Claisen neck. The thermometer bulb must be in the liquid but not low enough to be struck by a stirring bar. Put a separatory funnel in the offset neck of the Claisen adaptor. Put a magnetic stirring bar in the flask, and a magnetic stirrer beneath the flask.

Oxidation of cyclohexanol. Carefully add 10 ml of concentrated sulfuric acid to 25 ml of an ice-water slurry in a 250-ml beaker. Stir during the addition. Cool the liquid in the beaker to about 20 °C, and put it in the 100-ml flask of the apparatus. Then, stirring contantly, add 10.0 g of cyclohexanol to the flask. Dissolve 10.5 g of sodium dichromate dihydrate in 10 ml of water and pour it into the separatory funnel.

To prevent pressure buildup during reaction do not stopper the Claisen neck suspending the thermometer.

Cautiously add the concentrated H_2SO_4 to the ice-water slurry. Stir continually during addition.

It is advisable to wear gloves while working with the chromic acid. If chromic acid contacts your skin, immediately wash the area with soap and water, rinse with 5% sodium bicarbonate if available, then hold the area under running water for 15 min.

Remember that chromium(VI) compounds are carcinogens.

Add about 1 ml of the dichromate solution from the separatory funnel into the reaction flask. The thermometer should indicate a rise in temperature and the yellow color of the chromate ion should give way to the green color of chromic ion. When the temperature no longer increases, add more of the dichromate solution in increments that bring the temperature up to 45–50 °C and maintain it there. After addition is complete, continue stirring until the solution is at room temperature. Slowly add 0.5 g of oxalic acid down the thermometer neck of the Claisen head, rinsing it down with a small amount of water if necessary.

Avoid adding dichromate solution so rapidly that a runaway reaction results.

Workup. Remove the thermometer from the apparatus and rinse it with water before setting it down. Remove the separatory funnel and Claisen adaptor from the apparatus, and rinse them with water. Do not bother to dry them. Replace the Claisen adaptor into the flask neck and put the separatory funnel in the Claisen neck directly over the flask. Put a distillation head on the offset neck and complete an assembly for direct steam

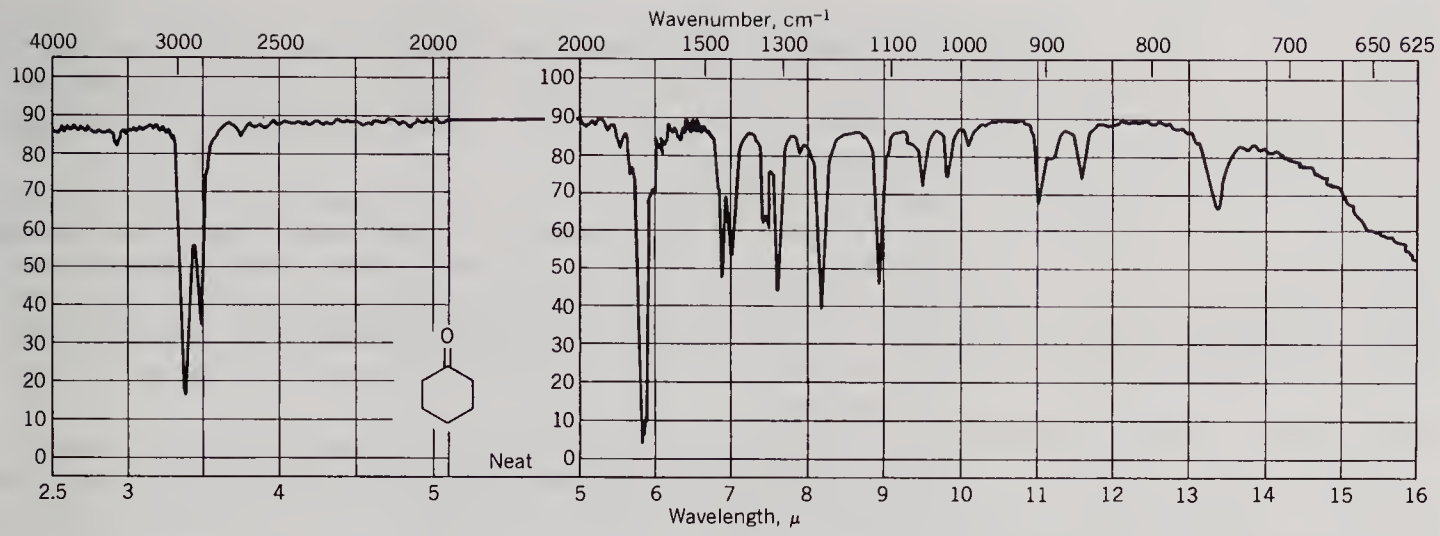


FIGURE E17.1 IR spectrum of cyclohexanone. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

distillation. Put 50 ml of water into the separatory funnel and, using a heating mantle, oil bath, or burner as heat source, steam distill the mixture. △△

Add 7.5 g of sodium chloride to the distillate and stir it to dissolve the salt. Put the mixture in a separatory funnel and extract it twice with 10 ml of technical grade ether (IUPAC ethoxyethane). Dry the extract over anhydrous magnesium sulfate. Filter or decant the solution into a round-bottom flask and distill it, collecting as product the fraction coming over at 154 to 158 °C. Put the ether in a recovery container; also the aqueous layer if the salt is to be recovered.

Time can be saved at the expense of a 10–15% lower yield by eliminating the ether extraction and distillation. Simply drain off the aqueous layer and dry the organic phase with anhydrous magnesium sulfate.

Analysis. As directed by your instructor, obtain IR and NMR spectra, refractive index, qualitative and/or quantitative GLC, and wet analysis tests for ketones (Part III). Turn in your labeled product to your laboratory instructor.

Writing the discussion. Discuss the percent yield as determined by weighing the product and as shown by GLC. Discuss the identification and purity of the product as evidenced by boiling point, GLC, IR, refractive index, and qualitative wet analysis tests (for Part III). Compare your IR spectrum with that of Figure E17.1.

E17.3 EXERCISES

Prelaboratory

1. Make a sketch of the apparatus you will use for the redox part of the experiment.
2. Explain why the temperature of the redox reaction should not rise above about 50 °C.
3. Suggest a reason why you are directed to add the concentrated H_2SO_4 to an ice-water slurry, and why you must stir the mixture during addition.
4. How will you treat your skin if chromic acid is spilled on it?
5. Suggest a reason why NaCl is added to the steam distillate before ether extraction.
6. Make a flow diagram for the redox reaction and workup for this experiment.
7. Review hazards associated with distillation (Sections 7.2 and 7.15) and with extraction (Section 6.2)

Postlaboratory

1. Potassium dichromate can be used in place of sodium dichromate dihydrate. Calculate the amount of potassium dichromate that would have been used in this project.

2. Chromic oxide, CrO_3, could also have been used in this project. Propose for the CrO_3 oxidation of cyclohexanol a mechanism like those shown in Experiment 15.
3. What would be the primary oxidation products of 2-butanol, 2,4-pentanediol, and 1-phenylethanol when oxidized under conditions to yield ketones? Show the structures and give IUPAC names.
4. Knowing that the reactants for oxidation of cyclohexanol are $Na_2Cr_2O_7$ and H_2SO_4, and that the products are cyclohexanone, chromic sulfate, sodium sulfate, and water, write a balanced redox equation. Write also a balanced redox equation showing the conversion of cyclohexanol to adipic acid, chromic sulfate, sodium sulfate, and water. Based on the balanced equations explain why strongly acidic conditions with excess oxidizer can lead to oxidation of a cyclohexanone product to adipic acid, especially at high temperature.
5. Using the mechanism of Experiment 14 and equation E17-2 as a starting point, propose a mechanism showing the conversion of cyclohexanone to adipic acid. In conversion of (I) to (II), use protonation of carbonyl oxygen followed by abstraction of an *alpha*-hydrogen.
6. Propose a mechanism analogous to that of postlab exercise 5 showing how potassium permanganate in basic solution could accomplish the same oxidation. Considering that hydroxide, rather than water, collides with the number two carbons of the esters (III) and (V), explain why basic $KMnO_4$ oxidation might be expected to occur more readily than acidic $Na_2Cr_2O_7$ oxidation. (Hint: See the reactants, products, and mechanism of $KMnO_4$ oxidation in Experiment 36.)
7. Write a procedure analogous to this one and the oxidations in Experiment 36 for the permanaganate oxidation of cyclohexanol to make cyclohexanone. Show it to your instructor and then use it in place of the dichromate oxidation of Experiment 17.

REFERENCES TO SIMILAR PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry* 3rd ed.; Longman: London, 1956; p. 337.
2. Mohrig, J. R.; Neckers, D. C. *Laboratory Experiments in Organic Chemistry,* 2nd ed.; Van Nostrand: New York, 1973; p. 81.
3. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; p. 249.

IX

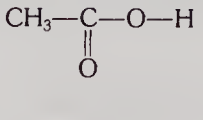
CARBOXYLIC ACIDS

Carboxylic acids, like aldehydes and ketones, contain the carbonyl group, C=O. In addition, they have a hydroxyl attached to carbonyl, forming a group called a carboxyl. As a matter of fact, the word *carboxyl* is a combination word, composed of *car*bonyl and hydr*oxyl*. The carboxyl is most often shown as

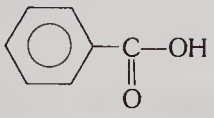
$$-\overset{\overset{O}{\|}}{C}-OH \text{ or } -COOH$$

While we are on the subject of derivations, it is interesting to note that the German word for acid, *Säure*, is the precursor of "sour," the word that characterizes the taste of acids.

Carboxylic acids can be aliphatic (I), or aromatic (II):



Ethanoic acid
(Acetic acid)
(I)

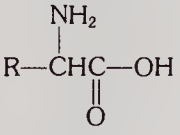


Benzenecarboxylic acid
(Benzoic acid)
(II)

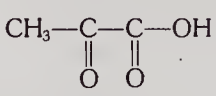
Carboxylic acids are often referred to simply as "acids." However, we must remember that "acid" is a word that also applies to *any* proton donor in the Brønsted sense and any electron pair acceptor in the Lewis concept. Carboxylic acids are most often involved chemically as proton donors.

Carboxylic acids were first isolated from natural sources, and, as shown in Table IX.1, their common names reflect their origins.

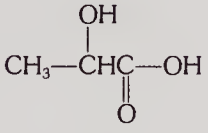
A great many carboxylic acids are biologically important, and include α-amino acids (III) and pyruvic acid (IV), the biochemical precursor to lactic acid (V), the end product of glycolysis and the compound that leaves us with sore muscles after exercise.



(III)

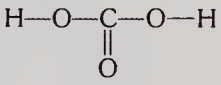


(IV)

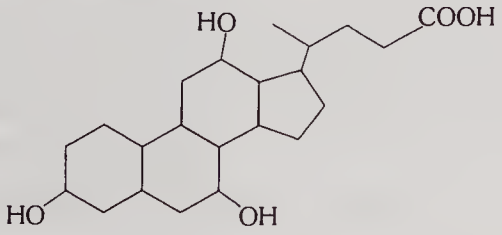


(V)

Carbonic acid (VI) and its salts form an important buffer that helps to maintain the pH of our body fluids, and cholic acid (VII) is one of the four bile acids that are instrumental (in salt form) as emulsifiers of fatty foods, promoting their hydrolysis and absorption from the intestinal tract.



(VI)



(VII)

In this section, you will find one preparation and one reaction: Experiment 18 involves hydrolysis of esters and Experiment 19 is the conversion of a carboxylic acid

TABLE IX.1 Some Carboxylic Acids and Their Origins

Structure	*Common Name*	*Derivation of Name*
H—COOH	formic	formica (ants)
CH_3—COOH	acetic	acetum (vinegar)
CH_3CH_2COOH	propionic	proto (first) pion (fat)
$CH_3(CH_2)_2COOH$	butyric	butyrum (butter)
$CH_3(CH_2)_3COOH$	valeric	valerian root
$CH_3(CH_2)_4COOH$	caproic	caper (goat)
$CH_3(CH_2)_{10}COOH$	lauric	laurel (bay shrub)
$CH_3(CH_2)_{12}COOH$	myristic	myristica (nutmeg)
$CH_3CH{=}CH{-}CH{=}CH{-}COOH$	sorbic	sorbus (mountain ash)
HOOC—COOH	oxalic	oxalis (sorrel)
HOOC CH_2COOH	malonic	malon (apple)
$HOOC(CH_2)_6COOH$	suberic	suber (cork oak)
HOOC $CH_2CH(OH)COOH$	malic	malon (apple)

to an acyl halide. Experiments 16, 20, 21, 22, 31, 34, 36, 37, and 42, and Techniques 4, 5, 6, and 7 also relate to carboxylic acids, as does a section on qualitative analysis in Part III.

EXPERIMENT 18 BENZOIC OR SALICYLIC ACID BY ESTER HYDROLYSIS

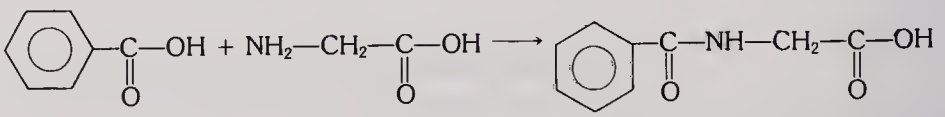
Time Required: 4 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Heating and reflux	(0.5)
Cooling	(0.5)
Testing acidity	(0.11)
Vacuum filtration	(4.3)
Recrystallization	(5.3)
Gravity filtration	(4.2)
Drying solids	(2.1)
Melting points	(3.3)
IR	(15.4)
Organic qualitative tests	(Q8.5, Q9.4)

INTRODUCTION

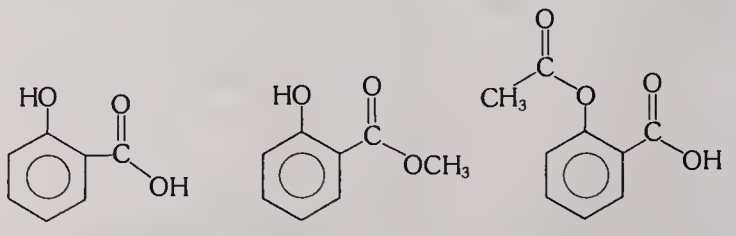
Benzoic acid (IUPAC benzenecarboxylic acid) occurs in nature in both free and combined forms. Most berries contain about 0.05% benzoic acid and gum benzoin contains as much as 20%. Because benzoic acid is relatively nontoxic, nearly tasteless, and prevents bacterial growth in concentrations as low as 0.1%, it is widely used for preserving foods. It is also used for curing tobacco and in the dyes industry. Although it is a mild irritant to eyes, mucous membranes, and skin, it can be safely applied to skin in topical antifungal ointments. Under the influence of liver enzymes, benzoic acid (I) combines with glycine (II) to form hippuric acid (III):



(I) (II) (III) (E18-1)

The ability of the liver to metabolize benzoic acid is sometimes used as a measure of hepatic (liver) function.

Salicylic acid (IUPAC 2-hydroxybenzenecarboxylic acid), (IV), occurs in the form of an ester in a number of plants, notably in leaves of wintergreen and the bark of sweet birch. It is used in the dye industry, for manufacture of artificial oil of wintergreen (V), with benzoic acid in topical antifungal preparations, and as a keratolytic agent (a substance used to help disintegrate and remove skin).

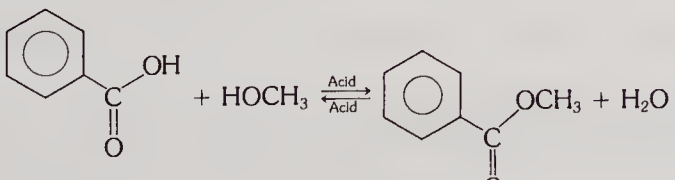


(IV) (V) (VI)

Notice the ring hydroxyl in salicylic acid. The acidic character of this phenolic hydroxyl makes salicylic acid much more irritating to tissues than benzoic acid. It is this additional acidity that makes it useful for topical keratolytic uses like treating warts and corns. On the other hand, even though salicylic acid possesses properties of analgesia (pain reduction), antipyresis (temperature reduction), and anti-inflammation, it is so irritating to the gastric mucosa (the lining of the stomach) that it cannot be ingested unless the phenolic hydroxyl has been masked as in aspirin (VI).

E18.1 DISCUSSION OF THE HYDROLYSIS

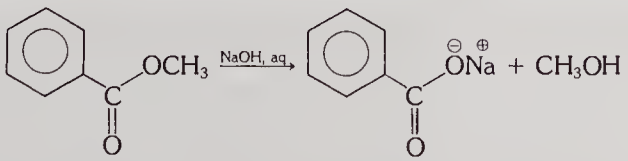
Methyl benzoate and methyl salicylate are esters, chemical combinations of carboxylic acids and alcohols. For example, benzoic acid (I) reacts with methanol (VI) to yield methyl benzoate (VII), the ester:



(E18-2)

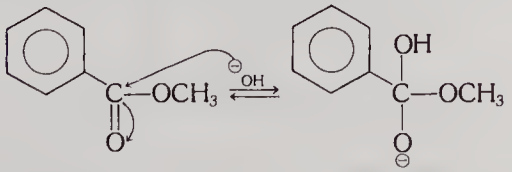
(I) (VI) (VII)

The formation of the ester is called **esterification** and the reverse process is **hydrolysis.** The position of equilibrium depends on the relative amounts of reactants and products: If a large amount of alcohol is present, the equilibrium is shifted toward the right; if a large amount of water is present, the equilibrium is moved toward the left. During hydrolysis, the oxygen-carbonyl bond is cleaved by water, usually aided by mineral acid or base. In acid-catalyzed hydrolysis, the amount of acid and alcohol obtained as products is smaller than from base-promoted hydrolysis, or **saponification.** The reason is that after the hydrolytic cleavage, base removes a proton from the product acid, thereby shifting the equilibrium far in the direction of hydrolysis, and yielding the salt of the acid:



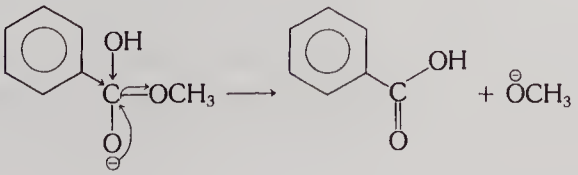
(E18-3)

The reaction proceeds stepwise. First, hydroxide collides with carbonyl carbon and, if the collision is forceful enough and properly oriented, the nonbonding electrons on hydroxide form a bond to carbonyl and the pi bond breaks:



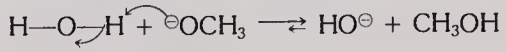
(E18-4)

Next, if the bonds to carbonyl carbon from phenyl, negative oxygen, and hydroxide contract at the same time that the bond from carbonyl carbon to methoxy expands, the electronic repulsions push methoxide off:

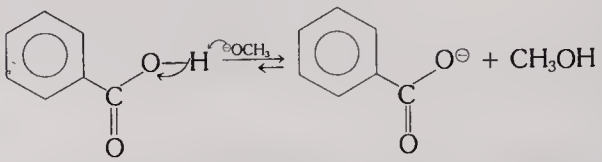


(E18-5)

Methoxide is the strongest base present in the reaction mixture. Therefore, it reacts very quickly in a Brønsted acid-base step to remove a proton from water or carboxyl:



(E18-6)



(E18-7)

If methoxide abstracts a proton and makes hydroxide as in equation E18-6, hydroxide subsequently removes a proton from carboxyl. Notice that the overall effect is that the hydroxide initially added to the reaction mixture is never regenerated. Hence it is not a catalyst.

E18.2 EXPERIMENTAL PART

Your instructor will assign, perhaps as an unknown, either methyl benzoate (IUPAC methyl benzenecarboxylate) or methyl salicylate (IUPAC methyl 2-hydroxybenzenecarboxylate) for you to hydrolyze.

Hydrolysis. Dissolve 4 g of sodium hydroxide in 20 ml of water. Allow the solution to cool to room temperature and add it to 2.0 g of the assigned ester in a 100-ml round-bottom flask. Add two boiling chips, and attach a reflux condenser. If standard taper joints are used, they should be lightly greased. Using a heating mantle, hot plate, or oil bath, heat the solution slowly at first, then at a vigorous boil for 10–20 min until the oily ester appears to be gone.

NaOH solutions can cause chemical burns.

Workup. After reflux, remove the mantle or flame and allow the reaction mixture to cool to room temperature. You can put the mixture into a cold water bath to hasten the process. Then pour it into a 100-ml beaker and cautiously add with stirring enough 3*M* sulfuric acid to make the pH of the solution about 1. It will probably take about 5–6 ml. With occasional stirring, cool the mixture of liquid and precipitate in an ice-water bath to about 5 °C. Collect the precipitate by vacuum filtration, pouring first the supernatant liquid into the filter paper, and then the crystals. Rinse with ice-cold water. △△ Pour the filtrate into a recovery container so that the methanol can be reclaimed by distillation in the chemistry stockroom. Recrystallize the impure product from water in a 100-ml Erlenmeyer flask.

Add the sulfuric acid to the reaction mixture slowly and carefully.

Analysis. As directed by your instructor, obtain a melting point; also NMR and IR spectra; and characterize the product by organic wet analysis (Section III).

Writing the discussion. Compare your NMR spectrum with that in Figures 16.18 and E18.3; compare your IR spectrum with Figures E18.1 and E18.2. Discuss the identity and purity of the product as determined by the analyses performed. If you were given an ester as an unknown, explain how results of analysis led to its identity. Discuss the percent yield, trying to identify places in the procedure where losses occurred. Make suggestions for improving yield.

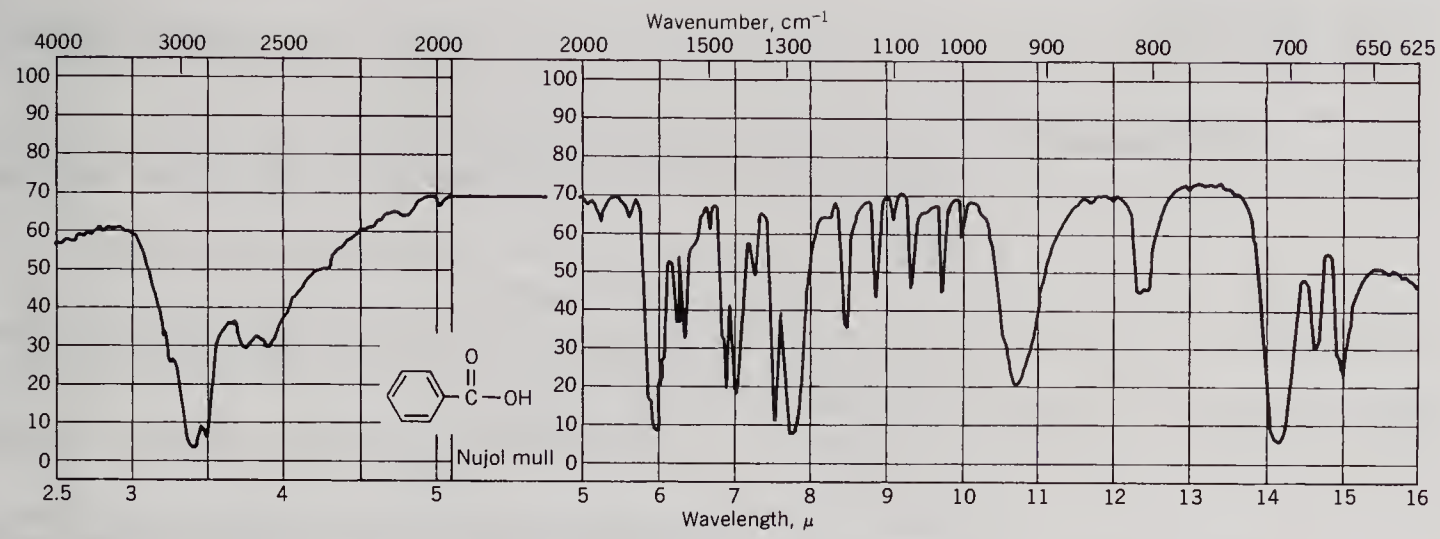


FIGURE E18.1 IR spectrum of benzoic acid. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

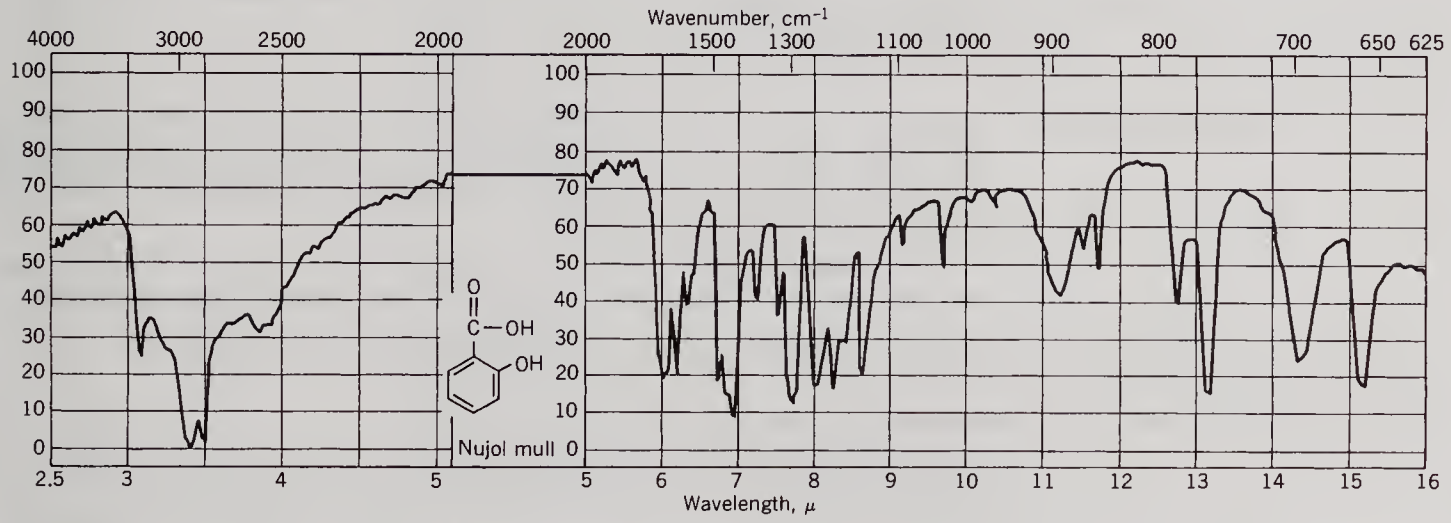


FIGURE E18.2 IR spectrum of salicylic acid. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

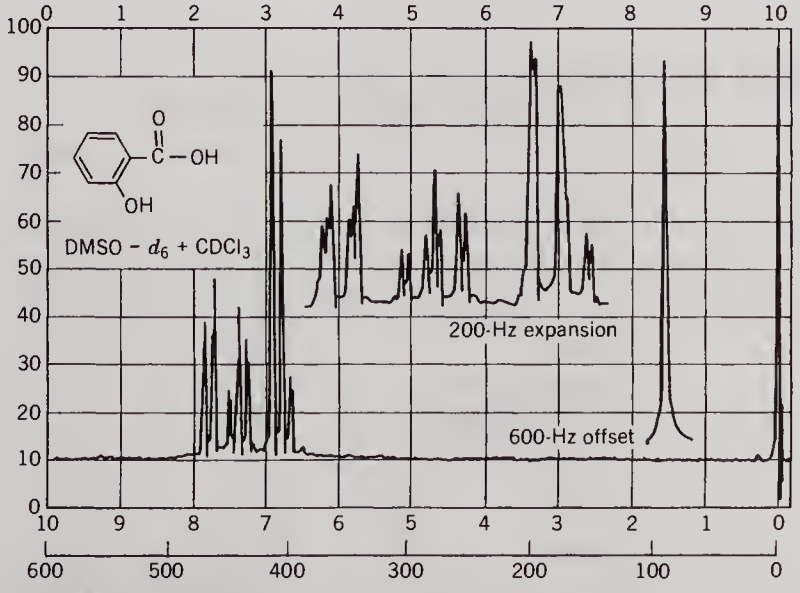


FIGURE E18.3 NMR spectrum of salicylic acid. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

E18.3 EXERCISES

Prelaboratory

1. The sodium salt of salicylic acid or benzoic acid is the initial product of hydrolysis. Why is sulfuric acid added to the salt solution? Write an equation illustrating this reaction.
2. Why is a reflux condenser used during heating of the reaction mixture?
3. Why are boiling chips used during reflux?
4. In interest of conserving time, when is a good time to set up the Büchner filtration system? To set up the hot filtration system? To get some water boiling to use for recrystallization?
5. Why do you think the supernatant liquid is poured into the Büchner funnel before the crystals?
6. Why should a shield be put between the worker and the vacuum filtration apparatus?
7. Make a flow diagram for the reaction and workup.
8. Review the procedural hazards associated with recrystallization (Section 5.3) and vacuum filtration (Section 4.3).

Postlaboratory

1. Water was chosen for you as a recrystallization solvent in this project. Explain why the choice of water was reasonable based on the following solubility data: benzoic acid: 2.2 g/100 ml at 75 °C, 0.27 g/100 ml at 18 °C, and salicylic acid: 0.76 g/100 ml at 75 °C and 0.18 g/100 ml at 20 °C.
2. If 1.75 g of salicylic acid is dissolved in 100 ml of water at 75 °C, how many grams of crystals can have crystallized at 20 °C? Use the information from exercise 1.
3. Write a balanced equation for the saponification of methyl salicylate.

REFERENCES TO RELATED PROCEDURES

1. Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry;* Wiley: New York, 1980; p 292.
2. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 770.

EXPERIMENT 19 PREPARATION OF 4-METHYLBENZOYL CHLORIDE

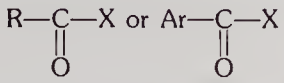
Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Mortar and pestle	(0.10)
Simple distillation	(7.2)
Trapping gases	(0.7)
Heating	(0.5)
Storing	(0.12)
Labeling	(0.13)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Organic qualitative tests	(Q7.1, Q7.2)

INTRODUCTION

Acyl halides are often used as chemical intermediates in chemical proceses. That is, they are synthesized not as final products, but as intermediate products along some synthetic route. An acyl halide has the general structure



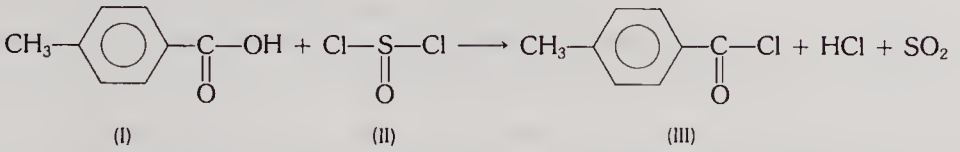
wherein R and Ar are alkyl and aryl, respectively, and X is Cl, Br, or I. The acyl group is all of the molecule except the halogen.

The procedure described in this experiment is written for the synthesis of 4-methylbenzoyl chloride. However, it is a generally useful method for making many acyl chlorides.

E19.1 DISCUSSION OF THE PREPARATION

Acyl halides make good intermediates for synthesis of acid derivatives because the halide, being only weakly basic, is a very good leaving group.

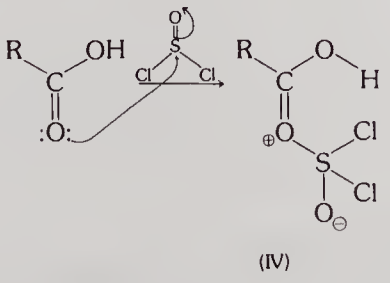
To convert 4-methylbenzoic acid (I) to 4-methylbenzoyl chloride (III) you will use the reagent thionyl chloride (II):



(I) (II) (III) (E19-1)

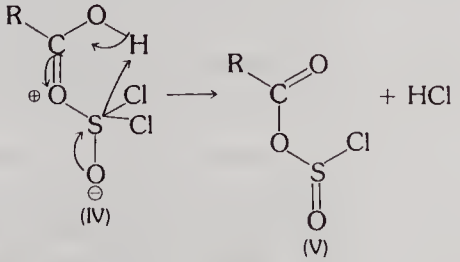
This reagent is extremely reactive and the conversion readily takes place. You could also use phosphorus trichloride or phosphorus pentachloride, but they yield viscous liquid inorganic byproducts, whereas thionyl chloride produces only gaseous byproducts which are easy to remove from the reaction mixtures.

A mechanism that accounts for the reaction is as follows:



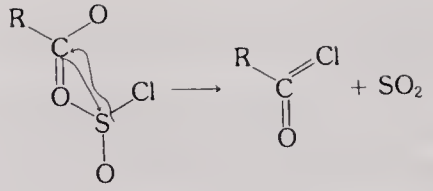
(IV) (E19-2)

Notice in particular the pseudo six-member ring in the ion (IV) which holds hydrogen and chlorine at just the right distance from each other for a correctly oriented and sufficiently forceful collision and subsequent loss of HCl, one of the gaseous byproducts:



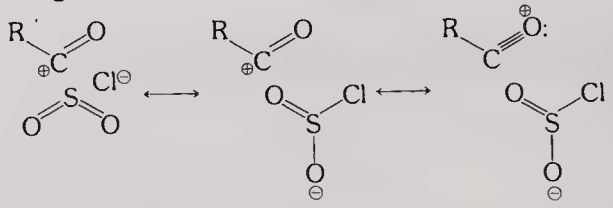
(IV) (V) (E19-3)

Compound (V) next decomposes, yielding the product acyl chloride and the second gaseous byproduct, sulfur dioxide:



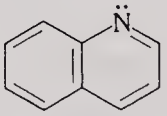
(E19-4)

It might appear that (V) does not have the reactant atoms in close enough proximity to each other for a facile rearrangement as indicated in equation E19-4. However, chlorine is actually closer to carbonyl than it appears: First, sulfur is a large atom and the O—S—Cl bond angle can therefore be less than 120°; second, the C—O single bond must be very weak and perhaps already broken prior to the transfer of chloride to carbonyl. Indeed, the existence of a closely associated ion pair has been postulated for reactions of this type. We should expect such an ion pair to have a resonance hybrid structure related to the following resonance forms as well as to structure (V):



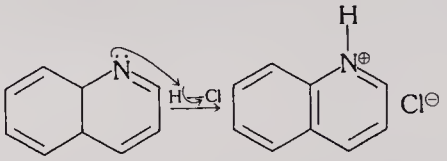
(VI) (VII) (VIII)

Thionyl chloride which has been exposed to moisture in the air contains acidic materials like SO_2, HCl, H_2SO_3, and HOSOCl. You can remove these compounds by distilling the thionyl chloride from a high boiling base like quinoline (IX)



(IX)

The nonbonding electrons on quinoline's nitrogen effectively scavenge protons from the acidic compounds, creating nonvolatile salts which do not distill with the thionyl chloride:



(E19-5)

Quinoline, with a boiling point of 238 °C, also will not distill over with the thionyl chloride at 79 °C.

E19.2 EXPERIMENTAL PART

Purification of thionyl chloride. Put 10 g of thionyl chloride, 1.5 ml of quinoline, and a boiling chip into a 25-ml round-bottom or distillation flask assembled for simple distillation. Protect the receiver from moisture in the air by attaching a recently cleaned, oven-dried, and charged drying tube. Slowly distill the thionyl chloride from the quinoline, collecting all of the fraction that comes over at 75–80 °C. Keep the distillate protected from moisture until ready for use.

Preparation of 4-methylbenzoyl chloride. Powder 25 mmoles of 4-methylbenzoic acid and dry it in an oven at about 80 °C for approximately 15 min. Put the dry acid in a dry 25-ml round-bottom flask and add 50 mmoles of thionyl chloride and a boiling chip. Attach a reflux condenser to the flask, a drying tube to the top of the condenser, and an acid trap to the drying tube. Using a steam or hot water bath, reflux the mixture gently for about 20 min, or until the evolution of HCl and SO_2 appear to have stopped. Test the vapors issuing from the top of the condenser at the beginning of the reaction

and again later to compare how quickly and to what extent blue litmus turns red. Acid gases will be in the condenser long after the reaction is done, however; so you must not think the reaction is incomplete simply because the condenser atmosphere is acidic. If you think the reaction is complete, gently blow out the gases from the flask end of the condenser with clean, dry air; then after a minute test for acid at the top of the condenser.

It is advisable to wear gloves while working with thionyl chloride and acyl chlorides. All work with the reagents of this experiment should be conducted in a hood. Acyl chlorides are lachrymaters and can cause serious chemical burns.

Workup. Cool the flask enough to handle it; then detach the condenser, trap, and drying tube. Discard the trap water. Reassemble the apparatus for simple distillation with a vacuum adapter attached to the condenser and a receiver flask attached to the bottom of the adapter. Have a second, tared receiver flask handy. Distill the contents of the flask slowly. A first fraction boiling at 70–80 °C should come over first. Put this fraction in a thionyl chloride recovery container. The temperature should then rise rapidly to about 220 °C, which is the boiling point of the product. Remove the condenser and drain it thoroughly; then rinse it with propanone and dry it with a gentle stream of air. Reassemble the apparatus, install the tared receiver, and slowly distill the product, collecting the fraction between about 218 and 222 °C. Keep this product unexposed to moisture. Weigh the receiver flask with acid chloride and calculate the percent yield. △△ Store the product in a container protected from moisture. It is best to use the product reasonably soon after preparation.

Analysis. As directed by your instructor, obtain the refractive index, IR, and NMR spectra, and perform organic qualitative wet analyses (Part III).

Writing the discussion. Discuss the identity and purity of the product as determined by the analyses performed. Using Techniques 16, 17, and 18, discuss whether your spectra identify the product. Compare your NMR spectrum with that of Figure E19.1. Discuss the yield, where losses might have occurred, and how it could be improved.

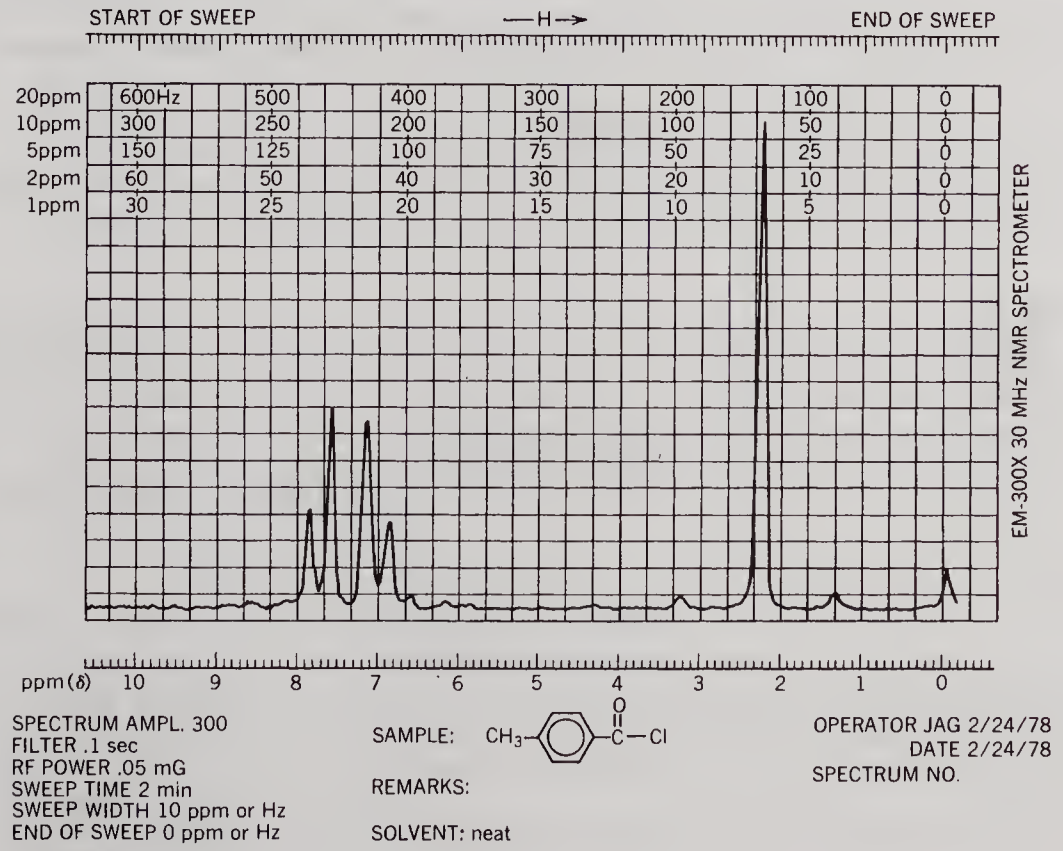


FIGURE E19.1 NMR spectrum of *p*-methylbenzoyl chloride.

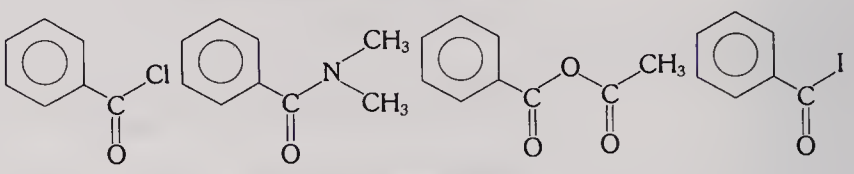
E19.3 EXERCISES

Prelaboratory

1. Calculate the number of grams of 4-methylbenzoic acid and milliliters of thionyl chloride to use. The density of thionyl chloride is 1.65 g/ml.
2. What equipment will you use to powder the acid?
3. Make and label a rough sketch of the apparatus you will use for the reflux period; a second one for the distillation step.
4. What heat source do you suggest for the distillation step?
5. What is the small first fraction that is likely to come over at 70–80 °C before the acid chloride distills?
6. If the temperature does not rise to about 220 °C after the 70–80 °C forerun, but drops instead, what slight modification of your procedure would be necessary?
7. Review the hazards associated with heating (Section 0.5) and distillation (Section 7.2).

Postlaboratory

1. Based on the basicity of the leaving group, arrange the following in order of reactivity with a nucleophile colliding with the carbonyl carbon:



2. Would you expect acyl halides to be medicinally useful? Explain.
3. Write a mechanism analogous to that of equations E19-2 to E19-4 showing how PCl_3 makes the same conversion and produces the byproduct $OPCl_2$.
4. Draw the resonance hybrid of structure (V), (VI), (VII), and (VIII) which represents the closely associated ion pair that decomposes to give the acyl chloride.

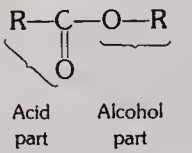
REFERENCE

1. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 792.

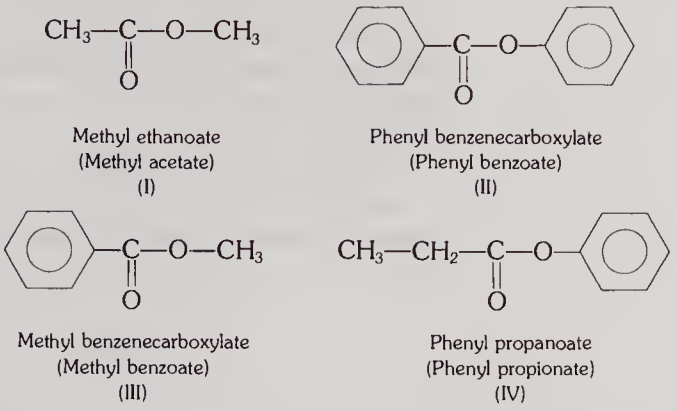
X

ESTERS

Esters are compounds that are combinations of carboxylic acids and alcohols, having the general structure



wherein R and R^1 are alkyl or aryl groups. Esters can be aliphatic (I), aromatic (II), or a mixture of the two (III, IV):



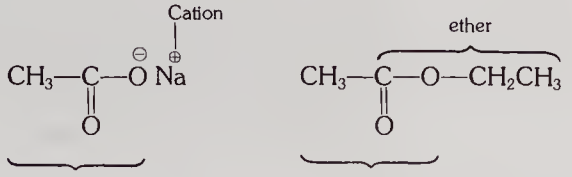
Methyl ethanoate
(Methyl acetate)
(I)

Phenyl benzenecarboxylate
(Phenyl benzoate)
(II)

Methyl benzenecarboxylate
(Methyl benzoate)
(III)

Phenyl propanoate
(Phenyl propionate)
(IV)

The word *ester* is a combination of two German words *Äther,* meaning ether, and Säure, meaning acid. This is because esters were originally considered to consist of an ether combined with a carboxylic acid as an organic salt. Compare sodium acetate (V) and ethyl acetate (VI):



(V) (VI)

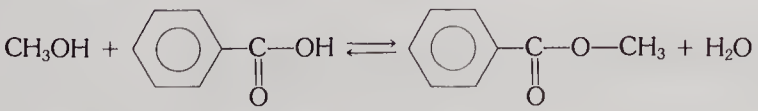
At one time esters were called ethereal salts. Notice that we name esters in the same manner as we name salts, employing the -ate suffix used in inorganic nomenclature for salts of acids ending with -ic.

Esters are commonly occurring natural products, and are biochemically important especially as major constituents of our bodies in the form of fat. The lower molecular weight esters generally have pleasant odors, and are constituents of many flowers and fruits, imparting to them some or all of their characteristic odors and flavors.

In this section we shall examine the preparation of aliphatic esters (Experiment 20) and aromatic esters (Experiment 21), and the saponification of an ester to make soap (Experiment 22). Experiments 7, 18, 44, and 46 also involve esters, as do Technique 7 and a section of qualitative analysis in Part III.

DISCUSSION OF ESTERIFICATION

The combining of an alcohol with an acid or one of its derivatives is called **esterification**. Esterification is a **condensation reaction**, a reaction that yields a small byproduct molecule such as water:



(X-1)

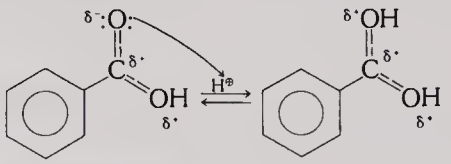
We call the combining of alcohol with the acid itself (rather than a derivative), as in equation X-1, **direct esterification** or **Fischer esterification**. In direct esterification, a stoichiometric ratio of reactants products an equilibrium which is not far enough to the right to produce a high yield. To obtain a higher yield, it is necessary to shift the equilibrium.

In Experiments 12 and 14 equilibrium was shifted by distilling the product as it

formed. This approach will not work for esterification because the boiling point of the ester is higher than that of the alcohol.

Fischer esterifications employ two methods for shifting the equilibrium: first, use of a large excess of the less expensive reagent, the alcohol or acid; second, use of a desiccant. The experimenter often uses concentrated sulfuric acid to scavenge the byproduct water and to a considerable extent remove it from participating in the reverse reaction, the hydrolysis of the ester.

Sulfuric acid also doubles as a catalyst. In absence of catalysis, direct esterification is very slow. The catalytic action of sulfuric acid is due to protonation of carboxyl oxygen, thereby making carboxyl carbon considerably more positive:

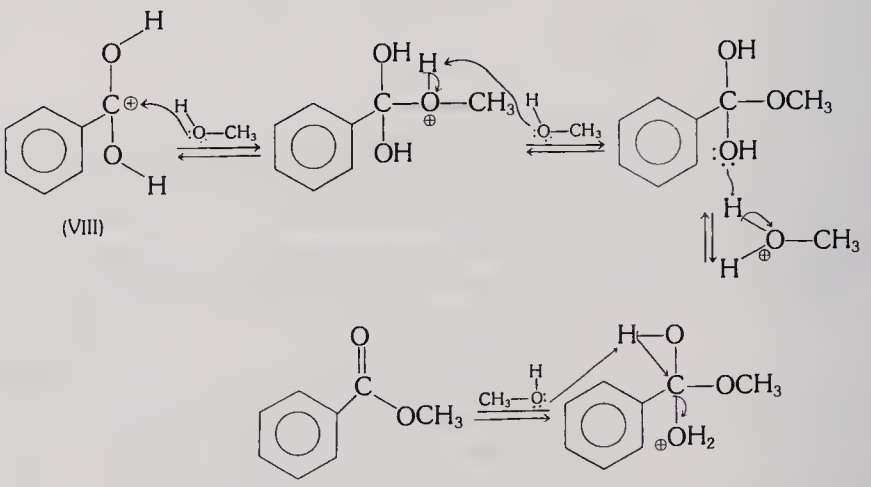


(X-2)

(VII) (VIII)

You can see that the carboxyl carbon of resonance hybrid (VIII) is much more positive than the carboxyl carbon of structure (VII), which has a positive charge only because of charge *separation*. The greater positive character increases the fraction of collisions with energy equal to, or in excess of the activation energy. That is, more collisions between the oxygen of the alcohol and carboxyl carbon are effective because it is easier to form new bonds when one species is highly charged.

The mechanism of Fischer esterification is



(X-3)

(VIII)

The reason for relatively long reflux periods relates directly to orientation, energy, and collision frequency rate factors. The collisions in the rate-determining step must have the alcohol oxygen oriented toward carboxyl carbon when collision occurs. The collision must be of sufficient energy than a new electron pair bond forms and the pi bond breaks. Not all collisions are properly oriented, and not all collisions are of sufficient energy. Esterification is a difficult enough process that many collisions must occur in order to get one that is productive. The long reflux, then, is simply a matter of allowing enough time for effective collisions so that maximum conversion to product can take place.

EXPERIMENT 20 PREPARATION OF ISOAMYL ACETATE

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook (1)

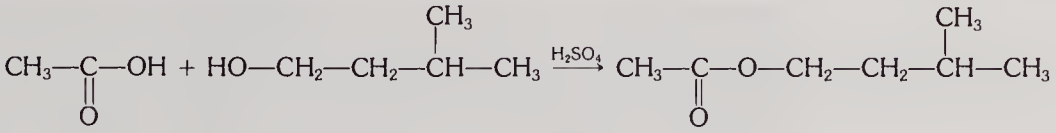
Glassware	(0.3)
Mixing	(0.4)
Reflux	(0.5)
Extraction	(6.2)
Testing pH	(0.11)
Drying	(2.1)
Simple distillation	(7.2)
Boiling points	(3.5)
Refractometry	(13.3)
GLC	(11.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Wet analysis	(Q8.6, Q9.5)

INTRODUCTION

Isoamyl acetate (IUPAC 3-methyl-1-butyl ethanoate) is often referred to as banana oil because it has an odor that is quite similar to that of bananas. This compound is also interesting because it is synthesized by honey bees, and when it is released from the bee's stinger it induces other nearby bees to sting also.

E20.1 DISCUSSION OF THE PREPARATION

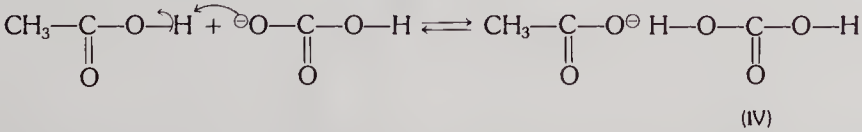
In this Fischer esterification, acetic acid (I) condenses with isoamyl alcohol (II) to make isoamyl acetate (III):



(E20-1)

(I) (II) (III)

The carboxylic acid is used in excess for two reasons: First, it is the less expensive of the two reagents and second, excess of acid is easier to remove during workup. At the end of the reaction two phases are present: an aqueous layer and the ester layer. Because acetic acid is completely miscible in water, an aqueous wash separates most of it from the ester, but a small amount is also dissolved in the ester layer. In a second wash with bicarbonate, remaining acid reacts with bicarbonate:



(E20-2)

(IV)

The salt of the acid is water soluble and remains in the aqueous phase. Decomposition of carbonic acid (IV) to carbon dioxide and water continually shifts the equilibrium toward the right, and the ester becomes free of acid. Unreacted alcohol also largely dissolves in water during the aqueous washes because its water solubility is 2.7 g/50 ml at 22 °C. In fact, its removal is complete enough that the final product purification step requires only simple distillation. If it were not so complete, fractional distillation would be necessary because the boiling points of iosamyl alcohol (130 °C) and the ester (142 °C) are quite close.

Inorganic salt in the final wash is useful not so much to reduce the solubility of the ester in the aqueous layer (0.16 g/100 ml) but to help prevent formation of an emulsion.

E20.2 EXPERIMENTAL PART

Preparation of isoamyl acetate. Into a 50-ml round-bottom flask put 4.4 g of isoamyl alcohol (IUPAC 3-methyl-1-butanol), 6.0 g of glacial acetic acid (IUPAC ethanoic acid), and a couple of boiling chips. Swirl the mixture to mix it; then cautiously add, with swirling, 1.2 ml of concentrated sulfuric acid. Assemble the flask into a reflux apparatus and reflux the mixture for 1 hr.

It is advisable to wear rubber gloves while working with concentrated sulfuric acid. Take care not to spill the organic materials into a heating mantle. Remove the flask from the mantle before charging it.

Workup. Cool the flask and pour its contents into a separatory funnel. Pour 25 ml of cold water into the flask, swirl it to rinse the flask, and then slowly add the mixture to the separatory funnel. Stopper the funnel and swirl it to mix the contents. Vent the funnel, then shake it thoroughly. Allow the phases to separate, then drain off and discard the aqueous layer.

Extract the organic layer with 10 ml of 5% aqueous sodium bicarbonate. Add the solution slowly; then, with the funnel unstoppered, swirl the mixture until CO_2 bubbles stop forming. Stopper the funnel and shake it, venting it frequently, until pressure no longer builds up inside. Drain off the *aqueous* layer and check it for acidity. If the layer is acidic to litmus, repeat the bicarbonate wash of the organic phase. Next, wash the organic layer with 10 ml of 10% aqueous sodium chloride. Wash carefully so as to avoid emulsion formation. △

Dry the ester over anhydrous magnesium sulfate until the liquid is clear. △△

Distill the ester in a simple distillation apparatus, collecting in a tared flask the fraction coming over between 135 and 143 °C. △△

Add the water to the separatory funnel cautiously because of the sulfuric acid present.

Do not stopper the separatory funnel during the bicarbonate wash until swirling has eliminated most of the gassing. Then vent the funnel often during shaking.

Analysis. As directed by your instructor, obtain an IR spectrum, a GLC chromatogram using a dinonyl phthalate or similar column at about 110 °C, and refractive index of the product; and perform qualitative wet analysis tests (Section III) on the product. Turn in the product in a labeled vial. △△

Writing the discussion. Discuss the percent yield relative to the esterification process, mole ratio of reactants, and your technical performance. Consider also the identity and

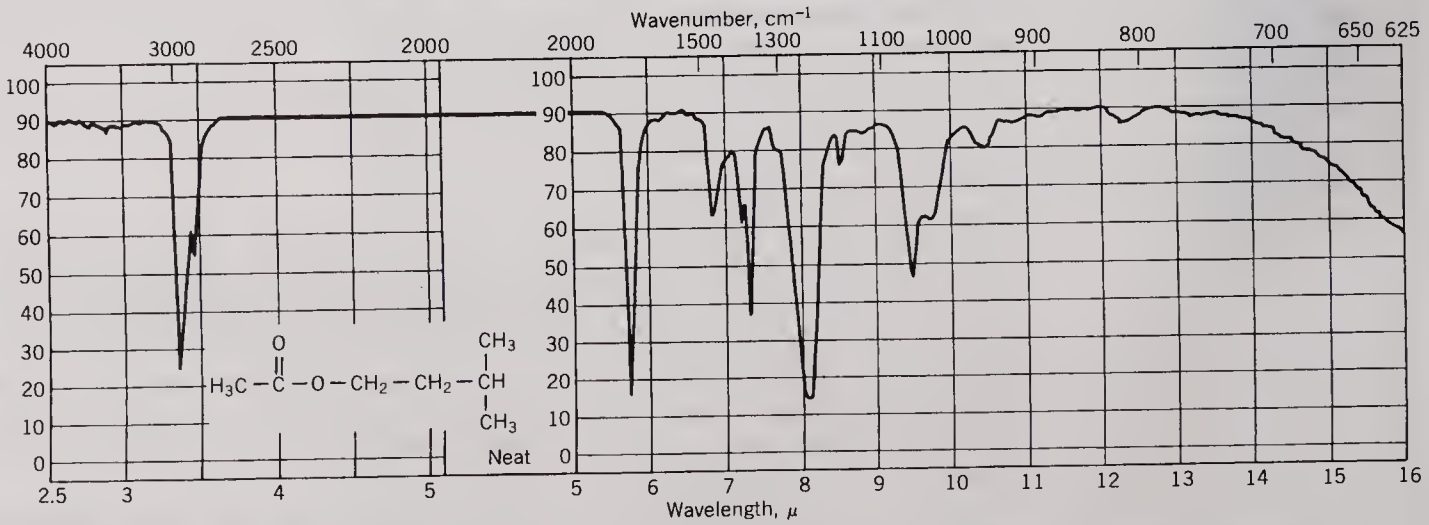


FIGURE E20.1 IR spectrum of isoamyl acetate. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

purity of the product as determined by analysis. Compare your IR spectrum with that of Figure E20.1.

E20.3 EXERCISES

Prelaboratory

1. Make a rough sketch of the apparatus you will use during reflux.
2. What is the purpose of the first aqueous wash?
3. Make a flow diagram of the separatory funnel operations.
4. How will you tell when the acids have all been removed during workup?
5. Why is 20% sodium chloride used for a wash rather than just water?
6. Review hazards associated with extraction (Section 6.2), heating reactants (Section 0.5), and distillation (Section 7.2).

Postlaboratory

1. Calculate the amount of 3-methyl-1-butyl ethanoate that would dissolve in 10 ml of water at 25 °C. Demonstrate that the loss would be insignificant based on 80.0% yield of ester.
2. The equilibrium constant for conversion of ethanol and ethanoic acid to ethyl ethanoate is 4. What would be the percent conversion to ester if equal amounts of reactants are used?

$$K_{eq} = \frac{[\text{ester}][\text{water}]}{[\text{acid}][\text{alcohol}]} = 4$$

3. *Emil Estair* has asked you whether ethyl acetate could be prepared using acetic anhydride and ethyl alcohol along with a zinc acetate catalyst. What is your response? Defend your position, using a balanced equation and a mechanism in your discussion.

REFERENCE

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 383.

EXPERIMENT 21 PREPARATION OF METHYL BENZOATE AND METHYL SALICYLATE

Time Required: 3 hr for methyl benzoate
6 hr for methyl salicylate

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Glassware	(0.3)
Reflux and heating	(0.5)
Cooling	(0.5)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Vacuum distillation	(7.11)
NMR	(16.4, 16.5)
IR	(15.4)
UV	(14.4)
Refractive index	(13.3)

INTRODUCTION

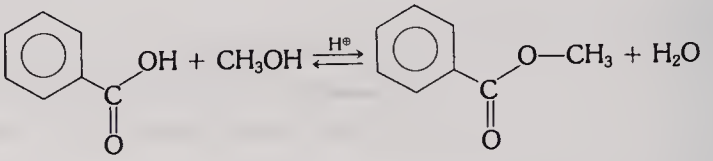
Methyl benzoate is an aromatic ester with a pleasant fragrance. Because it has a faintly fruity odor and is reminiscent of ylang-ylang, it is sometimes used in a blend of fragrances for perfumes.

Methyl salicylate (IUPAC methyl 2-hydroxybenzenecarboxylate) is also known as oil of wintergreen because it was from wintergreen that it was first extracted in 1843. Like aspirin, methyl salicylate has analgesic (pain-reducing) and antipyretic (temperature-reducing) properties. Indeed the salicylic acid from which the ester is made is the same acid used to prepare aspirin; and it is the structure of the acid which is responsible for these medicinal properties. Methyl salicylate is commonly used in liniments because of its skin-permeating capabilities, the warming sensation due to the acidic phenolic OH, and its pleasant odor. It is also used in foods for its wintergreen flavor.

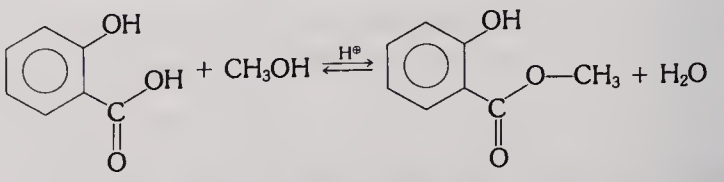
E21.1 DISCUSSION OF THE REACTION

To best understand this discussion you should first read the introduction to esters in Section X.

The preparation of methyl benzoate (IUPAC methyl benzenecarboxylate), (V), or methyl salicylate (IUPAC methyl 2-hydroxybenzoate), (VI), by direct (Fischer) esterification involves condensing absolute methanol (methanol free of other substances) with the corresponding acid:



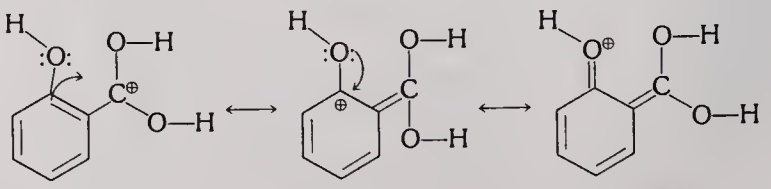
(E21-1)



(E21-2)

These preparations are very similar to that of Experiment 20. However, there are some subtle differences in approach. In these esterifications, the alcohol is less expensive than the acid; so it is the reactant used in excess.

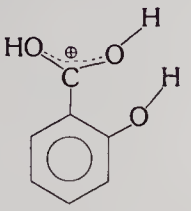
Whereas preparation of methyl benzoate requires a reflux period of only 3 hr, a maximum yield of methyl salicylate requires at least 6 hr. We can rationalize the longer reflux period for preparing methyl salicylate by considering electronic and steric effects. Let us first look at the electron donor characteristic of the phenolic hydroxyl in the protonated (catalyzed) acids:



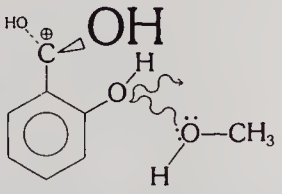
(VII)

Because of electron donation from oxygen, structure (VII) must have less positive character at carboxyl carbon than would the corresponding structure for benzoic acid. Therefore, the formation of a bond from the oxygen of methanol to the carboxyl carbon is more difficult and the activation energy is higher. Now let us consider the steric effect of an *ortho* hydroxyl. The collision of methanol with the partially positive carboxyl carbon

occurs perpendicular to the plane of the two hydroxy functions on that carbon. Resonance stabilizes the protonated acid in planar structures like that of (VII), and planarity is further enhanced by a pseudo six-member ring:



Nevertheless, the double bond character between carboxyl carbon and the phenyl ring is neither as complete nor as strong as that of a carbon-carbon double bond; and at the temperature of reflux rotation is not *completely* inhibited. Therefore, in two conformations during rotation the phenolic hydroxyl inhibits collision of methanol with carboxyl carbon from one side:



Phosphoric acid is used as the catalyst rather than the more commonly used sulfuric acid because the latter acid is an oxidizer which at reflux temperature tends to attack the organic compounds, degrading them to black tar and char.

During workup in the separatory funnel, you will add tetrachloromethane to the product mixture. Its function is twofold: First, it helps to make the separation of ester from the aqueous phase more complete, an aid more important for methyl salicylate than methyl benzoate; and second, it helps to prevent formation of emulsions.

During workup, you can readily remove excess methanol and phosphoric acid by aqueous washes in which both are infinitely miscible. Benzoic acid and salicylic acid are not very soluble in cold water but you can easily remove them by changing them to water-soluble medium salts with sodium bicarbonate washes.

E21.2 EXPERIMENTAL PART

The preparation of methyl benzoate and methyl salicylate are the same except for the reflux periods.

Preparation of the esters. Mix 20 mmoles of salicylic acid (IUPAC 2-hydroxybenzenecarboxylic acid) or benzoic acid (IUPAC benzenecarboxylic acid) and 12 ml of absolute methanol (methyl alcohol) in a 50-ml round-bottom flask. Cautiously add 2.4 ml of concentrated phosphoric acid by allowing it to run down the wall of the flask. Swirl the contents gently to mix the reactants thoroughly. Do not be concerned if all solid does not dissolve at this point. Add a boiling chip. Attach a condenser vertically to the flask. Use hose clamps, or wire the water hoses to the condenser and spigot. Using an oil bath, steam bath, or a heating mantle and variac, reflux the mixture for 3 hr. It does not hurt to reflux them longer. Use no more heat than necessary to effect gentle refluxing. You can shorten the reflux period at the expense of yield. You need not attend to the system during reflux, but can occupy yourself with other work that needs to be done. If your laboratory suffers from water pressure fluctuation, an occasional check of the condenser water flow would be appropriate.

It is recommended that rubber gloves and goggles be worn while handling solutions containing concentrated phosphoric acid.

Add phosphoric acid to the reaction mixture with caution so as to avoid spills of

acid or a sudden exotherm, causing boiling and sudden ejection of the acidic mixture. Clean up acid spills promptly.

Be careful not to spill methanol on a hot plate or into a hot heating mantle. Charge the flask in an area away from hot equipment.

Since the reflux period is a long one, clamp or wire on water hose connections, especially if not in attendance during the reflux period.

Workup. At the end of the reflux period, cool the reaction mixture to room temperature, perhaps in a cool water bath to expedite the process. Add 20 ml of water to the mixture, swirl it, and pour it into a separatory funnel. Rinse the flask with 8 ml of tetrachloromethane (carbon tetrachloride) and pour the rinse into the separatory funnel. Mix the contents of the funnel thoroughly; then let the layers separate. With stopper removed, drain off the lower CCl_4 layer and put the upper layer into a methanol recovery container. Put the organic layer back into the funnel, wash it with 20 ml of 5% aqueous $NaHCO_3$, drain off the organic layer, then discard the aqueous layer. Wash the organic layer with 10 ml of water, drain it into a small Erlenmeyer flask, and dry it over anhydrous magnesium sulfate for 15–20 min. Gravity filter the solution into an appropriate-size distilling flask. Rinse the magnesium sulfate residue in the filter with 5 ml of tetrachloromethane and add the rinse to the flask. △△

Using a simple distillation apparatus, distill off the tetrachloromethane and put it in its assigned recovery container. Distill the ester *in vacuo*, transferring to a smaller flask if necessary. The esters can also be distilled at atmospheric pressure with a flame but you have to be very careful to avoid decomposition, especially for methyl salicylate. The normal boiling point for methyl benzoate is 198–199 °C, and that of methyl salicylate is 222 °C.

Do not allow pressure to bulid up in the separatory funnel during the bicarbonate wash.

Analysis. As directed by your instructor obtain UV, IR, and NMR spectra, and the refractive index, and results from wet analysis of esters (Part III). The NMR spectrum of methyl benzoate is found in Figure 16.19. Methyl benzoate in methanol absorbs in the UV at 280 nm (ε 686), 272 nm (ε 830), and 228 nm (ε 10233); and methyl salicylate in methanol at 305 nm (ε 5300) and 237 nm (ε 11,200).

Writing the discussion. The following items are all pertinent to this project. Pick out the most appropriate and include them in your discussion: structure of esters, technique of vacuum distillation, potential for using methyl salicylate and/or methyl benzoate as sunscreens, medicinal uses of methyl salicylate, comparison of your spectra with those of Figures E21.1, E21.2, and E21.3, equilibria and esterification, the success or failure of your final distillation, your product yield related to workup, why a condenser is air-cooled when the vapors are above 150 °C, the inspection of glassware prior to vacuum distillation, the identity and purity of the product as determined by analysis.

E21.3 EXERCISES

Prelaboratory

1. Why does the presence of CCl_4 help to make a more complete separation in the separatory funnel?
2. Which layer in the separatory funnel always contains the ester?
3. Why is the ester solution washed with aqueous sodium bicarbonate in the separatory funnel?
4. Why does a water wash precede the wash with aqueous sodium bicarbonate?
5. Why must you carefully mix and continually release pressure when washing with aqueous sodium bicarbonate?

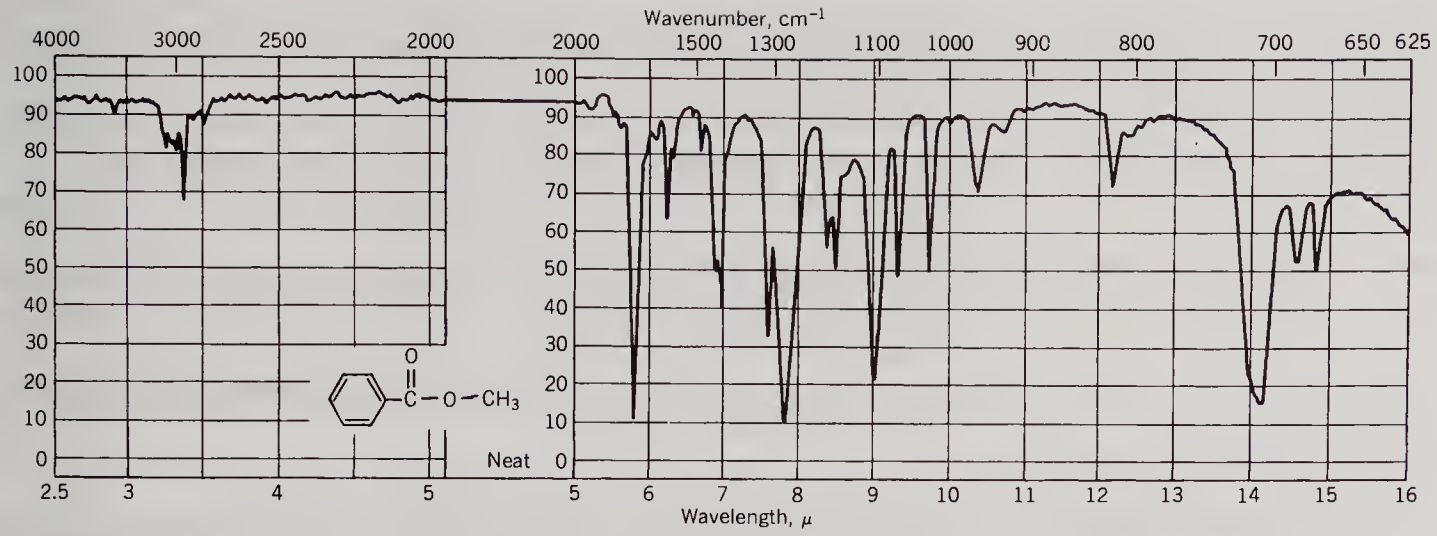


FIGURE E21.1 IR spectrum of methyl benzoate. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

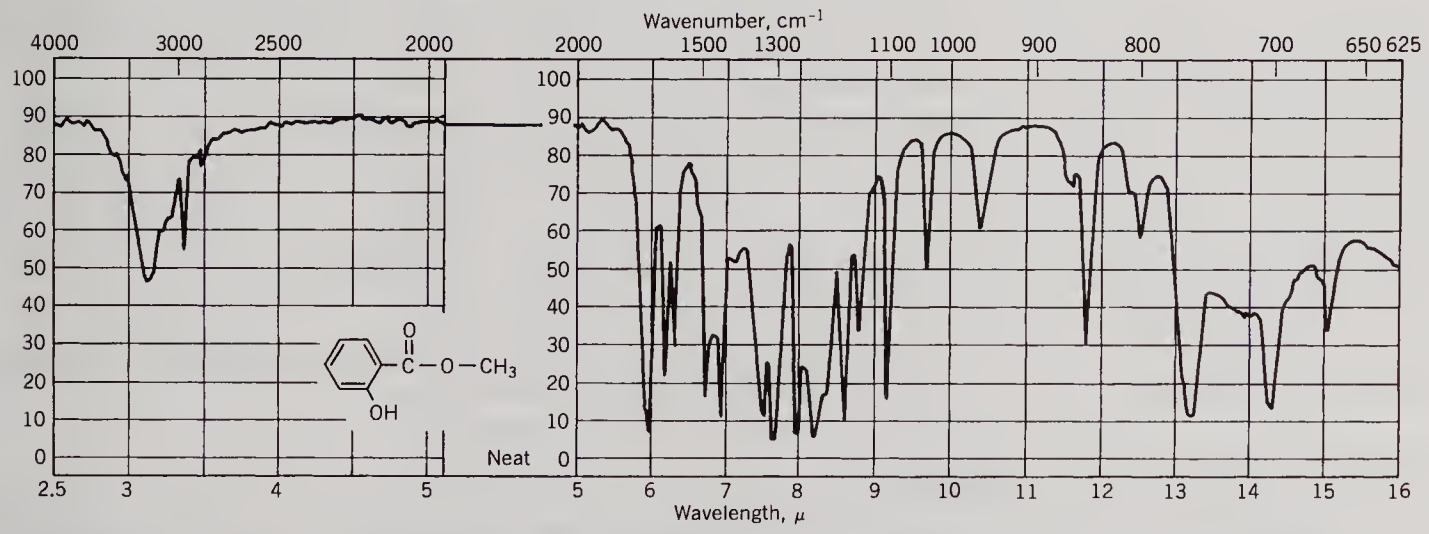


FIGURE E21.2 IR spectrum of methyl salicylate. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

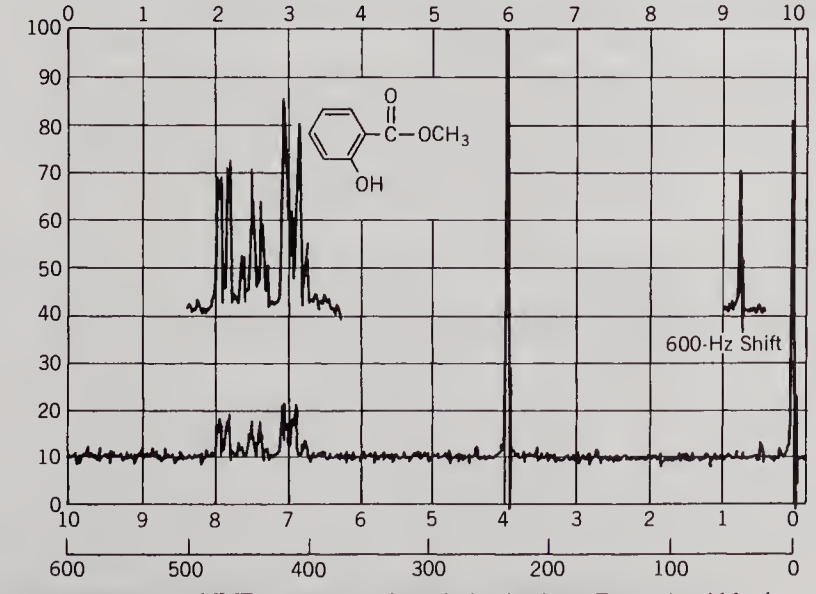
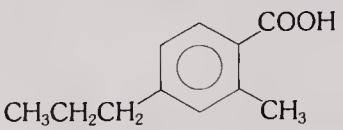


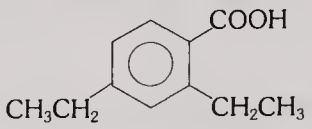
FIGURE E21.3 NMR spectrum of methyl salicylate. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

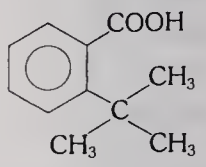
6. What two acidic materials are removed during the aqueous sodium bicarbonate wash? Write the equations showing the chemical reactions that occur during the bicarbonate wash.
7. Prepare a flowchart for the workup of the ester from end of reflux to final distillation.
8. List the clean, dry equipment you will use for the final distillation step.
9. What wall thickness will you use for vacuum line hose of your vacuum distillation apparatus?
10. When asked whether a water-cooled, or air-cooled, condenser should be used in the final distillation, *Sally Cylate* said definitely air-cooled because the distillate would be over 150 °C. What do you think?
11. Review hazards associated with heating reactants (Section 0.5), extraction (Section 6.2), and distillation (Section 7.11).

Postlaboratory

1. *Melanie Nisbrown,* trying to circumvent the long reflux period associated with direct esterification of 2-hydroxybenzenecarboxylic acid, decided to let 2-hydroxybenzenecarbonyl chloride react with methanol. Critique this idea.
2. *Ben Zoate* was given a substance known to be either methyl *m*-methoxybenzoate or methyl *p*-methoxybenzoate. Discuss how he could identify the compound using UV spectroscopy.
3. Arrange the following isomers in order of reactivity with CH_3OH/H^+. Explain.







4. The esterification of Experiment 21 is reversible. Outline a procedure for determining the equilibrium constant, K_{eq}, for this reaction.

REFERENCE

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; pp 781, 782.

EXPERIMENT 22 SAPONIFICATION OF ESTERS—SOAP MAKING

Time Required: 2–3 hr

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Vacuum filtration	(4.3)
Stirring	(0.4)
Labeling	(0.13)
IR	(15.3, 15.4)

INTRODUCTION

Saponification is base-promoted hydrolysis of esters. The word is derived from the Latin word *sapo,* which means soap.

Saponification of fatty acid esters in animal and vegetable fat to make soap has been known at least as far back as the days of the Roman Empire. Until the nineteenth century, soaps were made by boiling the fats with wood ashes, which contain considerable amounts of potassium carbonate which can act as a base to promote ester hydrolysis. The resulting salts of fatty acids are known as soaps. Potassium salts and unsaturated fats give rise to soft, more liquid soaps, whereas sodium salts and saturated fats yield harder soaps.

The preparation of soap from animal fat is a practical example of one of the many ways that chemistry provides useful products from materials of natural origin.

E22.1 DISCUSSION OF SOAPS

Soap is broadly defined as any substance which has soaplike properties, that is, which acts as a detergent, considerably lowers surface tension even in small concentration, and usually foams. This definition includes substances often referred to as detergents. In a more limited sense, **soap** is defined as an alkali metal salt of a carboxylic acid containing from 10 to 18 carbons.

A soap consists of a molecule containing a polar group, ordinarily ionized, which is soluble in water, and a nonpolar hydrocarbon portion which is insoluble in water. When very small amounts of soap are put into water, the molecules do not dissolve, but, rather, become concentrated at the water surface with their polar, saltlike ends immersed in the water and with their hydrocarbon chains protruding from the surface. It is this arrangement of soap molecules which accounts for the lowering of surface tension of water and the production of bubbles. If the concentration of soap is increased to some critical point, the mixture becomes turbid because of the formation of colloidal spherical **micelles.** A micelle is a submicroscopic grouping of molecules forming a tiny liquid droplet with the charged groups on the outside and hydrocarbon chains on the inside. See Figures E22.1 and E22.2.

The critical concentration for micelle formation depends on chain length and degree of unsaturation of the hydrocarbon portion of the soap.

The importance of micelles is their ability to act as solvents for oil-soluble materials. When a soap micelle dissolved in water comes in contact with an oil molecule, it absorbs the oil from an aqueous phase into its interior by van der Waals interactions in much the same way that distribution of an organic molecule occurs in a separatory funnel containing water and an organic solvent as immiscible phases. In this way, soap micelles in effect make oils and greases soluble in water and permit them to be washed from skin and clothing.

To be effective in solubilizing oils and greases, micelles must be composed of soaps containing 10 to 18 carbons. Below 10 carbons there is insufficient van der Waals interaction to solubilize fats, and above 18 carbons the soap is too insoluble in water to form a sufficiently concentrated colloidal suspension.

E22.2 SOAP MAKING

Fats and oils are glycerol (1,2,3-propanetriol) esters of fatty acids, such as glyceryl tristearate,

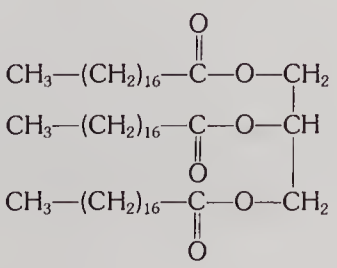


FIGURE E22.1 "Thank goodness *my cell* is where the polar part is outside and the hydrocarbons go inside."

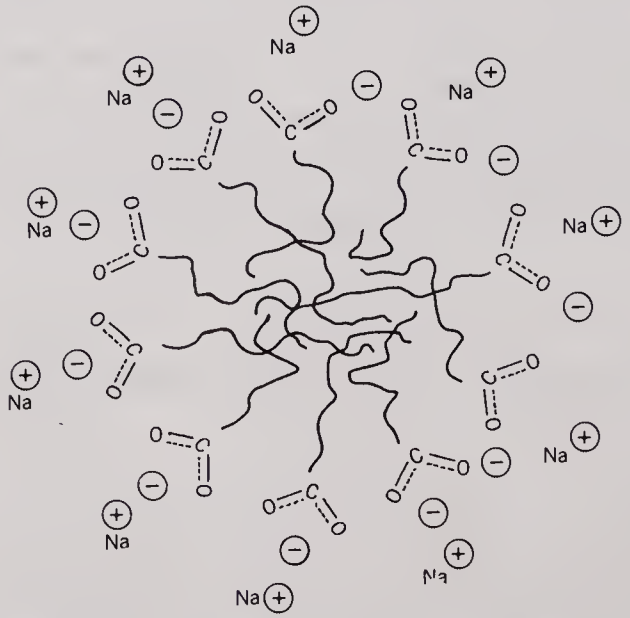
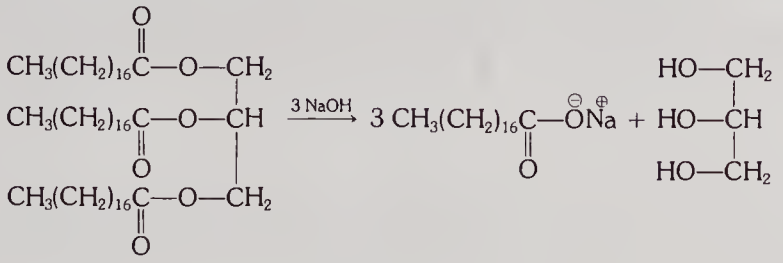


FIGURE E22.2 Micelle structure of a soap in water.

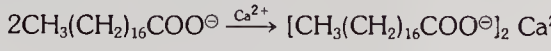
Saponification to make soap is simply the base-promoted hydrolysis of the ester:



(E22-1)

The customary practice of using excess base makes the resulting soap strongly basic. Commercial soaps contain generally less than 0.1% alkali. We can remove excess base by aqueous wash, but because of the formation of micelles, soap has an appreciable solubility in water, and recovery of the soap requires increasing the ionic strength of the solution with sodium chloride so as to salt out the soap.

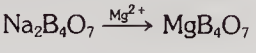
Optional ingredients that are added to bar soaps include zinc oxide to make the soap whiter, lanolin to act as an emollient, pumice to help remove heavy soil by abrasion, and perfume. Borax is sometimes added to help prevent formation of a soap precipitate (I) by hard water ions like Ca^{2+}, Mg^{2+}, and Fe^{3+}:



(E22-2)

(I)

The borax ($Na_2B_4O_7$) removes the hard water ions from the water by reacting with them itself to form the precipitate (II):



(E22-3)

(II)

E22.3 EXPERIMENTAL PART

You will be given 50 g of animal fat like bacon grease, unrendered pork fat, tallow, or lard. When you are finished, you will have a useful product to use in the laboratory. As a perfuming agent, you can use the purified product of Experiment 32 or Experiment 33.

If you are using lard, eliminate the purification step.

Purification of fat. Weigh into a 1000-ml beaker 50 g of animal fat. Add 50 ml of tap water and heat it on a hot plate or over a Bunsen burner until it has boiled about 5 min. Add 25 ml of cold water and allow the mixture to cool until the fat is firm. Make a hole through the fat layer next to the beaker pouring spout and decant the aqueous layer, which now contains water-soluble impurities. Depending on the appearance of the fat, you might need to repeat this step.

Saponification. Slowly add 8 g of NaOH pellets to 50 ml of distilled water. Stir to dissolve the sodium hydroxide, then allow the solution to cool to room temperature.

Push the purified fat down to the bottom of a 1000-ml beaker and melt it with *gentle* heating. While continually stirring, add the alkaline solution. Heat the mixture to 85–90 °C and stir it vigorously until it has attained the texture of *thick* honey. It might require 30 min or more for it to thicken; but have patience—it will become very thick.

Remember that concentrated NaOH can cause severe chemical burns.

Excess heating of the grease will cause it to spatter out of the beaker.

Stir and control heating so that the mixture does not spatter and/or foam out of the flask.

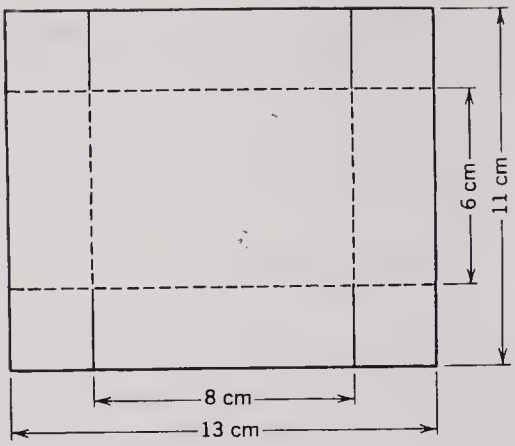


FIGURE E22.3 Soap mold diagram.

Bar soap. To prepare a mold, cut a piece of cardboard to the size specified by the numerical values given in the diagram of Figure E22.3. Mark it as shown; then cut along the solid lines and score the dotted lines so the cardboard will fold easily. Fold it to form a shallow box and staple the corners. Line the box with a clean, damp cotton cloth. Do not use glass, china, or aluminum containers because the excess alkali present in the product will attack such vessels. Heat the saponification mixture to 80 °C and add to it with stirring, optional ingredients in amounts as follows: zinc oxide, USP 0.2 g; lanolin, USP 0.5 g; pumice, USP 5.0 g; perfume 0.5 g; borax, USP 2.0 g. Stir the mixture well and pour it into the mold. Allow it to cure for about a week. △△

Because of excess alkali, you should not use your soap on tender skin or around your eyes.

Soap powder. Boil the honey-thick saponification mixture left over from making the bar soap for an additional ½ hr with occasional stirring and addition of water to make up for loss by evaporation. Next, add 100 ml of 90 °C tap water, and stir the mixture well. Cool it to 40 °C by adding 100 g of ice; then add and dissolve NaCl until precipitation of the soap appears complete. Allow the mixture to cool to 30 °C and collect the soap powder by vacuum filtration. △△ Allow it to dry for a few days; then weigh it. Store it in a labeled bottle.

Analysis. Prepare a KBr pellet or nujol mull of the soap powder and analyze by IR. Look for the presence of a strong asymmetrical stretching band near 1650–1550 cm^{-1} (6.06–6.45 μ) and a weaker symmetrical stretching band near 1400 cm^{-1} (7.15 μ), both of which arise from the carboxylate ion.

Writing the discussion. Discuss (1) the IR spectrum as evidence of product, (2) the physical behavior of the product as you use it, and (3) the percent yield relative to the process used.

E22.4 EXERCISES

Prelaboratory

1. In interest of time conservation, when is a good time to prepare the box into which you will pour the soap?
2. Make a flowchart for Experiment 22, showing the sequence of events which best conserve laboratory time.

Postlaboratory

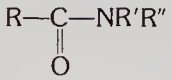
1. Draw a diagram like that of Figure E22.2 to show the micelle structure you would expect for a soap dissolved in a nonpolar solvent like hexane.
2. Suggest a method for casting the soap powder into a bar.

REFERENCES

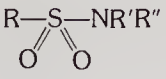
1. Durham, K. *Surface Activity and Detergency*; MacMillan: New York, 1961.
2. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 445.

XI AMIDES

The amides of greatest interest to organic chemists are those of carboxylic acids (I) and of sulfonic acids (II):

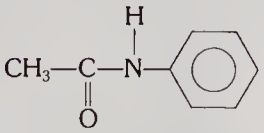


(I)

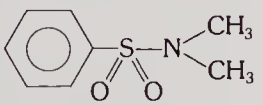


(II)

in which R, R′, and R″ can be alkyl, aryl, or hydrogen. Examples are



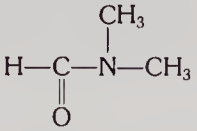
N-phenylethanamide
(*N*-phenylacetamide)
(III)



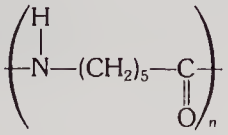
N,*N*-dimethylbenzenesulfonamide
(IV)

Most unsubstituted amides are solids. The *N*-alkyl amides of aliphatic acids usually are liquids and make excellent solvents for many organic compounds.

There are hundreds of useful amides, some of which are biologically active. *N*,*N*-Dimethylformamide (V) is an important solvent, nylon 6 (VI) is a polymeric amide, as is any protein, including silk:

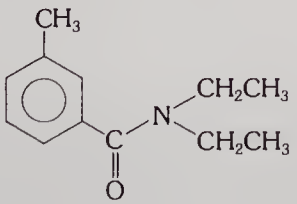


(V)

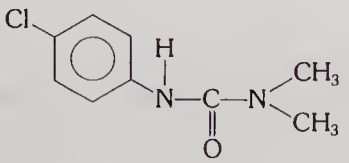


(VI)

N,*N*-Diethyl-*m*-methylbenzamide (VII) is an important insect repellent and monuron (VIII) is a herbicide:

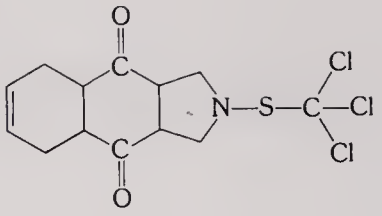


(VII)

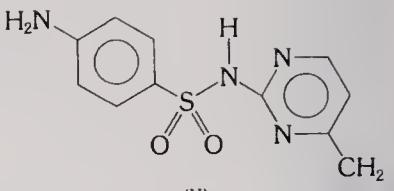


(VIII)

The fungicide, captan (IX), is actually an imide rather than an amide. Among the many sulfa drugs is sulfamerazine (X), used to treat urinary tract infections.



(IX)



(X)

There are three syntheses of amides in this section, one of which leads to a sulfa drug and another to an insect repellent. You will also encounter amides in Experiments 4, 27, and 45.

EXPERIMENT 23 PREPARATION OF ACETANILIDE

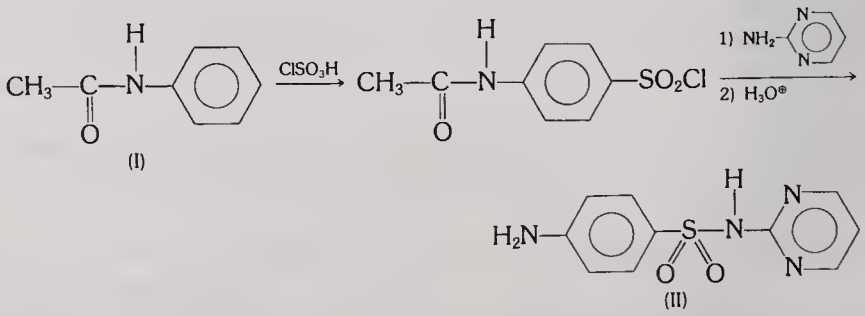
Time Required: 2 hr

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Heating	(0.5)
Cooling	(0.5)
Filtering	(4.2)
Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Characterization tests	(Q8.7)

INTRODUCTION

Acetanilide (IUPAC *N*-phenylethanamide), (I), is a moderately important chemical intermediate. In the mid-1940s it was synthesized in quantities up to six million pounds per year primarily because of its use in preparing sulfa drugs like sulfadiazine (II):



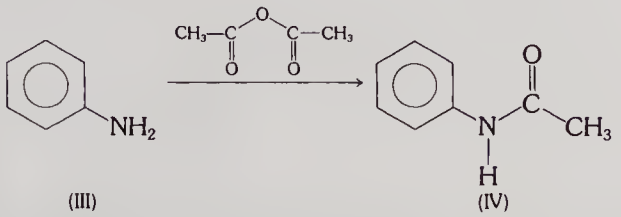
(I) (II) (E23-1)

Acetetanilide was put on the market as an antipyretic (fever-reducing) drug in 1886 under the name of antifebrine and at one time was widely used for its antipyretic and analgesic (pain-reducing) properties. However, its considerable toxicity has caused it to be replaced by the safer salicylates like aspirin, which was introduced in 1899.

The acetanilide you prepare in this experiment can be used in the synthesis of sulfanilamide in Experiment 24.

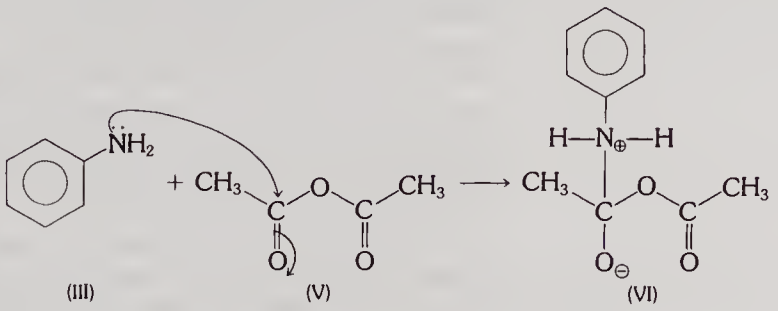
E23.1 DISCUSSION OF THE SYNTHESIS

You will prepare acetanilide (IV) by the acetylation of aniline (IUPAC benzenamine), (III):



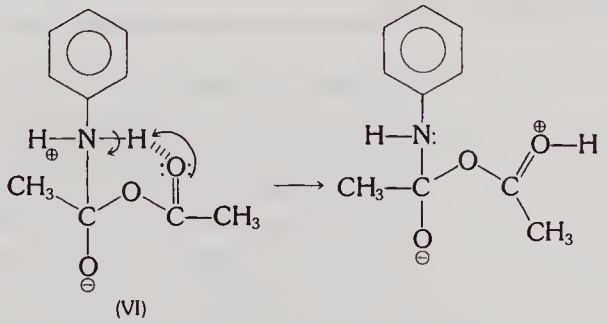
(III) (IV) (E23-2)

When amino nitrogen collides with sufficient energy and correct orientation with carbonyl carbon of acetic anhydride (IUPAC ethanoic anhydride), (V), the pi bond breaks:



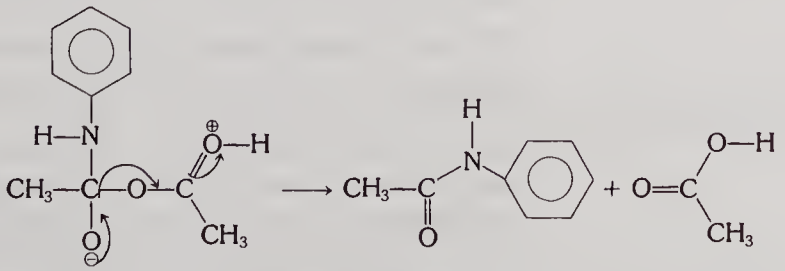
(III) (V) (VI) (E23-3)

It is likely that because of the pseudo six-member ring in (VI) that a proton is transferred from nitrogen to carbonyl oxygen:



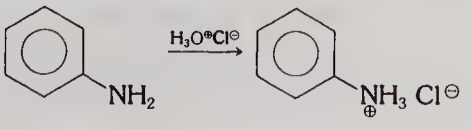
(VI) (E23-4)

This is an easy Brønsted acid-base transfer because the pseudo six-member ring holds the reacting atoms in near ideal spatial proximity to each other. Subsequent contraction of the negatively charged carbonyl region reforms the carbonyl pi bond and releases acetic acid (IUPAC ethanoic acid) as the leaving group:



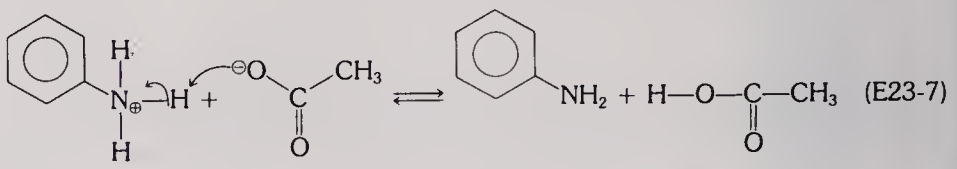
(E23-5)

The synthesis takes place in an aqueous environment, and because aniline is soluble only to the extent of 3.4 g/100 ml, you make it more soluble by converting it to its hydrochloride salt, anilinium chloride (IUPAC benzenammonium chloride):



(E23-6)

Because the presence of the acid reduces the nucleophilicity of the aniline, you circumvent this problem by buffering the solution with sodium acetate. The acetate ion removes protons from some of the anilinium ions, rendering them nucleophilic but keeping the concentration of aniline low enough to maintain solubility in water:



(E23-7)

The equilibrium lies slightly to the right because the K_a of ethanoic acid is 1.8×10^{-5} as compared to a K_a of 2.63×10^{-5} for anilinium ion. However, the major factor for complete deprotonation of anilinium is due to the shifting of equilibrium by reaction of aniline with acetic anhydride. Because the product acetanilide is insoluble in water, it crystallizes out as the reaction proceeds.

It is true that acetic anhydride reacts with water to yield acetic acid. However, the reaction with aniline is much more rapid than that with water because of the greater nucleophilicity of nitrogen as compared to oxygen. Nevertheless, you must make aniline react with the anhydride without delay and therefore add acetate as soon as the anhydride dissolves in the reaction mixture.

It is not uncommon for aniline to have decomposed somewhat on the shelf, yielding a dark colored impurity which you must remove or it will discolor the final product crystals. Adsorption of the impurity on decolorizing charcoal is effective.

E23.2 EXPERIMENTAL PART

Preparation of acetanilide. Put 125 ml of water in a 250-ml Erlenmeyer flask. Add 4.5 ml of concentrated hydrochloric acid, and swirl the flask a couple of times. Add 50 mmoles of aniline and swirl the mixture. If the solution is colored, add a small amount of decolorizing carbon, swirl the flask for about 1 min, and filter off the carbon. In a separate container, add 55 mmoles of sodium acetate (IUPAC sodium ethanoate) to 25 ml of water. Measure into a graduated cylinder 55 mmoles of acetic anhydride (IUPAC ethanoic anhydride).

Concentrated HCl can cause severe chemical burns.

Warm the aniline hydrochloride solution to 50 °C on a steam bath or hot plate; then add the ethanoic anhydride. Swirl the flask to dissolve the anhydride. Immediately on noting dissolution, add the sodium acetate quickly in one portion. Swirl the flask a couple of times and set it in an ice-water bath for 20 min.

Because of the toxicity of aniline, do all work in a hood.

Because aniline can be absorbed through intact skin, it is best to wear rubber gloves.

Workup. Filter the crystals in a Büchner funnel with suction and wash them with a small amount of ice-cold water. If necessary, recrystallize the product from water. Dry the crystals and weigh them. As directed by your instructor, obtain a melting point and IR and NMR spectra, and perform amine characterization tests on the starting material and product (Part III).

As directed by your instructor, put the product in a vial and submit it to your instructor or save it for future synthetic steps.

Writing the discussion. Discuss the identity and purity of the product as determined by analysis. Compare your spectra with Figures 16.13 and E23.1. Consider also the yield relative to the methods used and your technical performance.

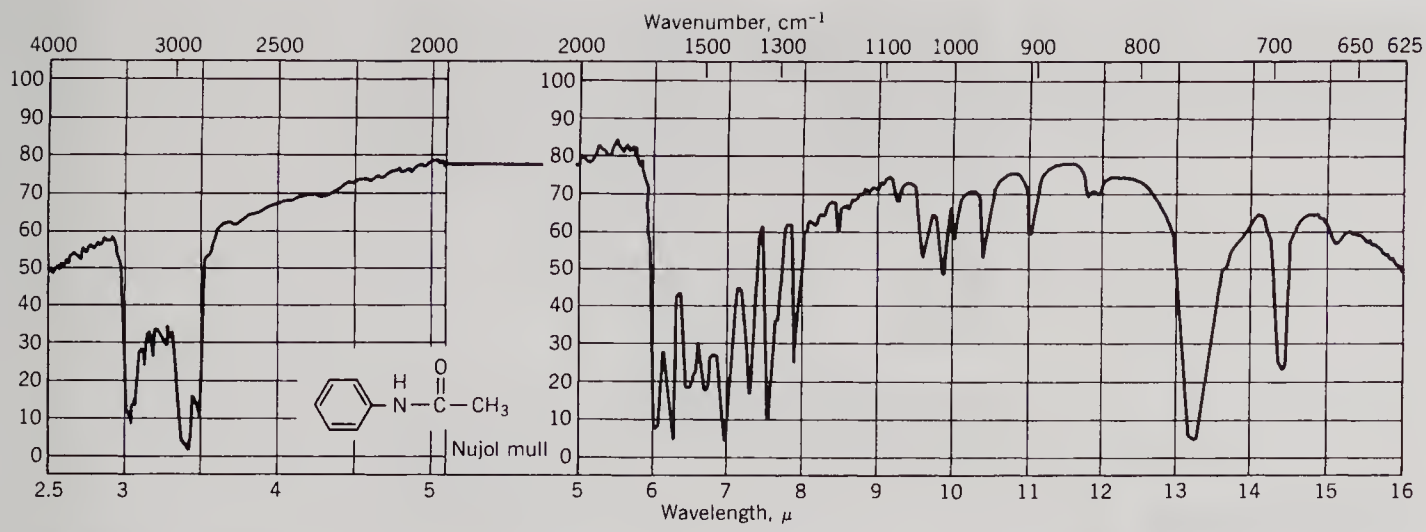


FIGURE E23.1 IR spectrum of acetanilide. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

E23.3 EXERCISES

Prelaboratory

1. Do you think it should make any difference whether anhydrous sodium acetate or sodium acetate trihydrate is used in the procedure? Explain.
2. What should be done if the aniline is colored?
3. Why must sodium acetate be added immediately after the acetic anhydride is dissolved? What is the function of sodium acetate?
4. Why is the ice-cold water rather than room temperature water used to wash the final product?
5. Review the procedural hazards associated with heating reaction mixtures (Section 0.5), recrystallization (Section 5.3), and suction filtration (Section 4.2).

Postlaboratory

1. *Anna Lynn* said that during the preparation of acetanilide that one should expect considerable amounts of the byproduct, *N,N*-diacetylaniline. Do you agree? Write (a) a balanced equation, and (b) a mechanism for its formation.
2. Write the equation that shows the conversion of aniline to its water-soluble salt.
3. The acetylation in the preparation of aspirin is analogous to that in the acetylation of benzenamine. Write a mechanism for the acetylation.

REFERENCES TO SIMILAR PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 577.
2. Fieser, L. F. *Experiments in Organic Chemistry,* 3rd ed., revised; Heath: Boston, 1957; p 151.

EXPERIMENT 24 PREPARATION OF SULFANILAMIDE

Time Required: 4–6 hr

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Trapping gases	(0.7)

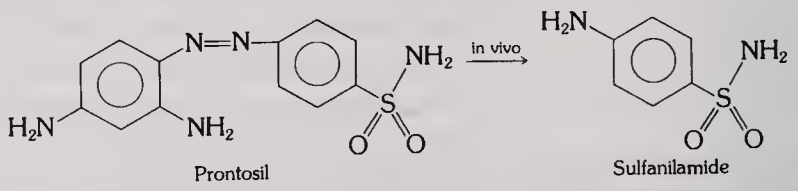
Suction filtration	(4.3)
Cooling and heating	(0.5)
Testing acidity	(0.11)
Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.1, 3.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Storing	(0.12)
Labeling	(0.13)

New Technique and Principle:

Protecting group

INTRODUCTION

Sulfanilamide (IUPAC 4-aminobenzenesulfonamide) was described in the chemical literature as early as 1908, but it was not known until 1935 that it had antibacterial activity. This activity was discovered in a roundabout way: In 1932, I. G. Farbindustrie in Germany patented a dye called prontosil. It was soon discovered that prontosil inhibited growth of bacteria. In 1935, it was shown that the dye was degraded in vivo (in living organisms) to sulfanilamide, which was shown to be the active agent.

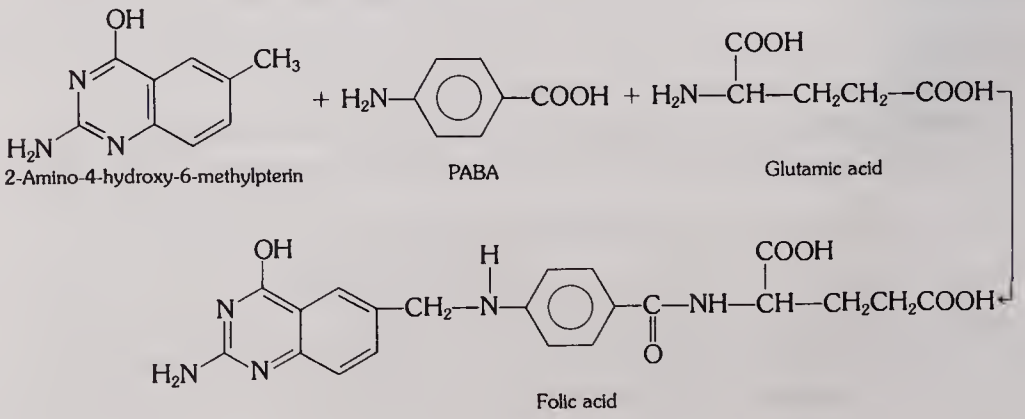


Prontosil Sulfanilamide (E24-1)

Since the discovery of the bacteriostatic (inhibiting bacterial growth) properties, many other similar sulfonamides have been prepared, both to increase the efficacy of the drug and to decrease the severe problem of **crystalluria,** the precipitation of the drug in renal tubules which causes kidney damage. The antibacterial sulfonamides are known as **sulfa drugs.** They are primarily bacteriostatic, although in high doses have in some cases proven to be bacteriocidal (killing bacteria). Sulfa drug use is not as common as it once was but is still important in treating urinary tract infections.

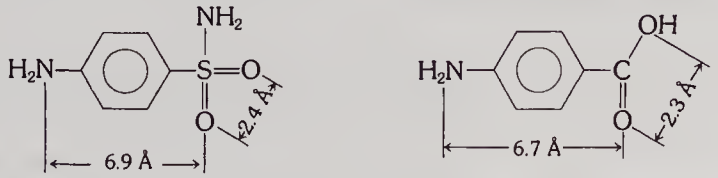
The sulfonamides inhibit bacterial growth by interfering with the synthesis of folic acid by the bacterium. Folic acid is a cofacter for an essential enzyme in the bacterium.

A sulfa drug prevents synthesis of folic acid by a process known as **competitive inhibition.** The three components comprising folic acid enter the bacterial cell. These components, 2-amino-4-hydroxy-6-methylpterin, *p*-aminobenzoic acid (PABA), and glutamic acid, diffuse randomly to an enzyme which assembles them and releases the product folic acid:



(E24-2)

The sulfonamides have intramolecular distances between the ring amino nitrogen and sulfonyl oxygen which are almost identical to the distance from PABA's ring amino nitrogen to its carboxyl oxygen; furthermore, the distance between sulfonyl oxygens is almost the same as that between carboxyl oxygens. In addition, the two compounds have very similar electronic characteristics.

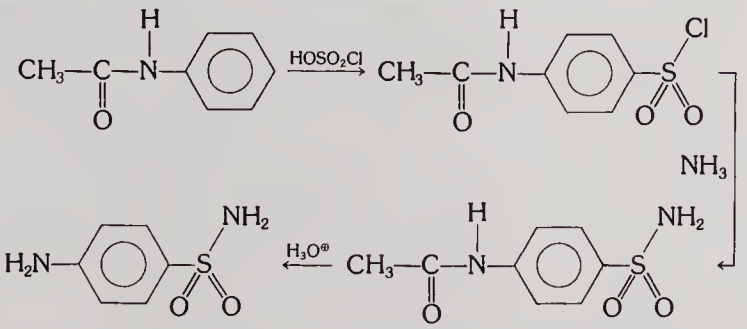


Therefore, a sulfa drug can substitute on the enzyme for PABA. As long as the sulfonamide occupies the PABA site on the enzyme, no folic acid can be synthesized.

Folic acid is essential for humans, too. But the sulfa drug does not interfere with cellular functions in humans because we do not synthesize folic acid. Instead, we ingest it as a vitamin.

E24.1 DISCUSSION OF THE PREPARATION

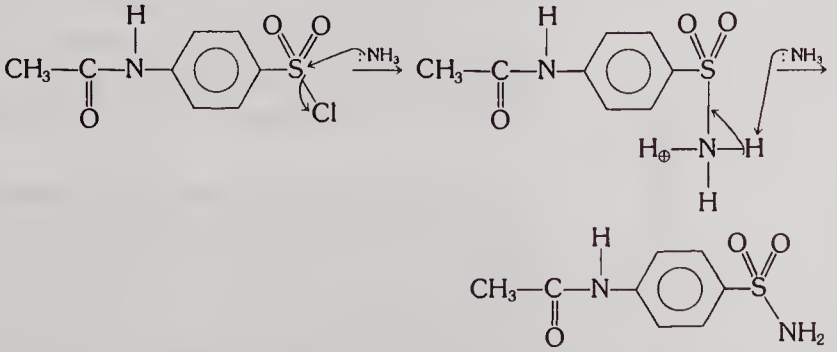
The synthesis of sulfanilamide is a three-step procedure:



(E24-3)

The first step is an electrophilic aromatic substitution in which chlorosulfonic acid acts as catalyst as well as reagent. The byproduct of the first step is hydrogen chloride gas, which is conveniently trapped in water. At the end of the reaction, excess chlorosulfonic acid is destroyed by a highly exothermic reaction with ice and water, causing vaporization of water and spattering. The product contains a sulfonyl chloride function and reacts with water also, but much more slowly than does the chlorosulfonic acid.

In the second step, the chloride is displaced by ammonia:



(E24-4)

The reaction with ammonia is much more rapid than that with water because of the much greater nucleophilicity of nitrogen as compared to oxygen. A large excess of ammonia is required to neutralize the hydrogen chloride byproduct of this reaction and still leave basic ammonia free of protonation.

The third step hydrolyses the acetyl (IUPAC ethanoyl) function. Had this function

not been present as a protecting group during the first step, the ring amino group would have reacted with the chlorosulfonic acid.

E24.2 EXPERIMENTAL PART

Acetylaminobenzenesulfonyl chloride preparation. Put 0.025 mole of dry acetanilide (IUPAC *N*-phenylethanamide) into a 125-ml Erlenmeyer flask. Use a hot plate or a low flame to gently melt the acetanilide. Cool the flask with swirling so that the molten compound is deposited in a thin layer on the bottom and lower portion of the flask.

Chlorosulfonic acid reacts with moisture in the air to produce fumes. Work only in a hood. Wash equipment only in a hood.

If a flame is to be used, check with your instructor regarding the flame-permit area and period permitted.

Chlorosulfonic acid reacts EXPLOSIVELY with water. The acetanilide must be dry, and at no time must water come in contact with the reactants. Measure the acid in a dry graudated cylinder.

Attach the Erlenmeyer reaction flask to an acid trap via a one-hole stopper with a short section of inserted glass tubing. Use a section of rubber tubing from the flask to the trap. It would be a good idea to put an intermediate trap (like that used for suction filtration) between the acid trap and the reaction flask. The intermediate trap should not contain water and should be clamped to a ringstand in order to prevent upsetting it.

Disconnect the reaction flask and cool it in an ice-water bath. Then remove it from the water and dry the outside of the flask. Add 0.125 mole of chlorosulfonic acid in one portion. Connect the flask to the trap again and swirl the contents of the flask until the reaction is obviously in progress. If the reaction becomes too vigorous, cool it slightly. After about 10 min, heat the mixture on a steam bath or hot water bath for 10 more minutes. Then cool the mixture.

Slowly pour the mixture into a large beaker containing about 50 g of crushed ice. This operation will cause some spattering. Rinse the Erlenmeyer flask with a little water and pour the rinse into the beaker. Stir the mixture to break up large lumps, then filter the solid in a Büchner funnel. Wash it with a small amount of water. Remember, the product should not be left in water any longer than necessary, since it reacts with it. △

You should wear rubber gloves and goggles while working with chlorosulfonic acid.

Pour the reaction mixture containing chlorosulfonic acid cautiously and slowly onto the ice. Use a large beaker to contain the spatters.

Destroy excess chlorosulfonic acid in a hood by adding to contaminated vessels cracked ice and allowing it to melt. Then rinse the vessels with plenty of water.

Acetylaminobenzenesulfonamide preparation. Put the crude acetylaminobenzenesulfonyl chloride into a 125-ml Erlenmeyer flask. Add 10 ml of concentrated ammonium hydroxide and stir the mixture well. Heat it on a hot plate, steam bath, or hot water bath for 15 min, then allow it to cool to room temperature. Add with swirling 6*M* hydrochloric acid until the liquid in the flask turns blue litmus red. Cool the mixture on an ice-water bath to about 10 °C, then filter it in a Büchner funnel. Wash the product with about 10 ml ice-cold water. △△

Use concentrated ammonium hydroxide in a hood.

Sulfanilamide preparation. Put the crude acetylaminobenzenesulfonamide into a 50-ml round-bottom flask and add 3.5 ml of concentrated hydrochloric acid, 7 ml of water, and a boiling chip. Reflux the mixture gently until all of the solid is dissolved; then reflux it for another 10 min. Cool the solution to room temperature. If solid precipitates during cooling, reflux the mixture another 5 min.

Decolorize the cooled solution, filter it, and put the filtrate into a large beaker. Rinse the filtrate container with a small amount of water and add the rinse to the beaker. Add, with stirring, a saturated solution of sodium bicarbonate slowly to the beaker until the mixture is neutral to litmus. Cool the product suspension in an ice-water bath and collect it in a Hirsch or Büchner funnel by suction filtration. △△ Recrystallize the product from water and dry it. △△

Weigh the product and calculate the percent yield. Determine the melting point and obtain IR and NMR spectra if so directed by your instructor. Put the sample into a labeled vial and turn it in.

Writing the discussion. Discuss your yield, speculating where along the route losses occurred. Discuss the identity and purity of the product as suggested by analyses performed. Compare your spectra with those of Figures E24.1 and E24.2.

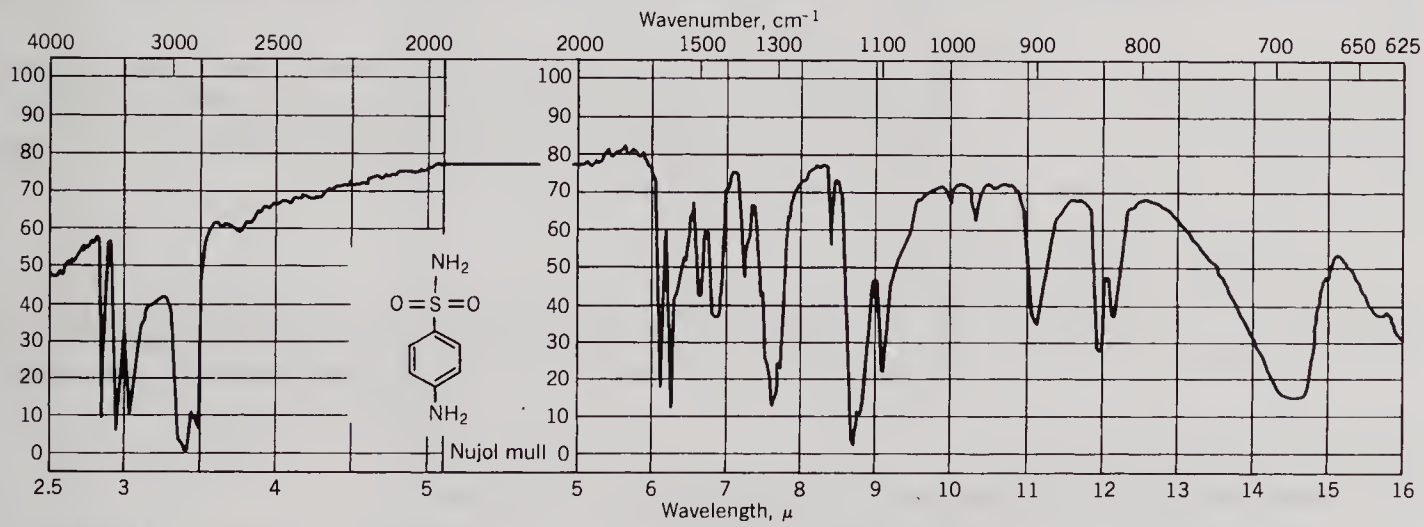


FIGURE E24.1 IR spectrum of sulfanilamide. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

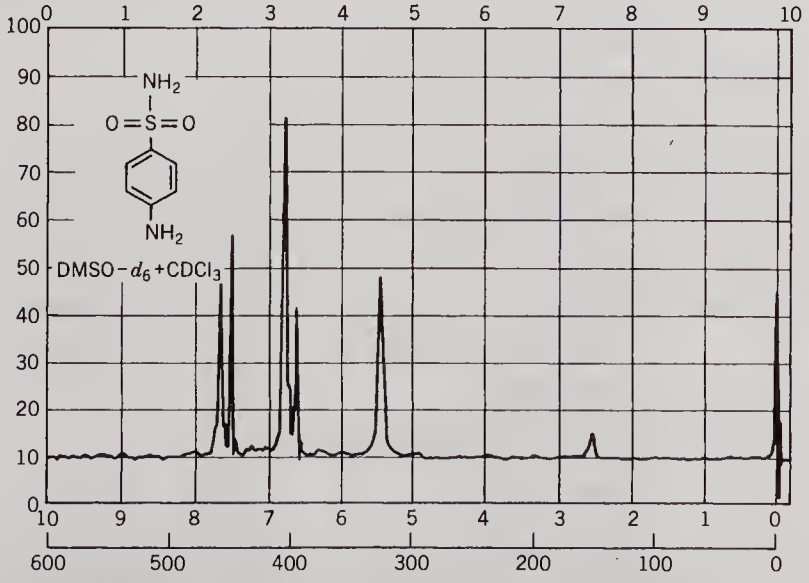


FIGURE E24.2 NMR spectrum of sulfanilamide. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

E24.3 EXERCISES

Prelaboratory

1. Make a drawing of the apparatus to be used for the preparation of 4-ethanoylaminobenzenesulfonyl chloride.
2. In what form will the acetanilide be put into the flask for the reactions?
3. What is the purpose of the intermediate trap in step one of the sequence?
4. Why does ammonia react with the *N*-ethanoylaminobenzenesulfonyl chloride faster than water does?
5. What is the purpose of the final step in the synthetic sequence?
6. Make a flow diagram for each step in the sulfanilamide synthesis.
7. Review the procedural hazards associated with heating reaction mixtures (0.5), recrystallization (5.3), and suction filtration (4.3).

Postlaboratory

1. Write a mechanism for the electrophilic aromatic substitution involved in the preparation of *p*-acetylaminobenzenesulfonyl chloride. Show the resonance structures of the benzenonium ion.
2. What would be the result of using equimolar amounts of *p*-acetylaminobenzenesulfonyl chloride and ammonia in the second synthetic step of this experiment?
3. Show how the ring amino group of aniline (acetanilide without the acyl function) would react with chlorosulfonic acid.

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3. Weinstein, L. "The Sulfonamides." In *The Pharmacological Basis of Therapeutics,* 4th ed.; Goodman, L. S.; Gilman, A., Eds.; MacMillan: New York, 1965; pp 1177–1201.

EXPERIMENT 25 PREPARATION OF *N,N*-DIETHYL-*p*-METHYLBENZAMIDE

Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.2)
Adding liquid reagents	(0.8)
Cooling	(0.5)
Stirring	(0.4)
Suction filtration	(4.3)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Simple distillation	(7.2)
Vacuum distillation of solid	(7.11)
Drying solids	(2.1)
Recrystallization	(5.3)
Melting points	(3.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)

Storing (0.12)
Labeling (0.13)

New Techniques and Principles:

Distilling a low-melting solid (E25.2 workup)

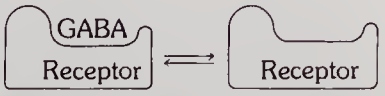
INTRODUCTION

N,N-Diethyl-*p*-methylbenzamide is an insect repellent, a close relative of *N,N*-diethyl-*m*-methylbenzamide which is marketed as Deet or Metadelphine. The latter isomer is a liquid, whereas the former is a low-melting solid. The *m*-methyl isomer is somewhat better suited for topical application because a liquid is not as easily rubbed off as a solid. However, the *p*-methyl isomer is just as innately effective and because it is a solid, is a better choice for application to clothing. To get it into cloth fibers, it is most efficiently applied from solution. Because the melting point of the *p*-methyl isomer is quite low (53.5–55.5 °C), application in lotion or cream form introduces enough associated impurities so that it behaves as if it were a liquid, and is as satisfactory as its *m*-methyl counterpart. An advantage to using the *p*-methyl isomer is that the cost of starting materials is considerably lower than for the *m*-methyl isomer.

Insect repellents belong to that class of "drug" which is noninteractive insofar as its designed effect on the human body is concerned. It is an interactive chemical in the body of the insect, presumably interacting as an agonist more or less specifically with a receptor protein. An **agonist** is a chemical which is specifically shaped and electronically constituted so that it fairly precisely fits a specially designed protein site known as a **receptor** (it *receives* the agonist) and generates some kind of biological effect.

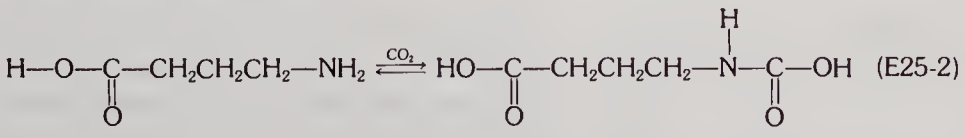
For the most part, mosquitoes live on sap from the leaves of various kinds of plants, but if the opportunity arises, the female will sup on blood. In fact, a blood feeding is necessary every few generations in order to maintain continued reproduction of healthy progeny.

According to the GABA hypothesis, as long as a certain receptor in the female is occupied by GABA (*gamma*-aminobutyric acid), found in large amounts in healthy female mosquitoes, she feels little need for blood-seeking. Because occupation of the receptor site is an equilibrium process, a plentiful supply of GABA keeps the receptor filled most of the time:



(E25-1)

The equilibrium can be shifted toward an empty receptor by removing GABA, which could occur during starvation; during periods when essential minerals, vitamins, or enzymes are not present; or in the presence of carbon dioxide, a compound that appears to excite and perhaps attract the mosquito. According to the hypothesis, when larger than normal amounts of carbon dioxide enter the mosquito when it is near a breathing animal, the carbon dioxide combines with GABA (I) to form a carbamate (II) which no longer fits the GABA receptor site:



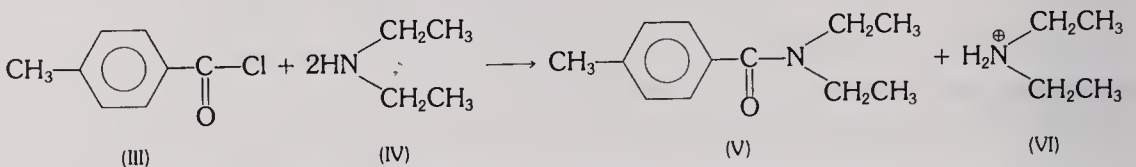
(E25-2)

(I) (II)

The equilibrium constant is about 1 so the reverse reaction readily occurs, but in the meantime the mosquito has had its dinner. The supposed function of the mosquito repellent is to be a substitute agonist for GABA.

E25.1 DISCUSSION OF THE PREPARATION

To prepare the repellent, you will cause *p*-methylbenzoyl chloride (4-methylbenzenecarbonyl chloride), (III), to react with diethylamine (IUPAC *N*-ethylethanamine), (IV):



(III) (IV) (V) (VI) (E25-3)

The technique is to dissolve the amine in anhydrous ether (IUPAC ethoxyethane) and stir it vigorously during the addition of the acyl chloride from a dropping funnel. You must use a fairly large amount of anhydrous ether because as the reaction progresses, the byproduct amine salt (VI) precipitates and interferes with stirring. Anhydrous conditions are maintained to prevent reaction of the acyl chloride with water. The acyl chloride is added slowly enough so that the exotherm of the reaction does not cause excessive boiling. Every time a little of the acyl chloride is run into the flask, a white cloud will rise from the liquid. This cloud consists of the diethylamine hydrochloride which occurs as a byproduct and you must not allow it to rise up, accumulate, and block the opening of the addition funnel or drying tube. You should permit the cloud to settle after each addition.

Two moles of amine are required for each mole of acyl chloride because the amine reacts not only with the substrate but also with the hydrogen chloride byproduct. In practice, slightly more than 2 moles is used so that the reaction will quickly go to completion. The excess amine is readily removed in an acidic wash of the liquid in a separatory funnel, wherein the amine is changed into its water-soluble hydrochloride salt.

Because the product is a low-boiling solid, it can be distilled. However, it would solidify in the condenser of an ordinary still. Therefore condensation of product is made to take place in the *receiver* by cooling it in an ice bath.

E25.2 EXPERIMENTAL PART

The starting acyl chloride can be prepared by the method of Experiment 19.

Preparation of N,N-diethyl-p-methylbenzamide. Put 55 mmoles of diethylamine (IUPAC *N*-ethylethanamine) into a 250- or 500-ml three-neck round-bottom flask and add 25 ml of anhydrous ether (IUPAC ethoxyethane). Stopper one side neck of the flask, put a drying tube in the other, and an addition or separatory funnel in the center neck. If a separatory funnel is used, put a second drying tube at the top of the separatory funnel. Lightly grease all ground glass joints in the apparatus.

Temporarily remove the drying tube in the separatory funnel and add 25 mmoles *p*-methylbenzoyl chloride; then replace the drying tube. Add the *p*-methylbenzoyl chloride dropwise to the flask, constantly agitating it by swirling and cooling it in a cold water bath. Keep the white cloud down in the flask. After addition is complete, allow the mixture to warm up to room temperature and then to sit for about ½ hr with occasional swirling.

The acyl chloride can cause severe chemical burns. Use it in a hood. Do not allow it to come in contact with water and cause a violent exotherm and production of HCl.

Do not turn electrical switches on or off in the vicinity of uncapped ether containers.

Handle diethylamine in a hood. It is volatile and strongly basic.

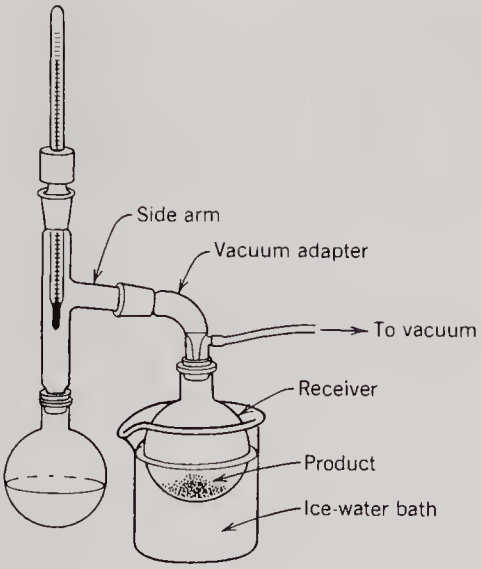


FIGURE E25.1 Vacuum distillation apparatus for low melting solid.

Workup. Filter off the white amine hydrochloride into a Büchner funnel, rinse it with a small amount of anhydrous ether, and put it into a recovery container. Put the filtrate into a separatory funnel and wash it successively with 10 ml of water, 15 ml of 6*M* aq HCl, and 10 ml of water. Dry the product solution with anhydrous sodium sulfate, and put it in a distilling flask arranged for magnetic stirring. Distill off the solvent at about 35 °C and put it in a recovery bottle. Continue distillation until the temperature rises to about 100 °C; then remove the condenser. Tare a round-bottom flask and attach it to a vacuum adapter, which in turn is attached to the side arm of the distillation apparatus, as shown in Figure E25.1. Do not use a condenser for the final distillation step, but set the receiver in an ice-water bath. Complete the distillation in vacuo, collecting the fraction distilling between 108 and 114 °C at 1 torr, or use the pressure-temperature nomogram of Figure 7.15 to determine the distillation temperature at the pressure indicated on a McLeod gage or manometer. If necessary, direct steam onto the sidearm to prevent solidification of the product. If melting point and color are not what you think they should be, recrystallize the product from hexane.

Do not allow the sidearm to plug up during distillation.

Analysis. As directed by your instructor, obtain melting point and NMR and IR spectra.

Writing the discussion. Discuss the identity and purity of the product as determined by analysis; compare your spectra with that of Figure E25.2 and those in the available literature; discuss the percent yield relative to the procedure used and your technical performance.

E25.3 EXERCISES

Prelaboratory

1. The density of *N*-ethylethanamine is 0.74 g/ml. Calculate the number of milliliters to use in this preparation.
2. Why are the joints of the ground glassware lightly greased?
3. Make a sketch of the apparatus you will use for the reaction.
4. Why is the product mixture washed with hydrochloric acid? How many moles of HCl is in 15 ml of 6*M* HCl? Should this be enough to react with excess amine?
5. Will the product be found in the upper or lower phase in the separatory funnel?

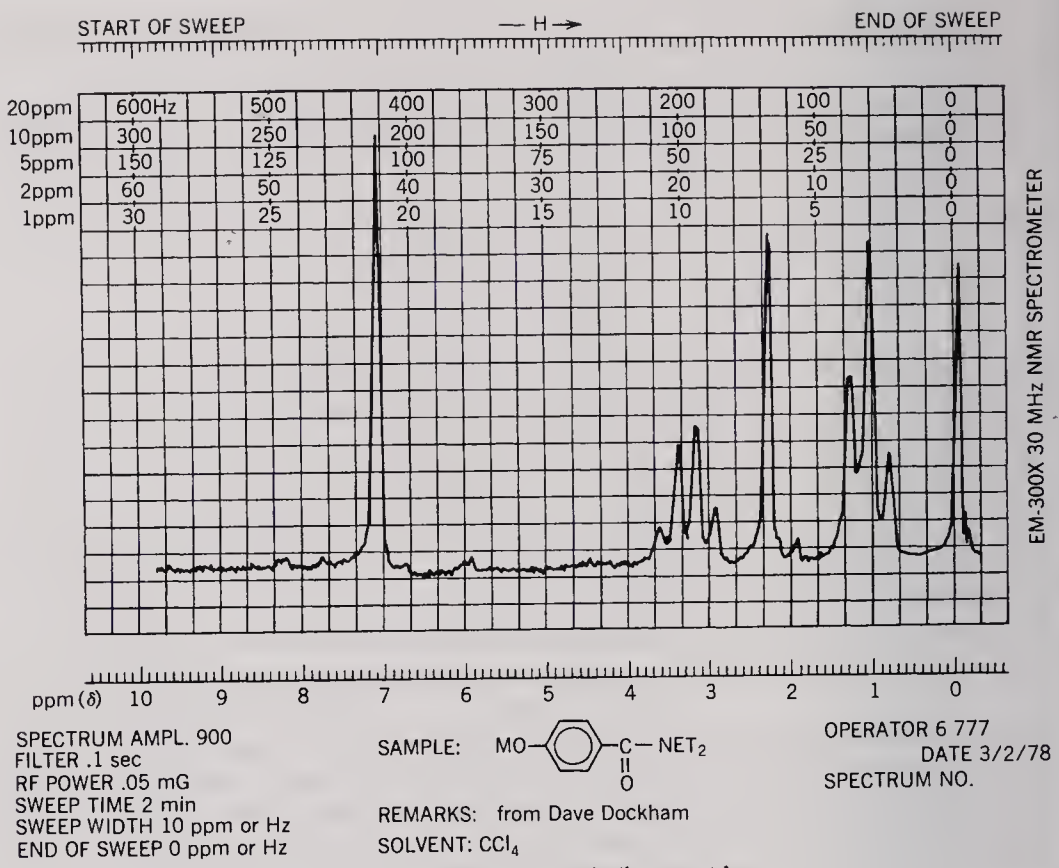


FIGURE E25.2 NMR spectrum of *N,N*-diethyl-*p*-methylbenzamide.

6. When is a good time to set up the distillation apparatus in order to make efficient use of your time?
7. Why is a water condenser not used in the final distillation?
8. What is the byproduct that is produced if 4-methylbenzenecarbonyl chloride reacts with water during the reaction?
9. From observation of the extent of the conjugated system of the product, what color, if any do you expect the product to be?
10. Review hazards for suction filtration (4.3), extraction (6.2), distillation (7.2, 7.11), and recrystallization (5.3).

Postlaboratory

1. Write the equation that shows what reaction would occur if nonanhydrous ethoxyethane were used in the preparation.
2. What is the normal boiling point of *N,N*-diethyl-4-methyl-benzamide?
3. Write a mechanism for the reaction of *N*-ethylethanamine with 4-methylbenzenecarbonyl chloride.
4. Name GABA by the IUPAC system.
5. *Stu Dent* asked Professor *R. E. Pellent* how one could prepare and workup *N,N*-diethyl-*m*-methylbenzamide. He was told that he should already have the answer. You know Stu is going to ask you next. What are you going to tell him?

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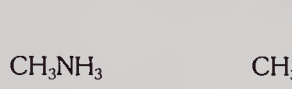
3. Kashin, P. "Development of an Orally Effective Insect Repellent," Report No. IITRI-L6021-12, 1967; U.S. Army Medical Research and Development Command: Washington, DC.

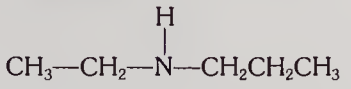
XII AMINES

Amines are substitution products of ammonia in which nitrogen is bonded only to carbon or hydrogen. They have the generalized structure R_3N in which R is hydrogen, alkyl, aryl, or various combinations of the same. Amines can be primary (I), secondary (II), or tertiary (III); and they can be heterocyclic (IV):



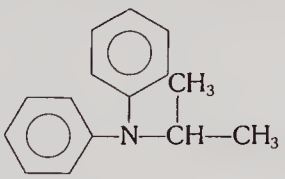
Methanamine
(Methylamine)

(I)



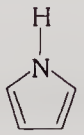
N-Ethyl-1-propanamine
(Ethyl-n-propylamine)

(II)



N,N-Diphenyl-2-propanamine
(Isopropyldiphenylamine)

(III)



Azole
(Pyrrole)

(IV)

The word "amine" is a combination of *am*monia and the suffix *-ine,* which is used in organic chemistry as a termination for names of organic bases.

Like ammonia, amines are moderately strong bases and behave chemically as such. They are capable of producing chemical burns.

The lower molecular weight amines have odors very much like ammonia. Amines containing five or six carbons tend to smell like raw fish, and as molecular weight increases, the odors become more obnoxious until molecular weight is so great that low vapor pressure reduces odor.

This section contains the preparation of two amines, one of which is optically active. Experiment 26 is a classical chemical reduction. Experiment 27 yields a racemic mixture of an optically active amine, which is resolved in Experiment 28. You will find amines in Experiments 3, 23, 25, 29, 30, 35, and 45, also in Technique 7, and in the qualitative analysis of amines in Part III.

EXPERIMENT 26 PREPARATION OF ANILINE

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Adding chemicals to reaction vessels	(0.8)
Cooling	(0.5)
Stirring	(0.4)
Heating	(0.5)

Testing pH	(0.11)
Direct steam distillation	(7.15)
Liquid-liquid extraction	(6.2)
Wet analysis	(Q7.2, Q8.7, Q9.6)
Refractive index	(13.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)

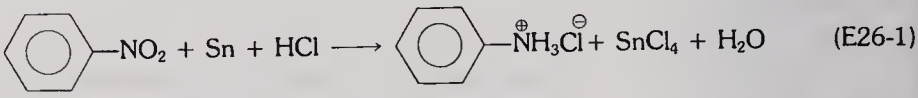
INTRODUCTION

In terms of total industrial production, aniline is the most important aromatic amine. It was first isolated in 1826 by the destructive distillation of dark blue indigo dye and named *krystallin* because it easily formed crystalline salts. In 1841, it was rediscovered in distillation products of indigo and was named aniline from the Spanish word *anil*, which means indigo. Anil is derived *via* the Arabic word *al-nil* from the Sanscrit word *nila* which means dark blue. The original IUPAC name aminobenzene is being supplanted by the name benzenamine in accord with chemical abstracts nomenclature practices aimed at simplifying indexing and computer recognition of names.

The preparation of aniline by reduction of nitrobenzene with tin and hydrochloric acid illustrates a classical and important means of preparing aromatic amines.

E26.1 DISCUSSION OF THE REACTION

The preparation of aniline by reduction of nitrobenzene proceeds as follows:



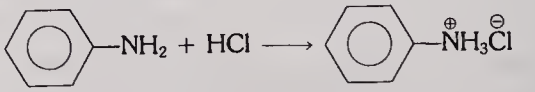
(E26-1)

Tin and hydrochloric acid are most commonly used for aromatic nitro group reductions in the laboratory because of the reasonable reaction rate and the relatively low cost. Iron is most commonly used in industry.

Although the actual mechanism of the reaction has not been worked out, it is known that the oxygen atoms of the nitro group are incorporated into water molecules, and that the hydrogen atoms of the product amino function come from the hydrochloric acid.

The reaction is an oxidation-reduction process, the reduction potential being great enough to cause a considerable exotherm. Therefore, the reaction vessel must be equipped with a reflux condenser, and provision must be made to cool the reaction if necessary. To control the exotherm, you will only slowly add the hydrochloric acid to the mixture of substrate and reducer.

Because the product amine is basic, it reacts with hydrochloric acid as soon as it is formed, producing the hydrochloride salt



(E26-2)

To obtain the aniline itself, you must remove the anilinium proton in a Brønsted-Lowry acid-base step, continually shifting the equilibrium in direction of product by distilling the aniline as it is formed. However, unreacted nitrobenzene distills with the aniline. To separate these two components of the steam distillate, you must acidify the mixture, converting the amine once more to its water-soluble hydrochloride salt. You can then remove the nitrobenzene by extraction and regenerate the amine by a second treatment with aqueous base.

E26.2 EXPERIMENTAL PART

Synthesis of aniline. Assemble for reflux an apparatus consisting of a 100-ml three-neck round-bottom flask with a reflux condenser in the center neck (see prelab exercise 8). Put a separatory funnel in one-side neck and a stopper in the other. Grease all joints lightly. Securely attach all components to a ringstand, leaving room beneath the flask to insert and remove an ice-water bath for temperature moderation. Prepare the ice-water bath before the reaction begins.

Put 3.1 g of nitrobenzene in the flask; then add 5.9 g of granulated tin. Measure out 14 ml of 12*M* hydrochloric acid and put it in the separatory funnel. Start the cooling water through the condenser.

Concentrated hydrochloric acid can cause severe skin burns.

After checking the toxicities of the chemicals to be used, you will find that all work should be preferably done in a hood.

Both aniline and nitrobenzene can be absorbed through intact skin. Wear gloves. Avoid contact with skin and eyes.

Run about 1 ml of the acid from the separatory funnel into the flask. Pick up the ringstand with its attached apparatus and swirl the reaction mixture. You might observe boiling. Add the acid in 1-ml portions over a period of about 20 min, swirling the mixture often.

During swirling of the reaction vessel, be careful not to shake loose the condenser or separatory funnel, or to spill acid out of the top of the funnel. Clamp all components of the reaction apparatus to the ringstand.

Keep the reaction from becoming too vigorous by use of the ice-water bath. After all of the acid has been added, and after noticeable reaction appears to have stopped, heat the mixture on a steam or hot water bath until the condensate in the reflux condenser is free of oily drops of nitrobenzene. It will probably take about 20 min. Carefully pick up the apparatus and swirl the refluxing mixture from time to time.

Workup. When the reflux period is over, cool the pot mixture in an ice-water bath. You can add some crushed ice directly to the flask once it is cool enough to hold comfortably. Do not add so much ice that it does not melt. While swirling and cooling the mixture continuously, add 10 ml of 50% aq NaOH. If the resulting solution is not basic to litmus, add more sodium hydroxide solution.

Assemble the reaction flask into a direct steam distillation apparatus with lightly greased joints and an ice-water-cooled receiver. Using a Bunsen burner or heating mantle as heat source, steam distill the mixture. Collect 10 ml more of the distillate after the milky appearance of the distillate is gone. △△

Use a bunsen burner only if your instructor says to.

Add 2 ml of concentrated hydrochloric acid to the cold distillate and put the mixture in a separatory funnel. Extract the mixture twice with 5 ml of ether and put the extract in an ether recovery container. Drain the aqueous layer into a beaker and, keeping it cool with an ice bath, add 50% aq NaOH until the solution is basic to litmus. Add 20 g of NaCl for each 100 ml of liquid, shake it well to dissolve the sodium chloride; then transfer the solution to a separatory funnel and extract it with two 5-ml portions of dichloromethane (methylene chloride). Put the aqueous layer in a recovery container if the salt is to be recovered. Dry the amine solution over one or two NaOH pellets, swirling until the solution is clear. △△

Decant or filter the dry solution into a distilling flask of appropriate size. Set up a simple distillation apparatus, greasing all joints lightly. Distill off the dichloromethane at 41 °C and put it into a recovery container. Stop the water flow in the condenser and drain it. Continue distilling, collecting the fraction boiling between 175 and 185 °C.

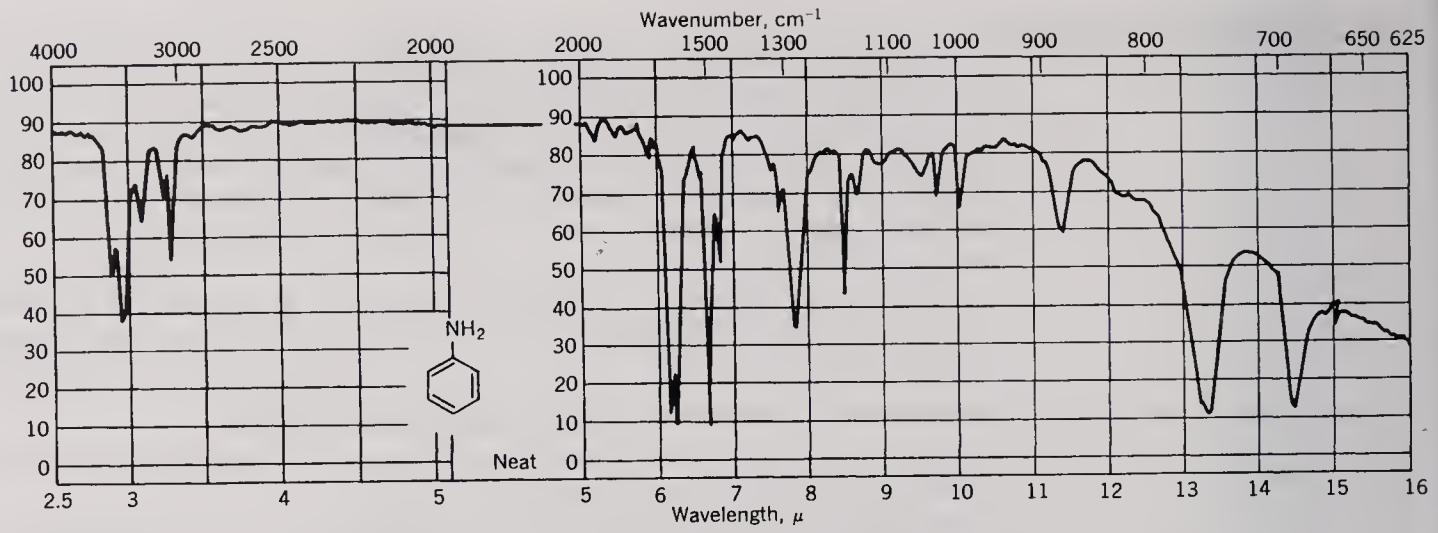


FIGURE E26.1 IR spectrum of aniline. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

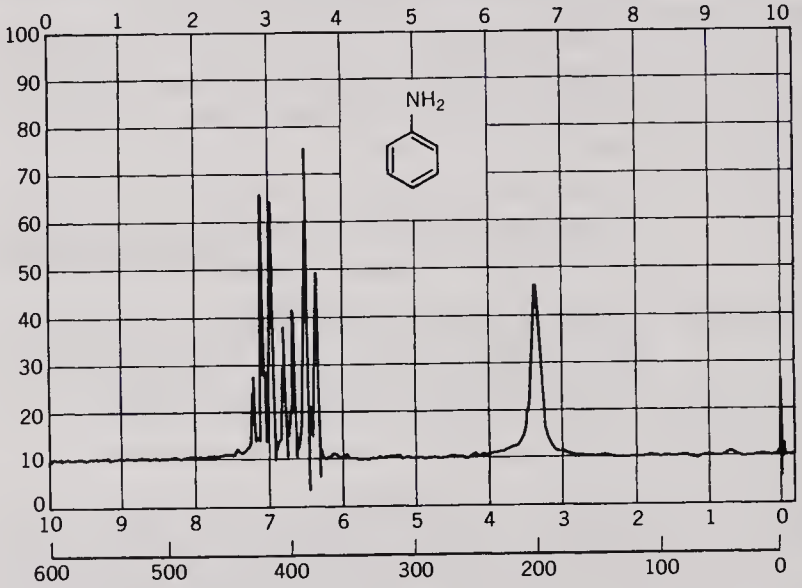


FIGURE E26.2 NMR spectrum of aniline. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Disassemble and clean up your equipment immediately after use. Put the product in a labeled vial and turn it into your instructor. △△

Calculate the percent yield and, at the direction of your instructor obtain the refractive index, IR, UV, and NMR spectra, a GLC chromatogram, and results of wet analysis.

Writing the discussion. Discuss your yield with respect to the method and techniques used, trying to ascertain where product losses occurred. Discuss the identity and purity of the product as indicated by analyses performed. UV maxima should be found at 287 and 235 nm. Compare your spectra to those of Figures E26.1 and E26.2.

E26.3 EXERCISES

Prelaboratory

1. Balance equation E26-1 using the half-reaction method described in the redox section of this book. What is the excess reagent in this experiment?
2. Calculate the grams of tin (119 g/mole), milliliters of nitrobenzene (123 g/mole, 1.20 g/ml), and milliliters of HCl aq (12*M*, 1.18 g/ml) to use.
3. Why are ground glass joints lightly greased in this experiment?

4. What is the purpose of adding NaCl to the steam distillate?
5. Why is it necessary to treat the product mixture with NaOH?
6. What compound is the ether extraction designed to remove?
7. Make a flow diagram of the synthesis and workup.
8. Review the hazards associated with heating reaction mixtures (Section 0.5) and steam distillation (Section 7.15).
9. Design for this experiment an alternate apparatus using a single-neck flask and a Claisen head.

Postlaboratory

1. *Stu Dent* used the Clemmensen reduction to reduce the keto function of *p*-nitroacetophenone to make 1-ethyl-nitrobenzene. *Anna Lynn* said he should have used the Wolff-Kishner method. What do you think? Explain.
2. Sketch the NMR spectrum you would expect for benzenamine.
3. In one commercial method producing aniline, cast iron scrap turnings and water are put into a cast iron vessel. Hydrochloric acid is added in an amount equal to 1/40 of its stoichiometric amount, causing the reduction to occur primarily via iron and water rather than iron and hydrochloric acid. The mixture is then heated to remove oxides from the surface of the metal. Then nitrobenzene is added and the mixture is vigorously stirred. Nitrobenzene is converted to aniline, and iron is converted to black iron oxide, Fe_3O_4, which can be sold as a black pigment. Write a balanced redox equation for this process of reducing nitrobenzene to aniline.

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2. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 563.

EXPERIMENT 27 SYNTHESIS OF RACEMIC 1-PHENYLETHANAMINE

Time Required: 6–7 hr

Review Techniques and Principles:

Glassware	(0.3)
Heating	(0.5)
Direct steam distillation	(7.15)
Liquid-liquid extraction	(6.2)
Simple distillation	(7.2)
Live steam distillation	(7.15)
Testing pH	(0.11)
Drying liquids	(2.2)
Mortar and pestle	(0.10)
Storing	(0.12)
Labeling	(0.13)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Refractive index	(13.3)
GLC	(11.3)
Wet analysis	(Q7.2, Q8.7, Q9.6)

New Techniques and Principles:

Reductive amination
Carbon dioxide trap
"Freezing" of glass

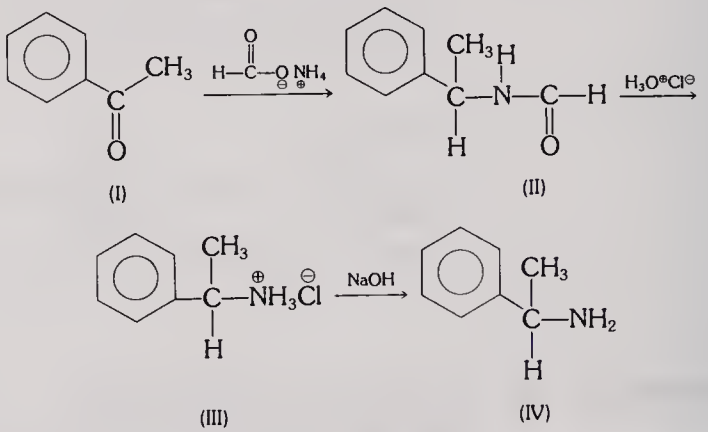
INTRODUCTION

One of the methods for synthesizing amines is reductive amination, so called because the amine is produced by reduction. The reducing agent in a reductive amination is commonly H_2 along with a catalyst like Ni, Pd, or Pt. However, formate ion is also able to act as a reducing agent in reductive amination, and when it is used, the reaction is called the **Leuckart reaction.**

In this experiment, you will prepare 1-amino-1-phenylethane by reductive amination, obtaining a racemic mixture.

E27.1 DISCUSSION OF THE SYNTHESIS

The overall reaction scheme involves three relatively simple steps:

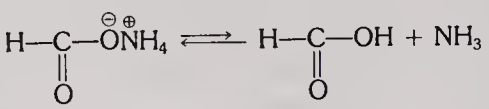


(E27-1)

It begins with acetophenone (I), proceeds via the amide (II) and the amine hydrochloride (III), then terminates with the product amine (IV).

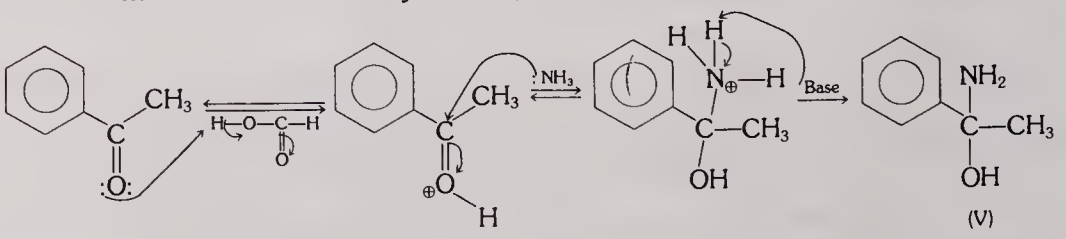
Step 1: Synthesis of Racemic *N*-(1-phenylethyl)-methanamide

Acetophenone is mixed with ammonium formate and heated. At first, two immiscible layers form, but as the temperature rises, a homogeneous solution results and the reaction begins. The ammonium formate is in equilibrium with formic acid and ammonia, although the equilibrium must be far to the left since the K_a of formic acid is 1.8×10^{-4}



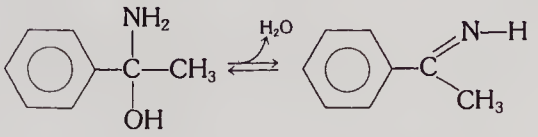
(E27-2)

The formic acid acts as a proton donor to acetophenone, thereby increasing the positive character of the carbonyl carbon, as shown in the first step of equation E27-3:



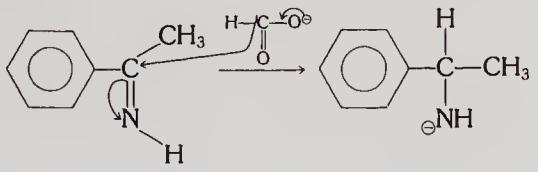
(E27-3)

Next, ammonia, colliding with correct orientation and sufficient force with the carbonyl carbon, loses a proton to some base present in the reaction mixture, yielding the 1-amino-1-hydroxy-1-phenylethane (V). This amino alcohol is unstable and readily loses a molecule of water to form the imine (VI).



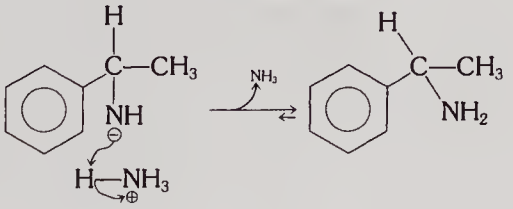
(V) (VI) (E27-4)

Next, the reduction step occurs via decarboxylation of formate ion and intermolecular hydride transfer:



(VI) (VII) (E27-5)

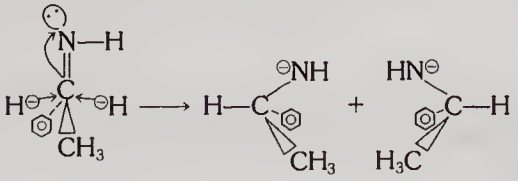
Some of the carbon dioxide produced during decarboxylation causes a noticeable frothing as it escapes from the reaction mixture. Strongly basic anion (VII) abstracts a proton from some nearby Brønsted acid, such as ammonium ion to yield the neutral amine:



(VII) (IV) (E27-6)

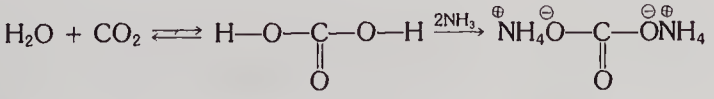
Subsequent reaction of amine (IV) produces the amide (II), which is the end product of the first step.

It is during the hydride transfer that racemization occurs because the imine is planar and collision of hydride with carbon is equally probable from either side:



(Racemic) (E27-7)

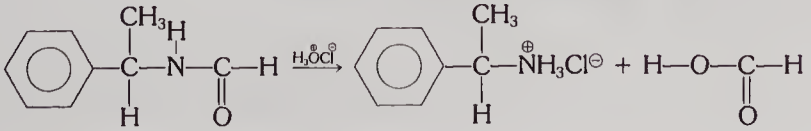
During the first synthetic step to make the amide, the temperature gradually rises to 185 °C; and water, acetophenone, and ammonium carbonate codistill. The ammonium carbonate is produced by attack of ammonia on carbonic acid which was formed by interaction of the byproducts, water and carbon dioxide:



(E27-8)

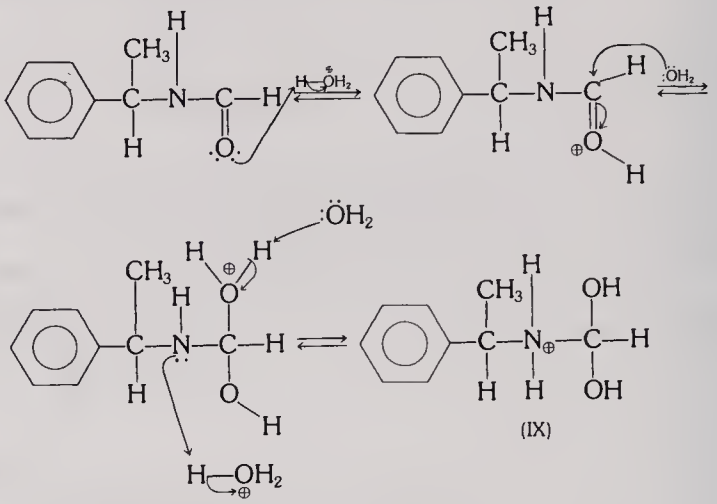
Step 2: Hydrolysis of *N*-(1-Phenylethyl)-meth-anamide

The hydrolysis of an amide proceeds in the same manner as that of an ester. The overall reaction is



(E27-9)

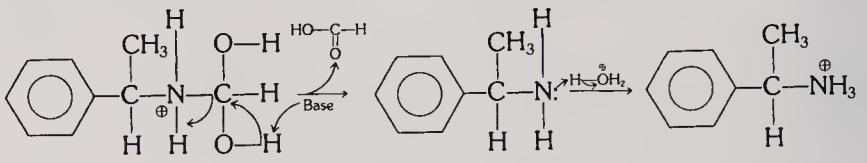
The way this hydrolysis comes about is shown in the next two reaction sequences. Equation E27-10 illustrates acid catalysis at the carbonyl oxygen followed by a properly oriented, sufficiently energetic collision of water with the carbonyl carbon. A series of Brønsted acid-base steps then ensue, which lead to ion (IX).



(E27-10)

(VIII) (IX)

Because the electron pair of the nitrogen in (VIII) has been made more basic than when delocalized in the carbonyl, it readily accepts a proton, forming ion (IX) which now contains all of the properly arranged elements of the amine product. Abstraction of a proton in the first step of equation E27-11 causes the amine to be formed:



(E27-11)

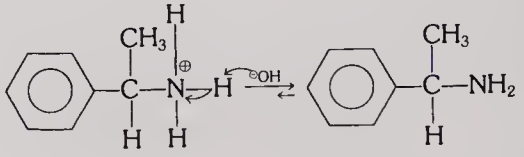
(IX) (IV) (III)

But because of the acidity of the solution, the strongly basic amine accepts a proton and becomes the amine salt (III).

In the workup of this reaction, toluene extractions are used to remove unreacted acetophenone, which you might observe as a small second phase during hydrolysis.

Step 3: Release of 1-Phenylethanamine from Its Salt

To obtain the product amine you must treat its conjugate acid (III) with a strongly basic hydroxide solution:



(E27-12)

(III) (IV)

The equilibrium is shifted to the right by steam distilling the amine from the mixture. The steam distillation purifies the amine at the same time.

E27.2 GLASS IN CONTACT WITH BASE

Whenever a strongly basic solution is to be used with ground glass systems, special precautions should be taken to prevent "freezing" of the joints. A good grade of stopcock

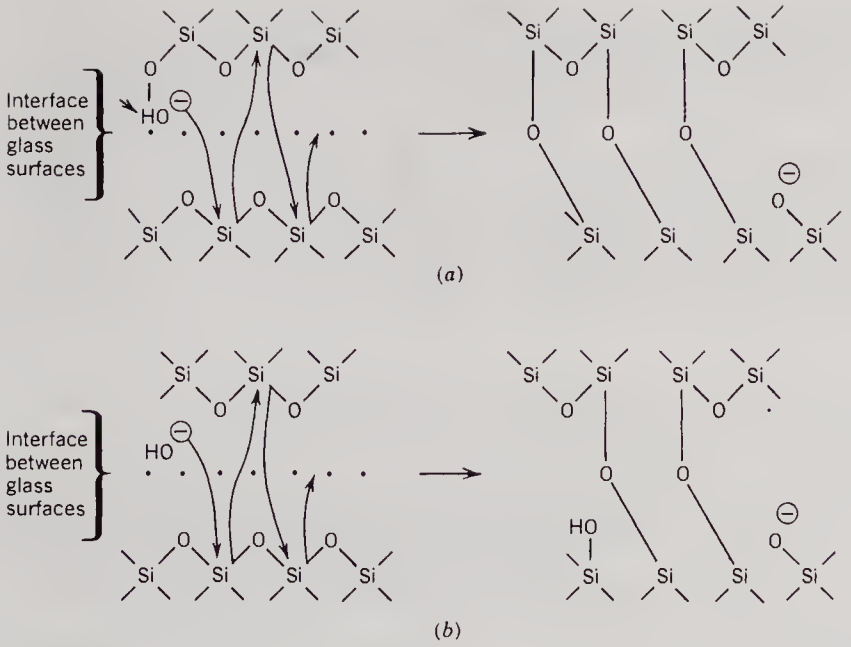


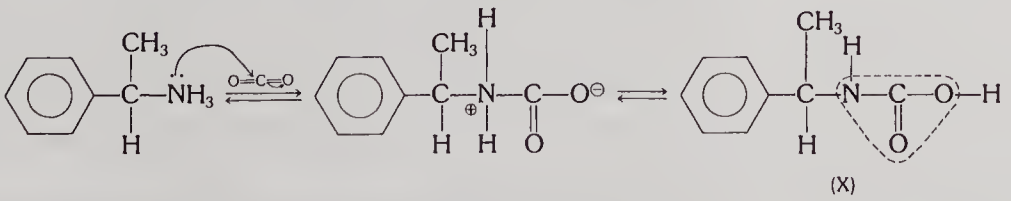
FIGURE E27.1 "Freezing" of glass surface.

grease should be used to coat the joints so that base cannot come in contact with them.

As you can see from Figure E27.1, glass is composed primarily of covalently bonded silicon and oxygen atoms arranged within a highly cross-linked polymeric system. Hydroxylic functions abound in glass, and Figure E27.1*a* illustrates how an amine can initiate a chain of reactions that can chemically bond together the surfaces of ground glass joints. The chain of reactions can also occur by attack of base on silicon itself, as shown in Figure E27.1*b*.

E27.3 PROTECTING THE AMINE FROM CO_2

The product amine (IV) reacts readily with carbon dioxide to form the carbamate (X):



(E27-13)

Recall that a carbamate is a compound containing the structural characteristic circumscribed in compound (X).

This capability of amines to form carbamates is biochemically useful for carrying carbon dioxide through the vascular system of animals. The activation energy of carbamate formation and of the reverse process is very low and the equilibrium is hardly favored one way or the other. Therefore carbon dioxide is readily picked up by amino-bearing side chains on plasma proteins and carried to the lungs, where it is just as easily released and exhaled.

If you want the highest yield of purest product from the distillation step you can keep the amine from reacting with atmospheric CO_2 by assembling a CO_2 trap like that shown in Figure E27.2. The inlet tube from the receiver of the distillation apparatus should be just barely below the surface of the saturated aqueous calcium hydroxide solution so that carbon dioxide does not enter the receiver. However, the tube must not

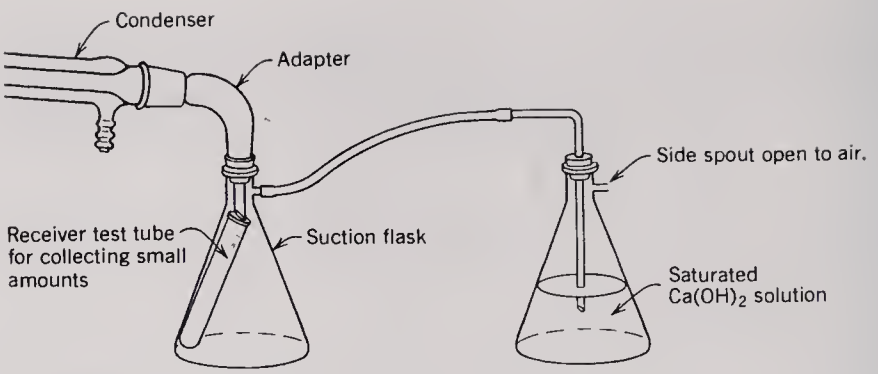


FIGURE E27.2 Carbon dioxide trap.

extend far enough into the solution so that an unexpected decrease in pressure in the distillation apparatus causes aqueous calcium hydroxide to back up into the receiver.

The principle of the trap is that calcium hydroxide reacts with the atmospheric carbon dioxide and produces insoluble calcium carbonate.

E27.4 EXPERIMENTAL PART

Synthesis of N-(1-phenylethyl)methanamide. Assemble a 50-ml round-bottom flask, Claisen head, condenser, and heating mantle as for direct steam distillation. However, through the opening of the Claisen head which is directly over the flask suspend a thermometer so that it will extend well into the liquid when the flask is charged. The thermometer is necessary for monitoring the temperature of the reaction mixture during the reaction. Stopper the offset opening of the Claisen head.

Put 10.0 g of acetophenone (IUPAC 1-phenylethanone), 17.0 g of ammonium formate (IUPAC ammonium methanoate), and one or two boiling chips into the flask. Heat the reaction mixture gently. Record the temperature of the two liquid phases at the beginning of distillation and the temperature at which the mixture becomes homogeneous and begins to boil rapidly. Continue heating gently for about 20 min until the temperature rises to 185 °C. Do not allow the sidearm or condenser to plug up during this period. You can help prevent it by not running too much cold water through the condenser and/or warming the condenser from time to time with steam. When the temperature has risen to 185 °C, cease heating. If it gets higher the amine might distill.

Due to the toxic nature of many of the reactants, most of the work should be done in a hood.

It is a good idea to work with rubber gloves and goggles, especially when handling the strongly basic solutions.

Do not allow the sidearm or condenser to become plugged during the synthesis of 1-phenylethylmethanamide: Pressure could build up in the reaction vessel to a dangerous level.

Put the distillate into a separatory funnel and allow the layers to separate. It might be helpful to warm the separatory funnel with a steam hose to get a better separation and to keep the ammonium carbonate from solidifying. Draw off and discard the aqueous layer; then cautiously and slowly return the acetophenone to the reaction flask. △

Cautiously *add the acetophenone back to the reaction flask. If the contents are still hot, it might cause foaming and overflowing due to rapid creation of vapors.*

Resume heating at no more than 185 °C for 1½ hr. △ If your instructor so directs you, you can put the acetophenone from the separatory funnel into a recovery container instead of back into the flask, and at the expense of a lower yield, omit the additional 1½-hr heating period.

Cool the reaction mixture to room temperature, put it in a separatory funnel, and wash it with 10 ml of water. Draw off the lower layer of crude *N*-(1-phenylethyl)methanamide and return it to the reaction flask. Extract the aqueous layer with two successive 5-ml washings of trichloromethane (chloroform). Discard the aqueous layer down a hood drain. Put the trichloromethane extracts into the reaction flask along with the crude amide. △△

Preparation of 1-phenylethanamine hydrochloride. To the crude amide and trichloromethane extracts in the reaction flask add 10 ml of concentrated hydrochloric acid and a boiling chip. Distill off the trichloromethane and put it in its recovery container. Boil the residue in the flask gently for 40 min, and then cool the reaction mixture to room temperature. If any product crystals deposit in the cooled mixture, add just enough water to make them dissolve when the mixture is agitated. Extract the mixture with three successive 5-ml portions of trichloromethane. If three layers form in the separatory funnel, drain off the two lower layers and save the upper layer. Put the trichloromethane layer (or two lower layers) into its recovery container. There might be some brown deposits left in the reaction flask which are not water soluble. You can use the trichloromethane extracts from the separatory funnel to wash the flask free of deposits. Then put the washings in the trichloromethane recovery container.

Preparation of 1-phenylethanamine. Incorporate a 250-ml round-bottom three-neck flask into an assembly for a live steam distillation, which is best carried out in a well-greased, ground glass system, since the amine attacks cork and rubber stoppers. If cork and rubber connections must be used, an attempt should be made to keep the reflux ring below the stoppers.

Put the aqueous amine salt solution from the separatory funnel into the flask and add a solution of 8.5 g of sodium hydroxide in 17 ml of water. Steam distill the mixture, applying additional heat to the reaction flask if necessary to prevent condensation of steam in the reaction vessel. Check the initial distillate with pH paper as it drops from the condenser, and record the pH. Continue to distill and check the condensate pH until it is 7, at which point no more amine is present. △

Extract the distillate with three 10-ml portions of toluene. Constantly swirling the extracts in an Erlenmeyer flask, dry them for 5 min over a dozen sodium hydroxide pellets, preferably crushed in a mortar with pestle. △△ Stopper the flask during drying. Distill the dry solution via simple distillation into a tared receiver preferably protected from atmospheric carbon dioxide by a saturated solution of calcium hydroxide. Please see Figure E27.2. Collect as product the fraction that distills within a few degrees either side of 185 °C. Put the toluene fraction in its recovery container. Calculate the percent yield. Store the amine in a tightly stoppered, properly labeled vial and, as directed by your instructor, either turn in the sample or save it for Experiment 28. Perform other tests such as IR spectrum, NMR spectrum, refractive index, and wet analysis (Part III) as directed by your instructor.

Writing the discussion. The following items are all pertinent to this project. Pick out the three most appropriate and include them in your discussion: the reason for frothing of the reaction mixture; your product yield related to the return or nonreturn of distilled acetophenone to the reaction mixture; the toxicity of trichloromethane; the method of drying the toluene solution; the color and projected purity of your product relative to the use of ground glass or rubber joints; the spectral data, refractive index, and/or boiling point as they relate to identity of your product; the length of time spent on the project.

E27.5 EXERCISES

Prelaboratory

1. What is the cause of the frothing as the 1-phenylethanone and ammonium methanoate react?
2. What precaution with respect to the distilling column sidearm must be taken during the Leuckart reaction?
3. What potential effects on the liver does trichloromethane have?
4. When the acetophenone, ammonium carbonate, and water codistillate are put into the separatory funnel, which two substances will be in one phase? Check the density of all three components. Which phase should be the lower one?
5. Ammonium formate and methylamine are part of the reaction mixture at the end of the Leuckart reaction. Extraction with trichloromethane is used to separate them from the product amide. Will they be in the aqueous or trichloromethane layer? Will they be in the upper or lower phase?
6. Make a flowchart for the synthesis and workup of *N*-(1-phenylethyl)methanamide.
7. The crude *N*-(1-phenylethyl)methanamide in the aqueous layer of the water wash is extracted into two 5-ml washings of trichloromethane. Will the trichloromethane/product phase be the upper, or lower, layer in the separatory funnel?
8. Make a flowchart for the preparation of 1-phenylethanamine hydrochloride from *N*-(1-phenylethyl)methanamide.
9. What will be the clue that tells you when the steam distillation of amine is complete?
10. During the three 10-ml extractions of the 1-phenylethanamine distillate with methylbenzene, will the methylbenzene/product layer be the upper, or lower phase (check densities)? Will the first lower phase be discarded, or returned to the separatory funnel for further extractions?
11. Do you think a water-cooled, or air-cooled, condenser should be used for the steam distillation? For the distillation of toluene? For the distillation of amine?
12. Why is the amine salt solution made basic before steam distillation?
13. Review hazards associated with distillation (Sections 7.2, 7.15) and extraction (Section 6.2).

Postlaboratory

1. *Mary Juana* often did not have the alert mind required of a good chemist. She was told to get materials ready for next week's experiment on saponification of fatty acid esters to make soap. So she prepared a 6*M* aq NaOH solution and a saturated NaCl solution and stored them in round-bottom flasks with ground glass stoppers. Critique her procedure, justifying your criticism.
2. Because anion (VII) in equation E27-6 is so strongly basic, it is conceivable that it could directly produce amide (II) by attack on ammonium formate. Write a mechanism showing how this could occur.
3. Ammonium carbonate decomposes at 58 °C. Predict the products and write (a) an equation and (b) a mechanism illustrating this reaction.
4. Write equations showing the preparation of 1-phenylethanamine using hydrogen and nickel rather than using the Leuckart reaction.
5. Write equations showing the reaction of 2-butanone in a Leuckart reaction.

REFERENCE

1. Ingersoll, A. W. In *Organic Syntheses;* Blatt, A. H., Ed.; Wiley: New York, 1943; Coll. Vol. II, p 503.

EXPERIMENT 28 RESOLUTION OF RACEMIC 1-PHENYLETHANAMINE

Time Required: 4–5 hr

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Recrystallization	(5.3)
Vacuum filtration	(4.3)
Drying solids	(2.1)
Drying liquids	(2.2)
Simple distillation	(7.2)
Carbon dioxide trap	(E27.3)
Polarimetry	(12.2)

New Techniques and Principles:

Resolution of enantiomers
Optical purity
Antifoam agents

INTRODUCTION

There are two ways that one of a pair of enantiomers can be obtained; first, by isolation from natural sources, as in the extraction of limonene from orange peels (E6), and second, by resolution, the separation of a racemic mixture into enantiomers. Optical purity, characterized by presence of only one enantiomer, is typical of natural products because living organisms usually enzymatically produce only one enantiomer of the pair. Resolution of a racemic or optically impure mixture involves using optically pure reagents that will react with the enantiomers and yield diastereomers that can be physically separated. The optically pure reagents are usually derived from a natural source.

In this experiment, you will resolve the racemic 1-phenylethanamine (1-amino-1-phenylethane) that you prepared in Experiment 27 by making it react with 2(R),3(R)-(+)-tartaric acid.

E28.1 RESOLVING RACEMIC 1-PHENYLETHANAMINE

As you already know, enantiomers have identical properties except for the direction in which they rotate plane polarized light. Therefore, the enantiomers of a racemic mixture cannot be separated by physical methods like distillation or crystallization. However, if the enantiomers are converted into diastereomers, they can be separated because the diastereomers have different properties. So the standard procedure for resolving a mixture of enantiomers is to convert them to diastereomers; physically separate the diastereomers by crystallization, distillation, sublimation, or other technique; and then regenerate the enantiomers.

The resolution of racemic 1-phenylethanamine depends on converting the enantiomers into diasteromeric salts which have considerably different solubilities in methanol. The diastereomers can therefore be separated by fractional crystallization, that is, separated from each other because one isomer crystallizes while the other remains dissolved. After separation, the free amines are recovered from their salts by reaction with sodium hydroxide. Actually the separation will not be as ideal as it sounds, and many repeated tedious crystallizations would be required to obtain a practically complete separation.

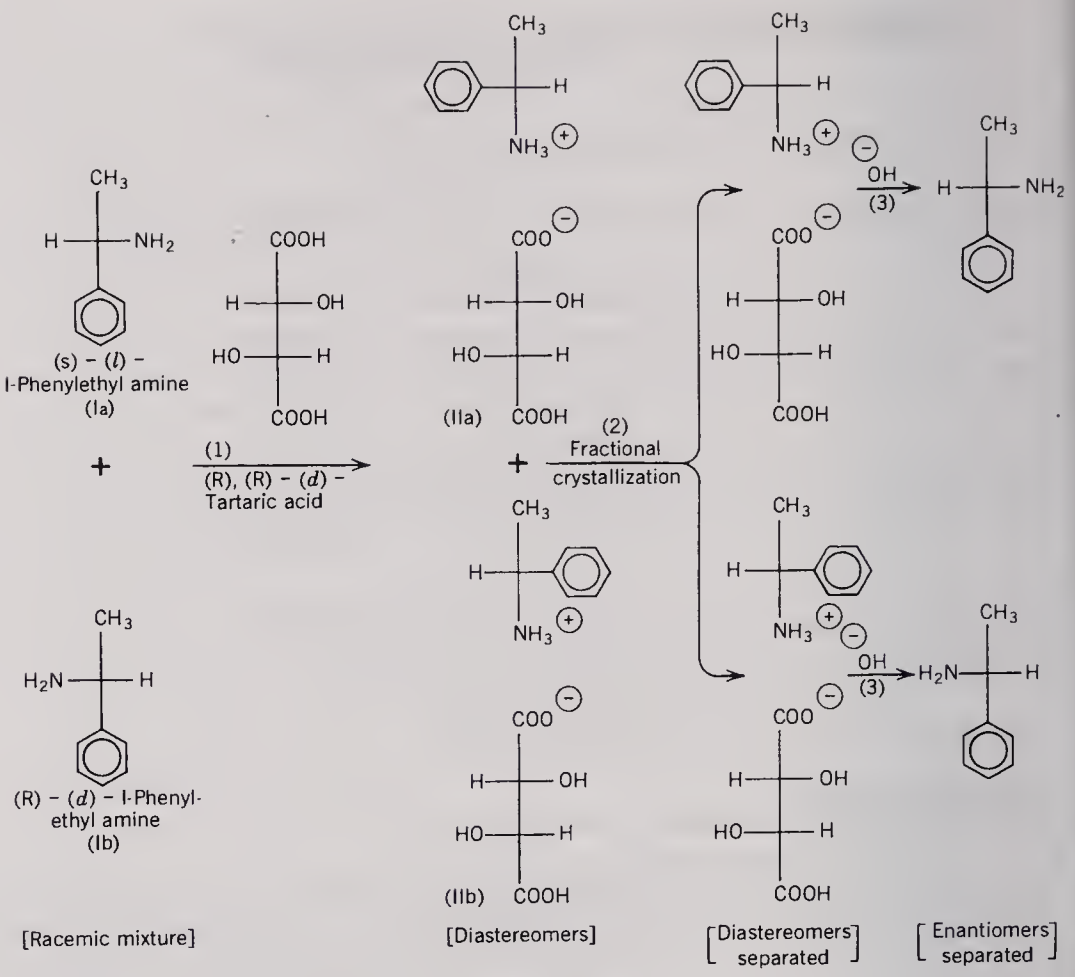


FIGURE E28.1 Resolution of racemic 1-phenylethanamine.

Figure E28.1 summarizes the resolution process: In the first step, the racemic mixture of amines (Ia and Ib), reacts with tartaric acid to yield diastereomers (IIa) and (IIb). The diastereomers are separated by fractional crystallization in the next step, and then converted back into the enantiomers by reactions with sodium hydroxide.

E28.2 OPTICAL PURITY

A complete separation of enantiomers would be ideal, but in practice, the separation is often not complete. Many successive fractional crystallizations might have to be carried out in order to obtain high **optical purity.** Optical purity is the ratio of the specific rotation of a sample to the specific rotation of the pure substance, and is expressed as percent. The optical purity of a given enantiomer could range from 0 (completely racemic) to 100 (pure). Unless you are doing the most precise work, you can calculate optical purity by:

$$\text{OP} = \frac{[a], \text{observed}}{[a]\text{pure substance}} \times (100)\% \qquad \text{(E28-1)}$$

For example, let us suppose that we have a sample of (−)-menthol which is contaminated only by its enantiomer, and that the observed specific rotation is −36°. (Although the units of specific rotation are most properly given as °ml/dm g, in actual practice only the degree sign is used.) Because the specific rotation of pure(−)-menthol is −40.°, the optical purity is $-36 \times 100/-40 = 90.\%$. The actual percent of each enantiomer can be found from

$$\%A = OP + \frac{100 - OP}{2} \qquad \text{(E28-2)}$$

and

$$\%B = \frac{100 - OP}{2} \qquad \text{(E28-3)}$$

wherein enantiomer A is the isomer present in greater quantity. The percent of (−)-menthol in the foregoing example is 90. + (100 − 90.)/2 = 95%.

E28.3 SEEDING

Sometimes a purer product can be obtained by seeding a recrystallization solution with crystals of the desired product. The advantage lies in supplying an established pattern which one kind of molecule fits, but not the other. "Seeding" is a term that arose in the context of recrystallization because "planting" seed crystals causes crystals of the desired kind to grow.

The technique of seeding is very simple: Place some seed crystals in the solution! The major problem that is likely to arise is that the seed crystals will dissolve if the solution is too warm or unsaturated.

In the crystallization of the amine tartrates in this project, it is quite common for both diastereomers to deposit on a single crystal. In such a case, needle-shaped crystals result. The resolved amine from such needles gives $[\alpha]_D^{25}$ of about −20°, as compared to $[\alpha]_D^{25}$ of −40.3° for the (−)-amine. The pure diastereomer of the (−)-amine, (s)-(−)-1-phenylethanamine (R),(R)-(+)-tartrate, deposits prism-shaped crystals, and it is with the prismatic crystals that the solution should be seeded.

E28.4 FOAMS AND ANTIFOAMS

In this experiment and in your future laboratory work from time to time you are likely to have problems with foaming. For example, during distillation a foam might rise up out of the flask into the column, making fractionation impossible.

Foams

A **foam** is a mass of tiny bubbles formed on the surface of an impure liquid. Pure liquids do not foam.

The surface of a pure liquid tends to remain as small as possible. How small? This depends on the strength of intermolecular attractions of molecules in the liquid. Water has stonger intermolecular attractions than ethanol; and ethanol has stronger intermolecular attractions than hexane. This means that the force to contract the surface of water would be greater than that to contract the surface of ethanol; and even greater than the force to contract the surface of hexane. The force within a given area of liquid surface that opposes expansion of the surface is called the **surface tension.** It is a physical property of the liquid.

Surface tension in a pure liquid is caused by the difference in attractions in the body of the liquid as compared to the attractions at the surface. Each molecule in the interior of the liquid is surrounded by other molecules and is therefore subject to attractive forces in all directions. At the surface of the liquid however, each molecule is attracted inward and sideways by its neighbor, but there is no outward attraction to balance the inward pull. Therefore the molecules at the surface tend to move inward, and the surface contracts.

Certain kinds of molecules, soaps, for example, have polar, water-soluble portions and nonpolar, water-insoluble portions. They do not dissolve in water but become concentrated at its surface with the polar ends immersed in the water and the hydrocarbon

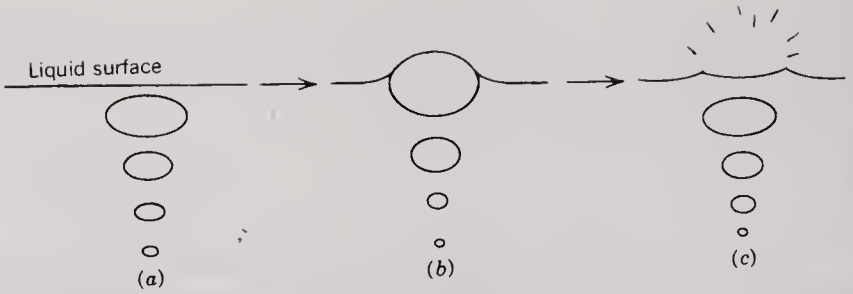


FIGURE E28.2 Bubbles of vapor rising and breaking at surface of boiling liquid. (*a*) Bubbles rise. (*b*) Bubble increases surface area. (*c*) Surface tension causes bubble to break.

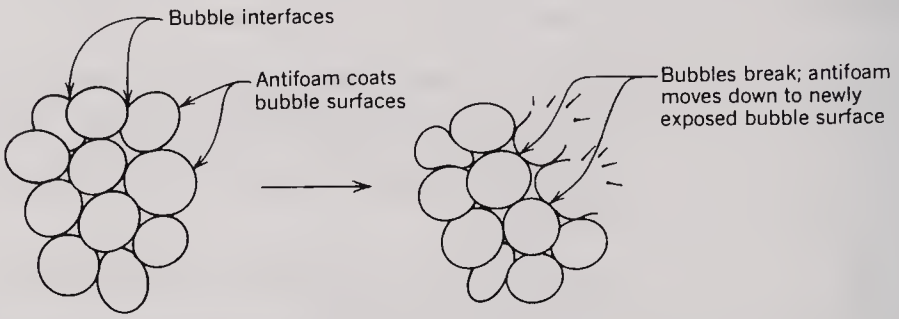


FIGURE E28.3 Antifoam coats bubble surfaces; surfaces thin out, stretch, and break as surface molecules move toward the interfaces where surface tension is greater.

chains protruding from the surface. Covering the surface of water with such molecules makes the composition of the surface different from that of the interior of the liquid, and because the hydrocarbon chains at the surface are attracted to each other only by van der Waals forces, the surface tension is vastly reduced. Such molecules are termed surface active agents, or **surfactants.**

When a pure liquid boils, vaporization causes vapor bubbles to form and to rise to the surface. When the bubbles arrive at the surface, they increase its surface area, but because surface tension tends to keep surface area at a minimum, the bubbles break. The sequence is shown in Figure E28.2. When a surfactant is present, bubbles arriving at the surface of a boiling liquid no longer break easily because the surface tension of the liquid no longer acts as strongly to decrease the surface area. Foaming results.

Antifoams

Foams are essentially unstable and will collapse to a liquid if the surface tension of the liquid can be restored. An **antifoam** is an agent which restores or maintains the surface tension of a liquid.

Antifoams alleviate foaming in one or more of three ways: (1) They displace the surfactant from the surface of the bubbles; then the bubbles collapse. Surfactant displacement occurs as the antifoam spreads over the surfaces of the foam bubbles and attracts the less polar end of the surfactant. In order to spread easily, the surface tension of the antifoam must be less than that of the foaming liquid. (2) Antifoams lower surface tension of parts of the bubble surface more than other parts so the bubble wall becomes very thin and breaks. Because the antifoam is a substance of very low surface tension, and because the interfaces between bubbles do not get covered by antifoam to the same extent as the outer surfaces of the bubbles, the surfaces of the bubbles acquire a lower surface tension than the interfaces. Therefore, the surfaces contract toward the interfaces, and the bubbles burst. Please see Figure E28.3. (3) Antifoams dilute the effect of the surfactant by imposing antifoam molecules between surfactant molecules. Therefore there is no longer a uniform surface of lower surface tension.

In order to be effective, an antifoam must have a lower surface tension than the foaming medium, be largely insoluble in the foaming medium, and be dispersible in the foaming medium.

There are several kinds of antifoams. The kind to use depends on the particular foaming system. In organic solvent systems, polydimethylsiloxane polymers are often effective in concentrations of 10^{-1} to 10^{-5}%.

E28.5 EXPERIMENTAL PART

Preparation of diastereomers and fractional crystallization. Put 6.25 g of (+)-tartaric acid and 90 ml of methanol in a 250-ml Erlenmeyer flask and heat the mixture to 60 °C. Stir it to ensure that the tartaric acid is dissolved. Add 5.0 g of racemic 1-phenylethanamine slowly enough that the solution does not froth and boil over. Stopper the flask and insulate it so that crystals will form very slowly. You will need to provide plenty of insulation. Bring to the laboratory a cardboard box of about five to six times the volume of the Erlenmeyer flask. Loosely crumple a couple of single sheets of newspaper and put them in the bottom of the box. Put the flask in the box, stuff more crumpled newspapers all around the flask, and put the lid on the box. Allow the crystals to form during a period of at least 24 hr. △△ You must obtain prismatic crystals, as opposed to needles. If a mixture of needles and prisms are formed, you can use one of two procedures: (1) Heat the mixture only to the point that the needles dissolve, but not the prisms; then allow crystallization to occur for another 24 hrs; or (2) remove a few prismatic crystals, then heat the mixture just enough to dissolve all remaining crystals. Let the solution cool somewhat; then seed the solution with the prisms. Procedure (2) will be the more appropriate when the ratio of needles to prisms is high. If you obtain only needles, beg, borrow, or steal a few prisms from a fellow student and proceed as in (2)! (Don't get caught at the latter; you might be sentenced to *prism*!) See Figure E28.4.

Once you obtain prismatic crystals, collect them on a Büchner or Hirsch funnel. Rinse them well with a small amount of cold methanol, dry them in air, and weigh them. Save the filtrate, which contains impure (+)-isomer.

(S)-(−)-Phenylethanamine. Put the approximately 4 g of prismatic crystals in a 125-ml Erlenmeyer flask, add about 15 ml of water, and stir the mixture. The salt will partly dissolve. Add to the mixture 2.5 ml of 50% sodium hydroxide solution. Swirl the mixture until all solids dissolve. Put the solution in a separatory funnel and extract the amine with two 8-ml portions of ether (IUPAC ethoxyethane). Put the aqueous layer into a tartrate recovery container. Dry the ether solution over anhydrous magnesium sulfate for about 10 min with occasional swirling. △△ Filter the ether solution into a distilling flask. △△

Using a simple distillation apparatus, distill off the ether and put it in its recovery container. Then distill the amine into a tared vial. If foaming occurs, add a drop or two of 10^{-3}% hexane solution of high viscosity polydimethylsiloxane. Use a carbon dioxide trap. Collect the amine at its boiling point ± 3 C°. Cap the vial immediately after removing the CO_2 trap. △△ Calculate the percent yield.

(R)-(+)-1-Phenylethanamine. Ask your instructor if you should recover this amine. If not, pour the filtrate containing it into a recovery container; if so, distill the methanol from the filtrate containing the (+)-isomer, and put the methanol in its recovery

FIGURE E28.4 Put in *prism by amino* judge.

container. △△ Dry and weigh the salt obtained. △△ Use the same procedure that you used for (S)-(−)-1-phenylethanamine, using proportional amounts of reagents.

Specific rotation. If your polarimeter requires a lot more sample than you have available, your instructor might want you to combine your product with that of one or more other students. If so, record your proportionate contribution to the total. Weigh the total combined amount to three or four significant figures. If necessary, dilute the sample with methanol in order to fill the polarimeter tube. Using a pipet, add 10.0 ml of absolute methanol to the sample. The total volume with negligible error will be equal to the 10.0 ml plus the the volume of the amine, which can be calculated from its density. From this information, you can calculate the g/ml concentration of amine. Determine the specific rotation of the (S)-(−)-1-phenylethanamine. The literature value is $[\alpha]_D^{22} = -40.3°$, neat. If you recovered the (+)-isomer, determine its specific rotation also. Calculate the optical purity of both samples, reporting the percent of each of the enantiomers in the sample. Turn in your properly labeled samples to your instructor.

Writing the discussion. In writing your conclusions, discuss your yield of (S)-(−)-1-phenylethanamine and at least two pertinent items related to the optical purity of your products.

E28.6 EXERCISES

Prelaboratory

1. Since the amount of amine you synthesized in Experiment 27 is unlikely to be exactly 5.0 g, recalculate the proportional amounts of tartaric acid and methanol to use.
2. Review hazards associated with recrystallization (Section 5.3), vacuum filtration (Section 4.3), and distillation (Section 7.2).
3. Will it be appropriate to store the final product amines in containers with rubber or cork stoppers?
4. When you are instructed to extract with two 8-ml portions of ether, does it mean to add a total of 16 ml of ether to the separatory funnel while shaking, or does it mean to remove a 8-ml portion of ether extract, then add a second 8-ml portion?
5. What would be the consequence of adding more methanol than called for to the amine-tartaric acid mixture?
6. After stoppering the flask containing the diastereomeric mixture, what precaution is taken to ensure slow crystallization?
7. What shape crystals are you hoping to obtain?
8. Why is the final amine product kept tightly capped?
9. Make a flowchart for the entire resolution process.

Postlaboratory

1. If in a mixture of (+)- and (−)-limonene the specific rotation is $[\alpha]_D^{25} = 25°$, in methanol, what is the optical purity of (+)-limonene in the mixture? Of (−)-limonene? What is the percent of each isomer in the mixture? The specific rotation is $[\alpha]_D^{25} = +125°$ in methanol for (+)-limonene.
2. Using the Cahn-Ingold-Prelog (R),(S) system, name the diastereomers (IIa) and (IIb) of the equation sequence in Figure E28.1 formed by reaction of racemic 1-phenylethanamine with (R),(R)-(+)-tartaric acid.
3. *Stu Dent* determined the specific rotation of an ( )-nicotine sample contaminated by several other optically active substances to be −120°, neat. The literature value for (−)-nicotine is −162°, neat. He calculated the optical purity and percent (−)-isomer to be 74.1 and 87.0%, respectively. Critique his work.

REFERENCES

1. Ault, A. *J. Chem. Educ.* **1965,** *42,* 269.
2. Theilacker W.; Winkler, H. *Chemische Berichte* **1954,** *87,* 690.
3. Ault, A. In *Organic Syntheses;* Baumgartner, V. H., Ed., Wiley: New York, 1973; Collect. Vol. V, p 932.

XIII AROMATICS

Aromatic compounds are planar and cyclic, possess a completely cyclic pi electron cloud in a relatively small ring, and have the Huckel number of pi electrons.

In the early 1800s it became clear that certain unsaturated compounds possessed distinctly different chemical properties from the open chain compounds upon which the foundations of organic chemistry were being laid. Because many of these substances possessed a pleasant fragrance, or aroma, they were called aromatic. For example, the fragrant compounds of cloves, cinnamon, wintergreen, vanilla, and anise are all aromatic in both senses of the word.

The model aromatic compound is *benzene,* which received its name because it was found to be the decarboxylation product of benzoic acid, isolated from gum benzoin. Early in the nineteenth century, the French chemist, August Laurent, proposed that benzene be called *phene* after the Greek word *phainein* (to bring light) because it had been found to be present in "illuminating gas." Phene is an alternate IUPAC name for benzene. Practice of nomenclature in the United States directs that we use benzene, not phene, as the parent name of a compound. However, we must use phenyl, not benzenyl, when naming a substituent.

In this section, we shall perform a classical aromatic nitration and prepare a diazonium salt as a chemical intermediate. Other experiments involving aromatic compounds (other than solvents) are Experiments 3, 18, 19, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34, 35, 36, 37, 38, 46, and also Techniques 4, 5, 6, 7, and 20.

EXPERIMENT 29 PREPARATION OF NITROANILINES

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Cooling	(0.5)
Adding liquids to reactions	(0.8)
Vacuum filtration	(4.3)
Heating	(0.5)
Testing pH	(0.11)
Recrystallization	(5.3)
Mixed solvent recrystallization	(5.3)
Drying solids	(2.1)

Melting points	(3.3)
IR	(15.3, 15.4)
UV–VIS	(14.3, 14.4)
Storing	(0.12)
Labeling	(0.13)

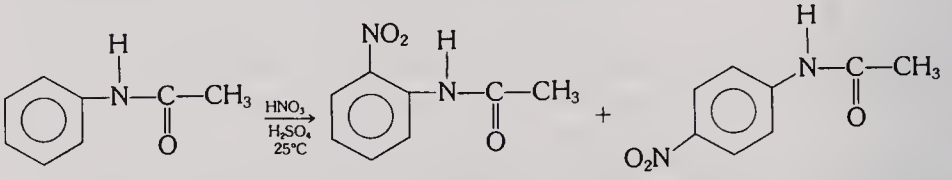
New Principle:

Protecting group

p-Nitroaniline (IUPAC 4-nitrobenzenamine) has industrial significance as a chemical intermediate, particularly for synthesis of dyes.

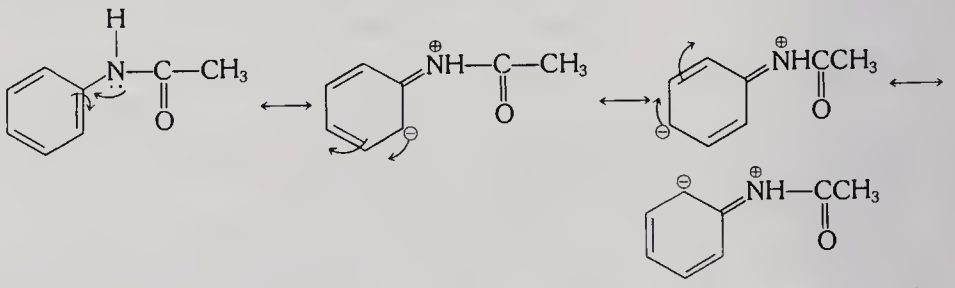
E29.1 DISCUSSION OF THE REACTION

To best appreciate this reaction, you should study in your lecture textbook the well-known mechanism for electrophilic aromatic nitration. The acetylamino (IUPAC ethanoylamino) group attached to the ring directs the electrophilic nitronium ion primarily to the *ortho* and *para* positions on the ring:



(E29-1)

That the nitronium ion should be directed to the *ortho* and *para* positions can be seen by examining the resonance structures of the substrate

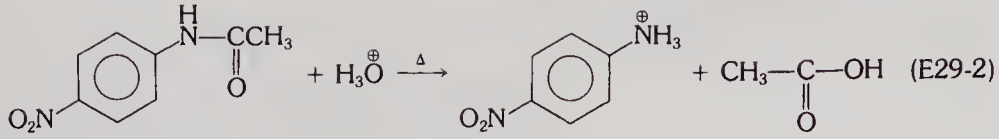


Notice that the negative charges appear at the *ortho* and *para* positions on the ring. Therefore, it is at these locations where an electron pair bond will be most easily made. Statistically, there should be twice as much *ortho* product as *para* product since there are two *ortho* positions. However, on a steric basis, there is no hindrance to collision at the *para* position, whereas the acetylamino function presents an obstacle to properly oriented collisions of the electrophile at the *ortho* position. Another consideration regarding position of attachment is the electron-withdrawing inductive effect of nitrogen. Being relatively electronegative, it draws electrons toward itself, exerting this influence most strongly on the nearest carbons, those *ortho* to itself. By isolating and comparing relative yields of both isomers from this nitration, you can perhaps draw rough conclusions about the relative importance of statistical, steric, and inductive factors.

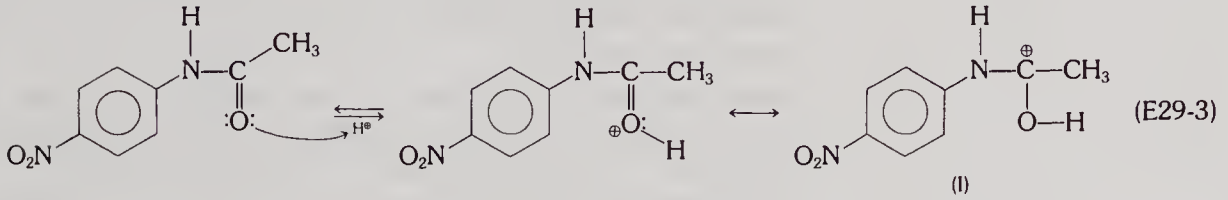
Another observable effect of the acetylamino function is the rate of the reaction. In this reaction the temperature is kept below 25 °C because the electron pair on nitrogen activates the ring, making the reaction take place more easily and faster than it would for benzene.

The glacial acetic acid used in the experimental part is for the purpose of helping to dissolve the reactants.

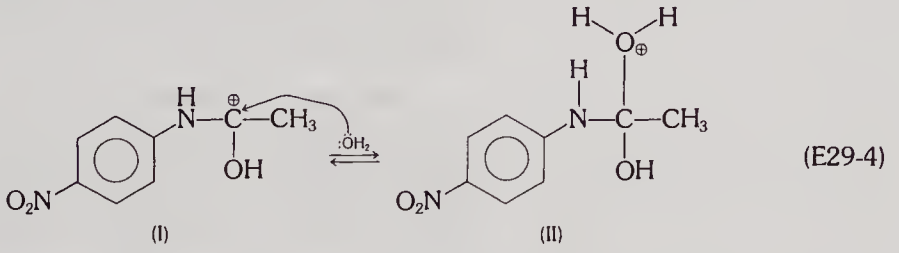
The second step in this two step experimental sequence involves removal of the acetyl group from the amino function. This is readily accomplished by hydrolysis, as shown for *p*-nitroacetanilide (IUPAC *N*-(4-nitrophenyl)ethanamide:



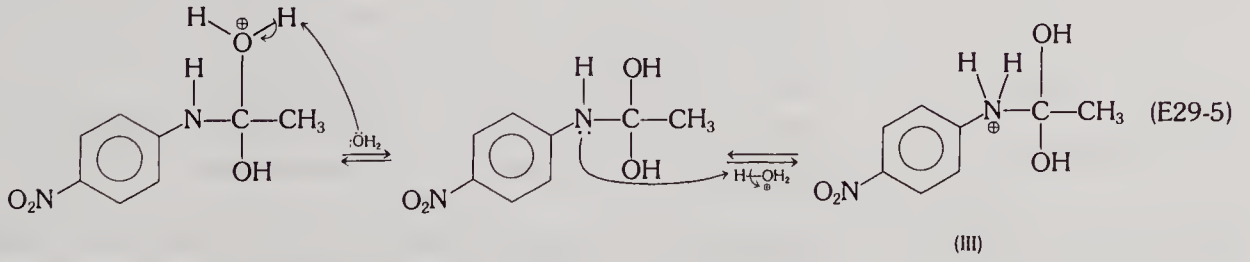
This step requires an acid catalyst to lower the activation energy for forming a new carbonyl carbon-oxygen bond. As you can see from structure (I) of equation E29-3, the carbonyl carbon is much more positive after a proton becomes attached to the carbonyl oxygen:



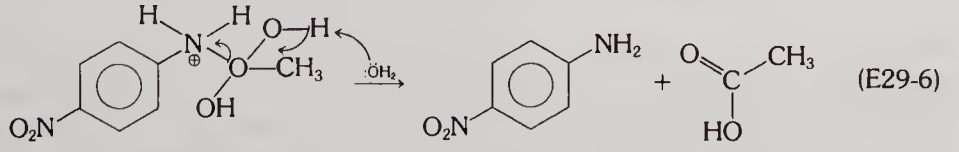
This greater positive character lowers the collision energy required for formation of a new bond when the oxygen of water collides with the positive site in the rate-determining step that produces oxonium ion (II):



Subsequent acid-base steps to remove a proton from oxygen and donate a proton to nitrogen follow:



In the next step, a final removal of a proton from (III) completes the hydrolytic cleavage:



Because *p*-nitroaniline is basic and in a strongly acidic solution, it becomes protonated. Ammonium hydroxide is added to the reaction mixture in order to remove the proton and produce the final product.

You might wonder why the selected substrate is not aniline (IUPAC benzenamine) itself. The reason is twofold: (1) The amino group of aniline is easily oxidized in the presence of nitric acid, and (2) the amino function, readily protonated in acidic solution, becomes a *meta* director rather than being an *ortho, para* director. In this reaction, therefore, the amino function must be protected from oxidation and protonation. The acetyl group functions as a protecting group. A **protecting** group protects some part of a molecule from its environment, and must be easy to put on the molecule, stable under the reaction conditions from which it protects the molecule, and easy to remove.

E29.2 EXPERIMENTAL PART

Nitration of acetanilide. Put 4.0 g of acetanilide (IUPAC *N*-phenylethanamide) into a 250-ml Erlenmeyer flask. Add 4.5 ml of glacial acetic acid and stir the mixture with a stirring rod to dissolve as much of the solid as you can. Cool the mixture to 15 °C and add 6 ml of concentrated sulfuric acid slowly with stirring. Cool the mixture to 5 °C in an ice-water bath.

Working in a hood, put 2.4 ml of concentrated nitric acid in a small Erlenmeyer flask; add 6.8 ml of concentrated sulfuric acid cautiously and with swirling. Mix the acids thoroughly. Cool the mixture to room temperature and put it in a small separatory funnel supported on a ring stand.

It is a good idea to wear rubber gloves and goggles while working with the concentrated acids. Clean up any spills immediately with water, taking care to avoid sudden exotherms when water is mixed with concentrated acids.

Due to the toxicities of the mixtures and compounds involved, all work should be done in a hood, including washing dishes. Toxic nitrogen oxides might be formed when the acids are mixed together.

Clamp the Erlenmeyer flask of p-nitroacetanilide to a ringstand while it is cooling in the ice-water bath. If the flask were upset and water entered the flask a dangerous exotherm and consequent spattering about of acid could result.

Add the nitrating mixture from the separatory funnel a few drops at a time to the cold acetanilide. Do not allow the temperature of the reaction mixture to rise above 25 °C. Keeping a thermometer in the flask, swirl the mixture constantly in the ice-water bath so as to maintain the low temperature. After all of the nitrating solution has been added, allow the mixture to stand for 20 min, continuing to keep the temperature at 25 °C.

Carefully pour the reaction mixture into a beaker containing 75 ml of an ice-water slurry and stir it occasionally over a period of 5 min. The nitration product can be isolated by vacuum filtration at this point, or you can proceed directly to the hydrolysis. △△

Pour waste reagents down a drain enclosed in a hood. The drain must not be a water trough that runs into a nonhooded sink.

Do not allow the reagents to get on your skin or clothing. From Appendix C you can see that the nitroanilines are very toxic and can be absorbed through intact skin.

Hydrolysis of the nitroacetanilides. If you did not isolate the intermediate nitroacetanilides by vacuum filtration, pour the contents of the beaker back into the Erlenmeyer flask and add a couple of boiling chips.

If you isolated the intermediate nitroacetanilide by vacuum filtration, put the filter cake into an Erlenmeyer flask and add 75 ml of 3*M* H_2SO_4 and a couple of boiling chips.

Heating the mixture on a hot plate or with a Bunsen burner, boil the solution gently for 20 min; then cool it to room temperature. Maintaining the temperature of the solution at about 25 °C by using an ice-water bath, add concentrated ammonium hydroxide in portions of about 5 ml until the solution is basic to litmus.

Vacuum filter the mixture in a Hirsch or small Büchner funnel. Then thoroughly wash the solid with water to carry away inorganic salts.

Dissolve the filter cake in a minimum amount of boiling ethanol. Allow the solution to cool until crystals begin to form; then put it in an ice-water bath to complete the crystallization. △△ Collect the crystals in a Hirsch funnel and pour the filtrate into an Erlenmeyer flask. This filtrate contains the *ortho* isomer. Recrystallize the crystals again from ethanol. The product is *p*-nitroaniline. △△

Heat the first alcohol filtrate containing the *ortho* isomer nearly to boiling and add water dropwise until the solution begins to appear cloudy. Add a drop or two of alcohol

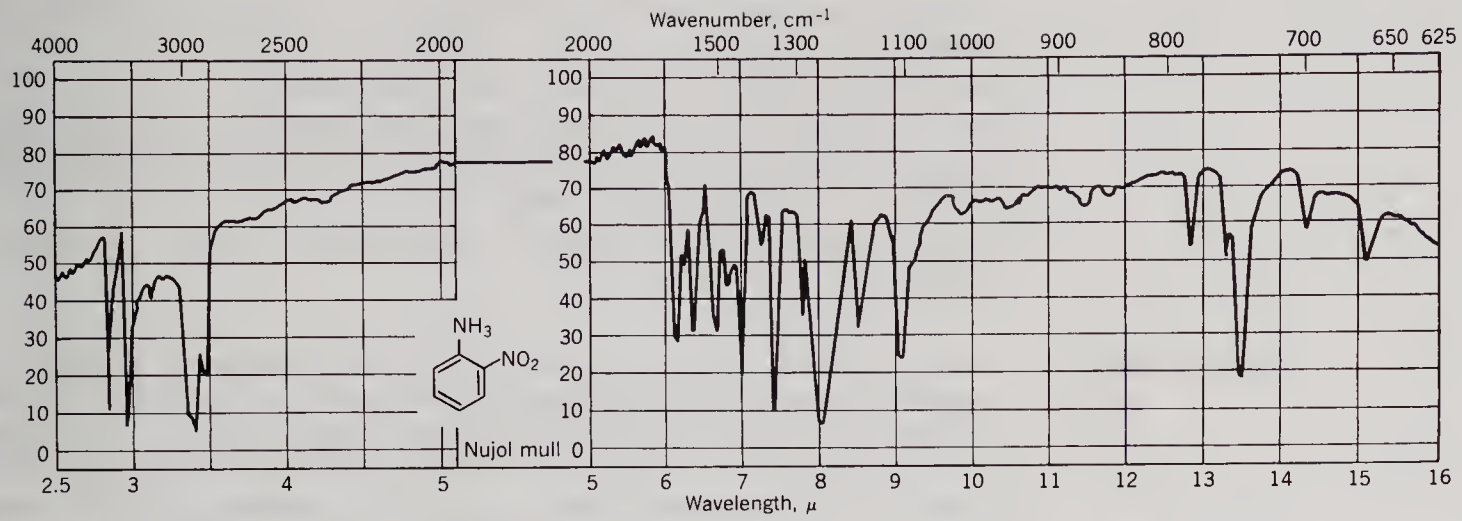


FIGURE E29.1 IR spectrum of o-nitroaniline. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

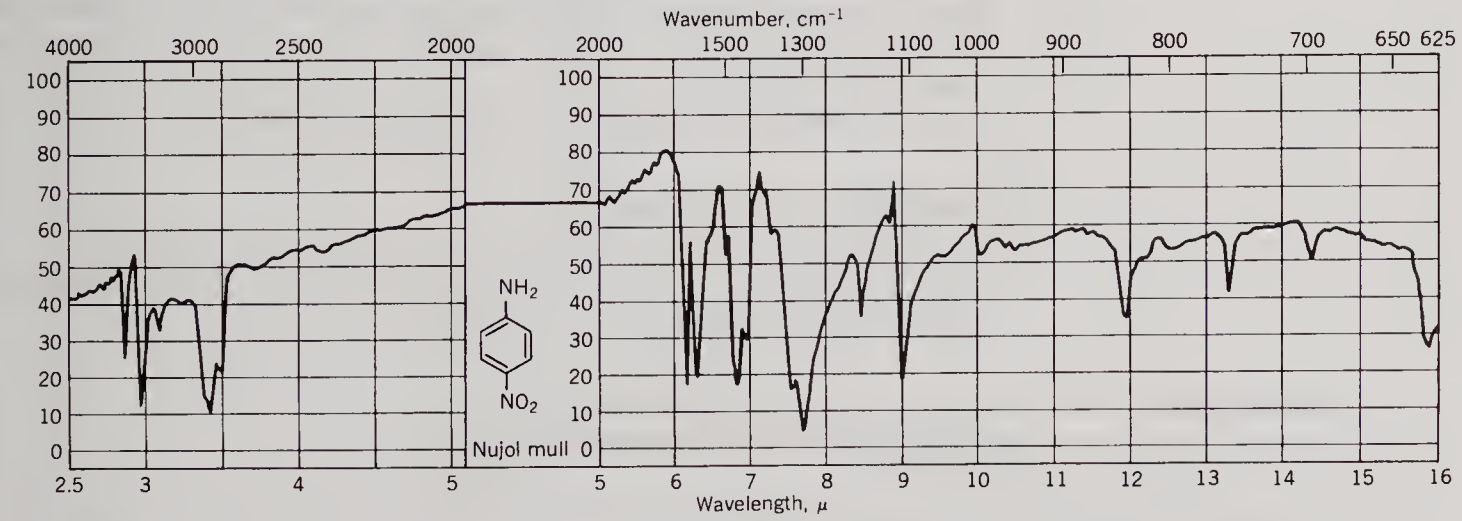


FIGURE E29.2 IR spectrum of *p*-nitroaniline. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

until the haze just disappears. Set the solution in the ice-water bath to crystallize. Filter the crystals in a Hirsch funnel. The product is o-nitroaniline. △△

Dry both sets of crystals, calculate yields, and obtain melting points; and as directed by your instructor, prepare IR and UV–VIS spectra. Turn in the samples in labeled vials. △△

If the products are not pure enough, try column chromatography.

Writing the discussion. Your report should include a discussion of the comparative yields of the two isomers with respect to ring orientation, the synthetic steps, and isolation methods. Also consider identification and purity of the isomers as indicated by the analyses. The UV spectrum of o-nitroaniline in methanol shows maxima at 385, 277, and 232 nm; of *p*-nitroaniline in methanol at 228 nm. Compare your IR spectra with those of Figures E29.1 and E29.2.

E29.3 EXERCISES

Prelaboratory

1. What is the purpose of the glacial acetic acid?
2. Why must the acid nitrating solution be added slowly to the acetanilide?

3. What is the purpose of adding concentrated ammonium hydroxide to the hydrolysis mixture?
4. Make a flow diagram of the workup for the hydrolysis step.
5. After the nitration step you have the option of either isolating the intermediate or of proceeding without isolation. Which option is likely to take less time? To give a higher yield? To make final purification easier?
6. Review hazards associated with vacuum filtration (Section 4.3) and recrystallization (Section 5.3).

Postlaboratory

1. Another way to explain the o-, *p*-orientation of the nitronium ion in nitration of acetanilide is to consider the stability of the benzenonium ion intermediate. Draw the resonance structures for the benzenonium ions produced by *para* and *meta* orientation and explain why *para* substitution gives a more stable intermediate benzenonium ion.
2. Aniline has a far more electron-dense ring than does acetanilide. Explain this on the basis of resonance structures involving the electron pair on nitrogen.
3. Write mechanistic equations like those of equations E29-2 to E29-6 showing how the basicity of *p*-nitroaniline leads to protonation and how ammonia removes the proton.
4. Explain the difference in color of the *ortho* and *para* nitroanilines.

REFERENCES TO SIMILAR PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 581.
2. Mohrig, J. R.; Neckers, D. C. *Laboratory Experiments in Organic Chemistry*, 2nd ed.; Van Nostrand: New York, 1973; p 217.

EXPERIMENT 30 DIAZONIUM SALT PREPARATIONS: 1-IODO-4-NITROBENZENE AND PARA RED

Time Required: 3 hr

Review Techniques and Principles:

Lab notebook	(1)
Stirring	(0.4)
Cooling	(0.5)
Vacuum filtration	(4.3)
Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.3)
IR	(15.5)
UV	(14.4)
Storing	(0.12)
Labeling	(0.13)
Wet analysis	(Q7.1, Q7.2)

INTRODUCTION

Diazonium salt reagents are among the most versatile reagents known, ranking in this regard almost on a par with Grignard reagents. However, diazonium salt reactions have fewer functional group limitations than do Grignard reactions. Some diazonium salt

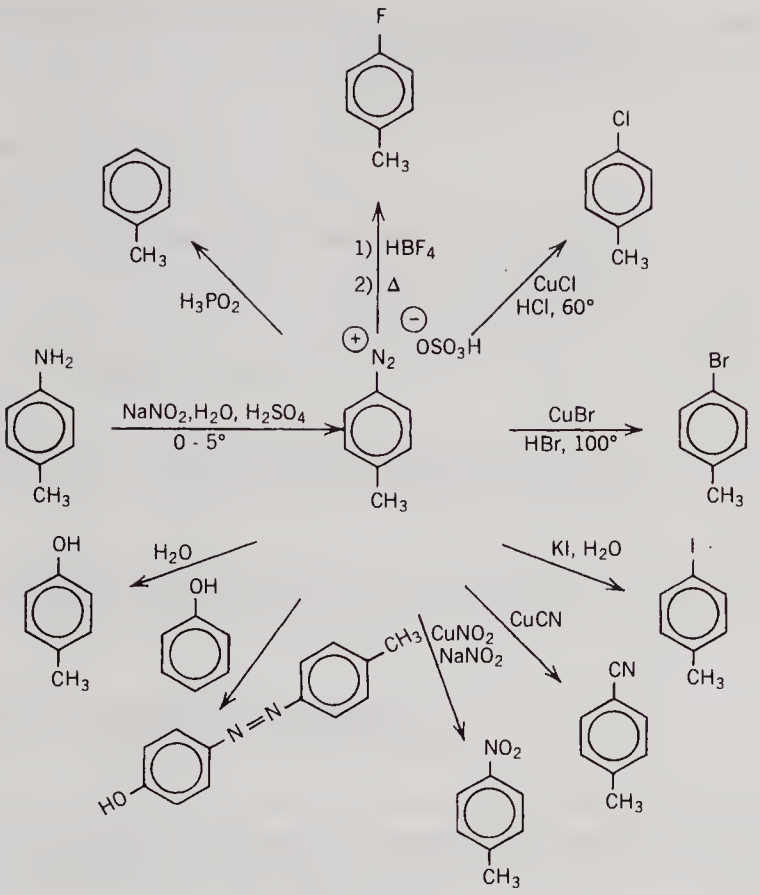


FIGURE E30.1 Diazonium salt reactions.

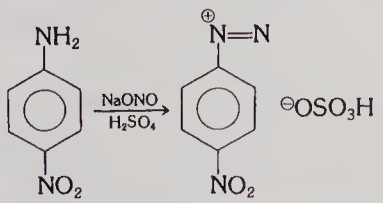
reactions are shown in Figure E30.1, the central structure being an example of a diazonium salt.

The azo portion of the word "diazonium" comes from the French word for nitrogen, *azote*; *di-* is a prefix meaning two; and the suffix *ium* refers to a positive species. Hence "diazonium" means a two nitrogen, positively-charged species.

In this experiment you will diazotize *p*-nitroaniline (IUPAC 4-nitrobenzenamine), that is, make it into a diazonium salt. Then, you will treat the salt in two ways: First, you will replace the diazo portion of the salt with iodide in a nucleophilic substitution reaction; and second, you will cause the diazo portion to couple with β-napthol (IUPAC 2-hydroxynaphthalene) to make the dye, para red.

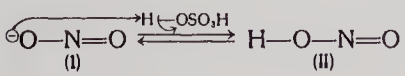
E30.1 DISCUSSION OF DIAZOTIZATION

The diazotization of *p*-nitroaniline proceeds as follows:



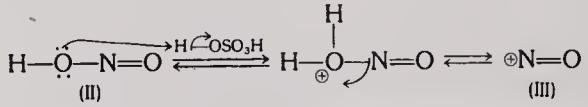
(E30-1)

First, nitrite (I) removes a proton from sulfuric acid to form the unstable nitrous acid (II):



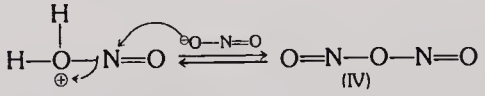
(E30-2)

Next, nitrous acid becomes protonated, loses a molecule of water, and is transformed into nitrosonium ion (III):



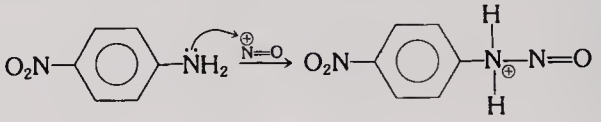
(E30-3)

Alternately, the mechanism might proceed via a dinitrogen trioxide intermediate (IV) rather than a nitrosonium ion:

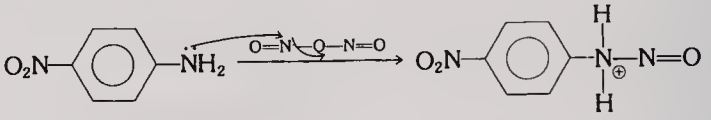


(E30-4)

When nitrosonium in E30-5 or dinitrogen trioxide in E30-6 undergoes a properly oriented collision of sufficient energy with aniline, a nitrogen-nitrogen bond is created:

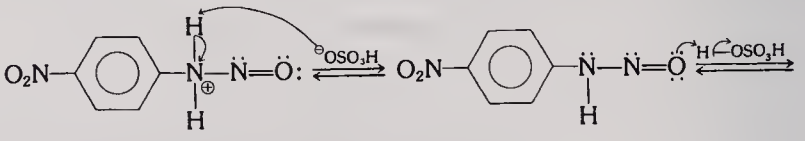


(E30-5)

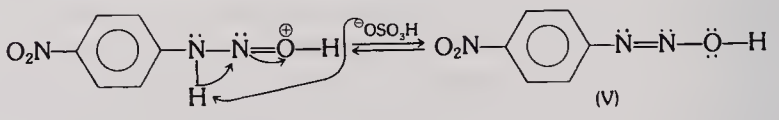


(E30-6)

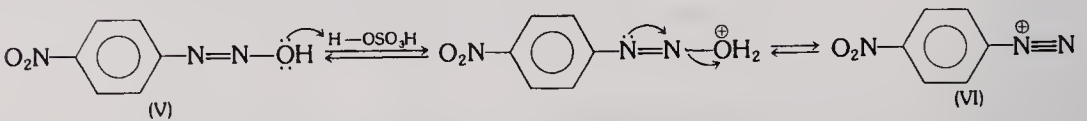
A series of Brønsted acid-base proton transfers follows, yielding diazotic acid (V):



(E30-7)

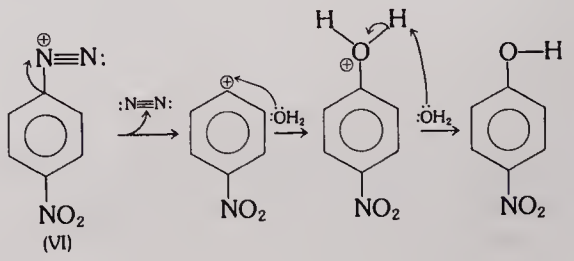


Still another proton transfer, followed by loss of water yields the *p*-nitrobenzenediazonium ion (VI):



(E30-8)

Diazotization must be carried out at low temperature in order to prevent reaction of the diazonium salt with water to yield 4-nitrobenzenol (*p*-nitrophenol). The diazonium salt solution must be kept in an ice-water bath until use, and used as soon as possible. It is believed that the reaction of water with *p*-nitrobenzenediazonium ion (VI) proceeds by an S_N1 reaction:

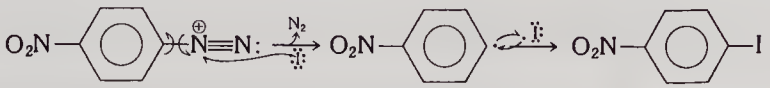


(E30-9)

The rate determining step is loss of nitrogen gas as the leaving group. Because aryl cations are so unstable, even the exotherm associated with having nitrogen as a leaving group is insufficient to make the aryl cation form readily.

E30.2 DISCUSSION OF IODIDE SUBSTITUTION

It is possible that iodide reacts to some extent with *p*-nitrobenzenediazonium by an S_N1 mechanism. However, it is evident that an oxidation-reduction process must also be involved because molecular iodide is a byproduct of the reaction. Iodide is apparently a good enough reducing agent to form phenyl-free radical as an intermediate:

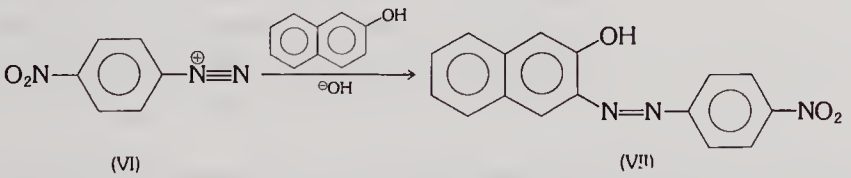


(E30-10)

A considerable amount of foaming results during the reaction due to the loss of nitrogen, and necessitates use of a large container. The 1-iodo-4-nitrobenzene product is insoluble in water and precipitates as it forms.

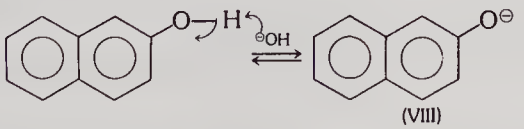
E30.3 DISCUSSION OF THE COUPLING REACTION

The coupling of 2-naphthalenol (β-naphthol) with diazonium ion does not involve loss of nitrogen as a leaving group. Instead, the diazo part of the substrate ion (VI) becomes incorporated by electrophilic aromatic substitution into a conjugated pi system that gives the product molecule, para red (VII), its red color.



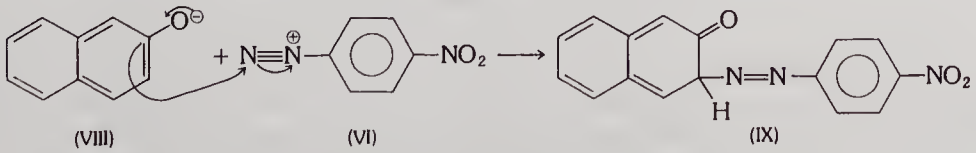
(E30-11)

2-Naphthalenol first loses a proton by sufficiently energetic, properly oriented collision with hydroxide:



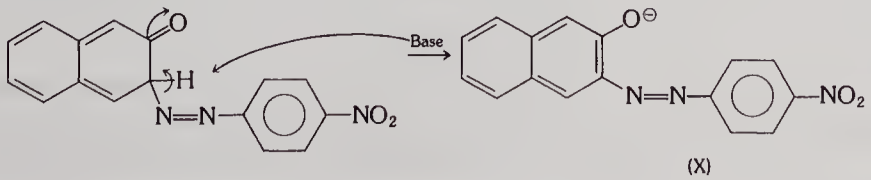
(E30-12)

Upon reaction of the nucleophilic naphthalenolate ion (VIII) with nitrogen of the diazonium salt (VI), coupling occurs, forming cyclic ketone (IX):



(E30-13)

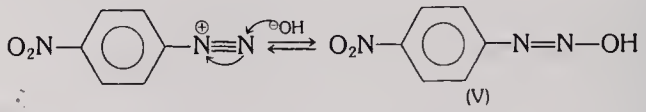
In order to regain the stability associated with aromaticity, the ketone readily tautomerizes to its enolate counterpart (X) by removal of the proton attached to the sp^3 ring carbon:



(E30-14)

Product is formed in one more step by accepting a proton from some acid.

It is important to use the correct balance of acid and base in this reaction because too much base produces *p*-nitrobenzenediazotic acid, (V), which can not couple:



(V) (E30-15)

On the other hand, too little base does not remove the proton from 2-naphthalenol to create the highly negative ion necessary in a coupling reaction. Therefore, trisodium phosphate is added as a buffer to maintain the correct solution pH.

E30.4 EXPERIMENTAL PART

Preparation of 4-nitrobenzenediazonium bisulfate. Put 15 ml of water in a 125-ml Erlenmeyer flask, and carefully add 1.5 ml of concentrated sulfuric acid. Swirl the mixture and add, with constant swirling, 1.5 g of 4-nitrobenzenamine (*p*-nitroaniline). Cool the mixture to 5 °C in a salt-ice bath.

Use pure 4-nitrobenzenamine. The diazotized 2-nitrobenzenamine has been reported to be explosive (ref. 1).

Concentrated sulfuric acid can cause serious chemical burns. Add acid to water; not vice versa.

Prepare a solution of 0.75 g of sodium nitrite dissolved in 3 ml of water, and cool this solution also to 5 °C. Add the sodium nitrite solution to the 4-nitrobenzenamine solution, with swirling and cooling, at a rate such that the temperature does not rise above 10 °C. Keep the mixture in the ice bath until ready to use it. Precipitate will probably be present, but it will go into solution during the reactions that follow.

Do not let diazonium salts dry. They might be explosive.

Preparaton of 1-iodo-4-nitrobenzene. Put 2.5 g of potassium iodide in a 400-ml beaker. Add 12 ml of water and swirl the mixture to effect dissolution. Cool the solution to 5 °C, and slowly add, with swirling, 15 ml of the 4-nitrobenzenediazonium bisulfate solution. Vacuum filter the precipitate in a Hirsch or small Büchner funnel and wash it with cold water.

Recrystallize the product from 95% ethanol, collect the crystals by vacuum, and dry them.

Analysis. Obtain a melting point and, as directed by your instructor, IR and NMR spectra, and wet analysis for halogen. The literature melting point is 171 °C. This product can be used in Experiment 31.

Put the product in a labeled vial and give it to your instructor.

Preparation of para red. Dissolve 0.1 g of sodium hydroxide pellets and 1.0 g of trisodium phosphate in 30 ml of water. Add 0.15 g of 2-naphthalenol (β-naphthol) and dissolve it also. Then cool the solution in an ice-water bath to 10 °C and pour it all at once into the remainder of the diazonium salt solution which was not used to make 1-iodo-4-nitrobenzene. Stir the mixture thoroughly for 5 min; then add enough 1*M* sulfuric acid to make the liquid acid to litmus. Collect the product by vacuum filtration, wash it with plenty of water, and dry it.

As directed by your instructor, obtain IR and VIS spectra. The product will decompose while you are attempting to get a melting point.

Put your product in a labeled vial and submit it to your instructor.

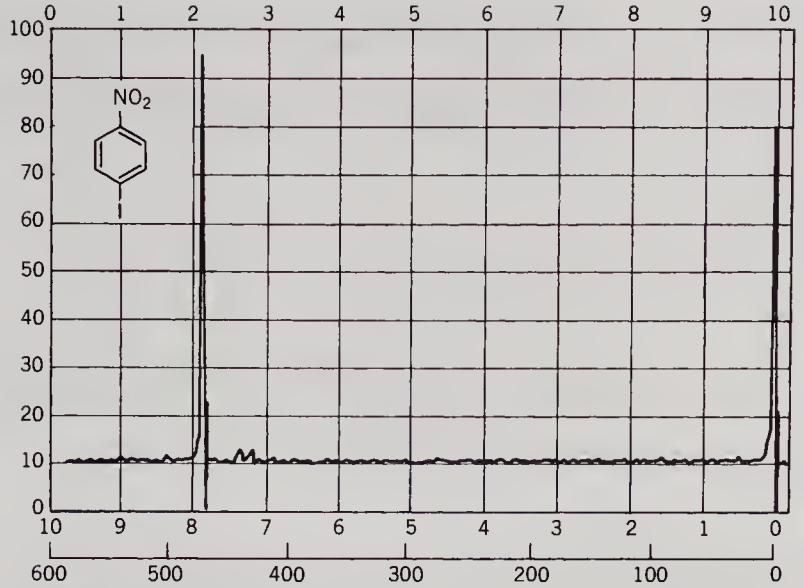


FIGURE E30.2 NMR spectrum of 1-iodo-4-nitrobenzene. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Writing the discussion. Discuss the identity and purity of the products as determined by analyses performed. Consider rationalizing the color of para red in terms of the wavelengths of light absorbed. Discuss the percent yields and make suggestions for improvement. Compare your spectra with Figure E30.2 and those found in the available literature.

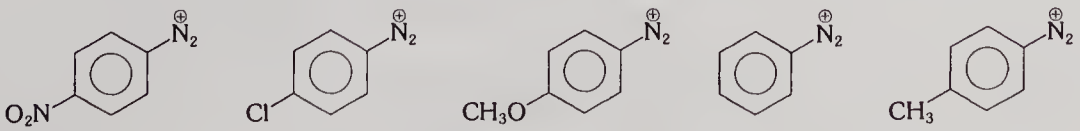
E30.5 EXERCISES

Prelaboratory

1. Why must the reaction mixture be kept cold while preparing the diazonium salt?
2. What two visible signs of a reaction will you observe when iodide is added to 4-nitrobenzenediazonium bisulfate?
3. Sketch the NMR spectrum you anticipate for 1-iodo-4-nitrobenzene.
4. Why must the pH be properly adjusted for the coupling reaction? What reagent is added in order to help maintain the correct pH?
5. Make a flow diagram for the entire experiment.
6. Review hazards associated with vacuum filtration (Section 4.3) and recrystallization (Section 5.3).

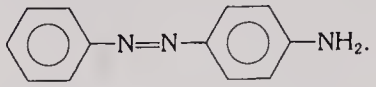
Postlaboratory

1. Various phenyl cations have different stabilities, depending on their substituents. Electron donor substituents stabilize, whereas electron withdrawers destabilize. Arrange the following diazonium salts in order of reactivity, assuming the rate of the reaction depends on the stability of the cation intermediate:



2. Write an equation showing how molecular iodine is formed as a byproduct during the reaction of iodide with benzenediazonium bisulfate.

3. Explain why the coupling of *p*-nitrobenzenediazonium bisulfate occurs primarily *ortho* to the hydroxyl of *beta*-naphthol but primarily *para* to the amino group of aniline.
4. Start with benzene as the only hydrocarbon and show how you could convert it to (a) iodobenzene, (b) 1-chloro-4-iodobenzene (c) aniline yellow,



REFERENCES TO RELATED PREPARATIONS

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 597.
2. Doyle, M. P.; Mungall, W. S. *Experimental Organic Chemistry;* Wiley: New York, 1980; p 239.
3. Pavia, D. L.; Lampman, G. M.; Kriz, Jr., G. S. *Organic Laboratory Techniques,* 2nd ed.; Saunders: Philadelphia, 1982; p 250.

XIV

FAMOUS NAME REACTIONS

The discovery of new chemical reactions has often led to naming the reaction after its discoverer. There are a great many of these named reactions, some of which are so important and useful that they are invariably referred to by name. Therefore it behooves us to become familiar with the names of such reactions as well as the processes.

In this section you will be introduced to five famous name reactions.

EXPERIMENT 31 THE GRIGNARD PREPARATION OF BENZOIC ACID

Time Required: 4–5 hr

Review Techniques and Principles:

Lab notebook	(1)
Adding chemicals	(0.8)
Heating	(0.5)
Cooling	(0.5)
Testing pH	(0.11)
Suction filtration	(4.3)
Extraction	(6.2)
Evaporating liquids	(0.6)
Recrystallization	(5.3)
Melting points	(3.2)
Drying solids	(2.1)
IR	(15.3, 15.4)
Labeling	(0.13)
Wet analysis	(Q8.5, Q9.4)

New Techniques:

Flaming an apparatus
Grignard reaction startup

INTRODUCTION

Grignard reagents are named for Victor Grignard (1871–1935), who was a professor at the University of Nancy in France. In 1912, he was awarded the Nobel prize in chemistry for his work with organomagnesium compounds.

The use of Grignard reagents has been reported to be of more practical importance in the laboratory than any other synthetic method. There have been over 6000 publications dealing with Grignard reagents and syntheses using them. These reagents are primarily useful for making new carbon-carbon bonds.

E31.1 DISCUSSION OF THE GRIGNARD REACTION

A Grignard reaction, the preparation of a Grignard reagent, is generally shown as follows:

$$RX + Mg \xrightarrow{\text{Ether}} RMgX \qquad \text{(E31-1)}$$

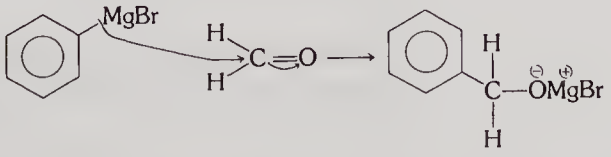
However, there is evidence that the product reagent is really a complex mixture of materials resulting from multiple equilibria, the simplest of which is

$$2RMgX \rightleftharpoons R_2Mg + MgX_2 \qquad \text{(E31-2)}$$

Both alkyl halides and aryl halides react with magnesium in an ether solvent to produce Grignard reagents. Alkyl iodides are more reactive than bromides, and bromides more than chlorides; fluorides are not reactive enough to be useful. Aryl chlorides react too slowly to be useful.

The ether solvent plays an important role in stabilizing the Grignard reagent. The nonbonded electrons of oxygen in the ether interact with the partly positive magnesium in the reagent, solvating it and keeping it in solution. Many ethers are unsatisfactory, but the most common one is ether (IUPAC ethoxyethane) because of its low cost and low boiling point which makes it easy to remove at the end of the reaction.

The characteristic chemical property of a Grignard reagent is its carbanion character. In phenylmagnesium bromide, for example, the carbon attached to magnesium has a considerable negative charge, facilitating bond formation to a partly positive center like the carbon of a carbonyl. Such facility gives rise to a low activation energy, and reactions like the following one are likely to proceed rapidly:



(E31-3)

Because of the highly negative character of magnesium-attached carbon, the reagent has strong Brønsted base properties. This means that any reasonably acidic protons will react with a Grignard reagent. Amines, terminal acetylenes, alcohols, water, phenols, and carboxylic acids are all sufficiently acidic. Because water behaves as an acid in presence of a Grignard reagent, it is absolutely essential that its solution be anhydrous. Otherwise the reagent will be destroyed:

$$CH_3MgI + H_2O \longrightarrow CH_4 + \overset{\ominus\,\oplus}{H}OMgI \qquad \text{(E31-4)}$$

The reagent can also be destroyed by reactions with carbon dioxide (E31-5), with oxygen (E31-6), or by Wurtz-like coupling (E31-7):

$$CH_3MgCl + CO_2 \longrightarrow CH_3{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\ominus\,\oplus}{O}MgCl \qquad \text{(E31-5)}$$

$$2CH_3MgCl + O_2 \longrightarrow 2CH_3\overset{\ominus\,\oplus}{O}MgCl \qquad \text{(E31-6)}$$

$$CH_3MgCl + CH_3Cl \longrightarrow CH_3CH_3 + MgCl_2 \qquad \text{(E31-7)}$$

The carbon dioxide and oxygen reactions can be circumvented by running the reaction under an inert atmosphere or with ether as solvent. The high volatiiity of ether creates a vapor atmosphere which pretty well excludes air from the reaction vessel. The Wurtz coupling cannot be totally eliminated, but its incidence can be decreased by working with dilute solutions and by thorough mixing during preparation of the reagent.

Getting a Grignard reaction to start is often annoyingly difficult. There are generally three reasons for the difficulty: (1) A very common reason is failure to use absolutely dry materials. (2) Another cause is trying to use an alkyl or aryl halide which is not reactive enough. (3) Another common reason is that the magnesium might have an oxide surface. Of course, more than one of these factors could be simultaneously involved.

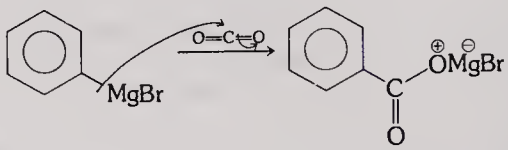
The problem with traces of water is corrected by rigorously following the drying procedures described in Section E31.3.

Nonreactivity of halogenated substrates can sometimes be overcome by adding a crystal of iodine. The iodine apparently reacts with the magnesium, forming magnesium iodide. The iodide ion, being tremendously nucleophilic, next displaces the more sluggish halide on the substrate, producing iodoalkanes or iodoarenes to react with magnesium. One can alternatively add a few drops of iodoethane (ethyl iodide) which, being extremely reactive, forms ethyl magnesium iodide which again acts as a source of iodide ion. Iodoethane also helps by scavenging water and O_2 and helps to break up a MgO coating on the magnesium.

The problem of the magnesium oxide coat is attacked by scratching or crushing some of the magnesium in situ (in location of use).

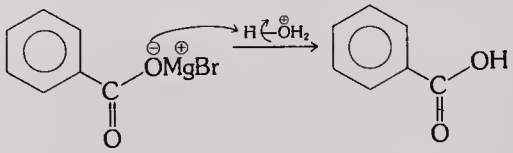
E31.2 DISCUSSION OF THE BENZOIC ACID PREPARATION

Carbonation of the Grignard reagent proceeds as follows:



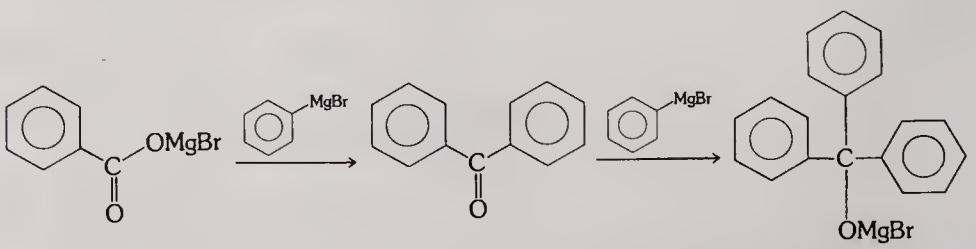
(E31-8)

The magnesium salt of the carboxylic acid must be hydrolyzed. A strong acid is required to donate protons to the weak conjugate base of benzoic acid. Water will not suffice.



(E31-9)

A number of byproducts can arise in the carbonation process, as shown in the following sequence:



(E31-10)

Therefore in the final reaction mixture, you would be likely to find benzoic acid (IUPAC benzenecarboxylic acid) along with benzene, phenylbenzene, benzophenone, and tri-

phenylmethanol. In the workup, the byproducts are extracted into ether, leaving the sodium salt of the benzoic acid (prepared by reaction with sodium bicarbonate) in the aqueous phase.

E31.3 THE TECHNIQUES

The apparatus. Assemble a moisture-free apparatus like that of Figure E31.1. A three-neck flask works well with one neck stoppered, one with a separatory or additional funnel, and one fitted with a condenser. Alternately, you can use a single-neck round-bottom flask with Claisen head. Install drying tubes containing anhydrous calcium chloride or calcium sulfate at the openings of the condenser and separatory funnel. Put the magnesium in the flask. Next, heat the entire apparatus in an oven at 100 °C for 15 min or else heat the exterior with a low Bunsen burner flame. The flaming should heat all parts of the apparatus to a temperature that is uncomfortable to the touch—all parts, that is, except around a Teflon stopcock (which could soften) and around the junctions of inner and outer tubes of the condenser (which could crack). Begin the flaming at the bottom, thoroughly heating the flask and magnesium before proceeding to the upper parts of the apparatus. But the magnesium must not be overheated or it will oxidize. By working upward gradually, all water vapor in the apparatus will be driven up into the desiccant of the drying tubes. Then allow the apparatus to cool to room temperature.

All other equipment used for measuring and transferring reagents and solvent must also be dried and protected with a drying tube.

Flame the apparatus in absence of any flammable solvents. No student should be flaming an apparatus once anyone has started working with ether. Be sure to know the flame-permit time and area assigned.

Allow all flamed containers to cool completely before introducing ether or the halogenated substrate.

Drying solvent and substrate. Use anhydrous ether (IUPAC ethoxyethane) from a newly opened can because ether that has been open to the air might have absorbed

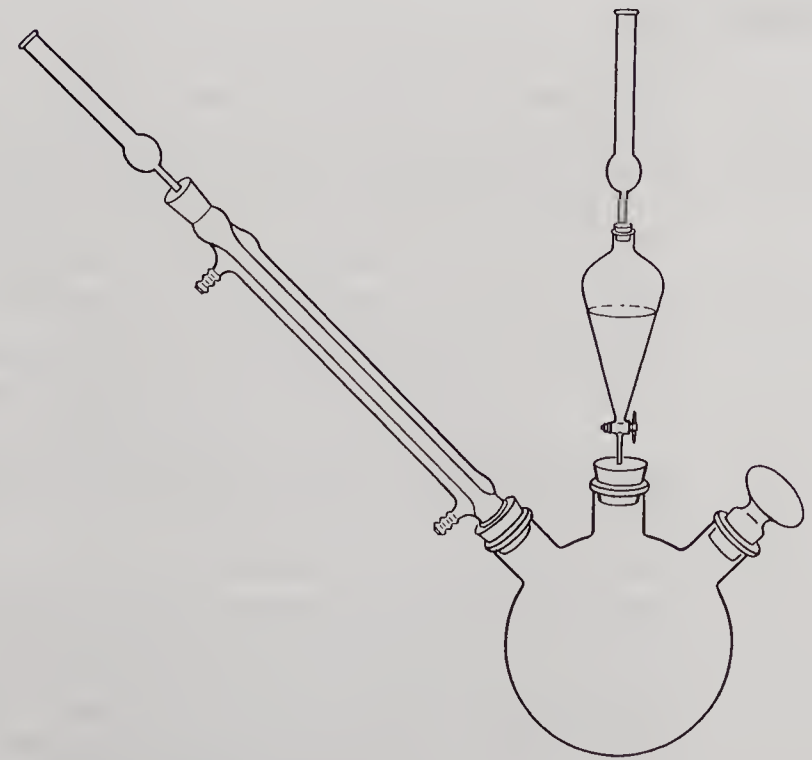


FIGURE E31.1 Grignard apparatus.

moisture. If there is any doubt about its anhydrous character, leave the solvent standing over ample anhydrous calcium chloride overnight and then distill it in a flamed still containing lithium aluminum hydride.

The halogenated substrate can be dried by passing it through a column of activated alumina into a flamed container.

Grignard reaction startup. With ether covering the magnesium in the flask and with halogenated reagent and ether in the funnel, run a small amount of reagent solution into the flask from the funnel. Then observe the contents of the flask for evidence of reaction. You should watch for bubbles at the magnesium surface and/or a gray-brown cloudiness and/or refluxing of the solvent. If the reaction does not appear to start within 2 or 3 min, take the following steps, probably in the order given. In between each step, watch for 2 or 3 min. Keep an ice-water bath at hand to cool the flask and prevent a runaway reaction as evidenced by a reflux ring rising more than halfway up the reflux column.

1. Warm the mixture with a 50 °C water bath until the ether begins to boil. Then withdraw the bath and note whether the boiling stops. If it does not, proceed to (2).
2. Remove the stopper in the flask. With a non-fire-polished stirring rod, gently scratch and crush the magnesium against the bottom of the flask. Take care not to push too hard so as to slip and crack the flask. Replace the stopper and observe. If no reaction ensues, try heating again. Crush again. Heat again.
3. Add a small crystal of iodine. Observe. Warm if necessary. Observe.
4. Add three drops of ethyl iodide. Heat. Observe.
5. Put a concentrated solution of the halogenated reagent in a large test tube. Add some dry magnesium turnings. Crush the turnings thoroughly. Add a crystal of iodine. As soon as the reaction begins to accelerate, pour it into the flask.

Running the reaction. Introduce the halogenated reagent into the flask at a rate that will maintain the reflux condensate ring about one-third of the way up the column with probably about two or three drops per second dripping back into the pot.

E31.4 EXPERIMENTAL PART

Phenylmagnesium bromide preparation. Set up an apparatus like that shown in Figure E31.1, using a 125- or 250-ml three-neck flask. Add 25.0 mmoles of dry magnesium turnings and heat the apparatus to dry it. Put 25.0 mmoles of dry bromobenzene or iodobenzene into 8 ml of anhydrous ether, mix it well, and add it to the separatory funnel without delay. Put 12 ml of anhydrous ether in the flask with the magnesium. Run about 1 ml of bromobenzene solution into the flask. If the reaction does not start of its own accord, proceed as described in Section E31.3.

Keep an ice-water bath handy for preventing a runaway reaction.

Work in a hood, at least when reagent-containing vessels are open.

Once the reaction has started, add the bromobenzene solution at a rate that will maintain refluxing. When all of the reagent has been added, reflux the mixture on a hot water bath for 15 min; then allow it to cool.

Grignard preparation of benzoic acid. Weigh about 8 g of dry ice. Put it into a clean, dry towel and strike it with a hammer or against the floor to crush it. Place the dry ice in a 200-ml beaker and proceed immediately with the next step before moisture from the air freezes on the dry ice. Pour the cooled Grignard reagent slowly over all parts of the dry ice. The reaction will be vigorous, with much bubbling. After addition to the dry ice is complete, stir the mixture until all of the excess carbon dioxide has sublimed away. △△ You can let the mixture stand, unstoppered, overnight during the subli-

mation, or *cautiously* proceed by slightly warming the mixture on a warm water bath or by adding small amounts of warm water or hydrochloric acid.

Use tongs or an insulated glove to handle the dry ice. Its −78 °C temperature will produce frost bite.

Avoid adding the Grignard reagent to the dry ice too rapidly or it will boil over. The same caution applies to adding the hydrochloric acid.

Add about 10 ml of 10% hydrochloric acid to the contents of the flask. Heat the contents on a steam or hot water bath. Cool the mixture and filter off the solid, using a Büchner funnel and vacuum filtration.

Put the solid, crude product in a beaker and add, with stirring, the minimum amount of saturated sodium bicarbonate solution that will dissolve it. Filter off any undissolved residue. Put the solution in a separatory funnel and extract it twice with 15-ml portions of technical grade ether. Put the extracts in an ether recovery container. Put the bicarbonate solution in an appropriate container and remove the excess ether by evaporation. Cautiously acidify dropwise the solution to pH 1 with concentrated hydrochloric acid. Collect the product in a Hirsch or Büchner funnel by suction filtration. △△

Acidify the bicarbonate solution carefully to avoid violent foaming.

If necessary, recrystallize the product from water. Dry the sample and obtain a melting point; also NMR and IR spectra if your instructor requires them. Put the sample into a labeled vial and turn it in to your instructor.

Writing the discussion. You should consider the ease of starting your Grignard reaction, trying to rationalize what factors led to any difficulty. Consider your percent yield and discuss it relative to the process and your technique. Relate the melting point and IR spectrum to the identification and purity of the product. See Figures 16.18 and E18.1 for NMR and IR spectra, respectively, for benzoic acid.

E31.5 EXERCISES

Prelaboratory

1. Why must the entire Grignard apparatus be flamed?
2. What parts of the Grignard apparatus must not be flamed?
3. Why should an ice-water bath be kept ready for use during the reaction?
4. At what rate should the halogenated reagent be introduced into the flask?
5. What precaution is taken in handling dry ice?
6. Make a flow diagram of the procedure you will follow in these preparations.
7. Make a drawing of a Grignard apparatus employing a single-neck round-bottom flask and a Claisen head rather than a three-neck flask.
8. Review operational hazards for heating reactants (0.5), suction filtration (4.3), extraction (6.2), and recrystallization (5.3).

Postlaboratory

1. Write mechanistic, electron displacement equations to show how phenylbenzene is formed during preparation of the phenylmagnesium bromide.
2. The pK_as of water and benzoic acid are, respectively, 16 and 4. Explain why strong mineral acid and not water is used to hydrolyze the carboxylate salt in equation E31-9.
3. Explain which of the following halides would be unsatisfactory as a substrate for preparing a Grignard reagent: 4-bromophenol, iodoethane, chlorobenzene, iodobenzene, o-iodobenzaldehyde.
4. What side reaction might cause aryl iodides to give poor yields of Grignard reagent?

REFERENCES TO RELATED PROCEDURES

1. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 756.
2. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory*; Wiley: New York, 1986; pp 185–191.

EXPERIMENT 32 THE WILLIAMSON SYNTHESIS

Time Required: Two lab periods

Review Techniques and Principles:

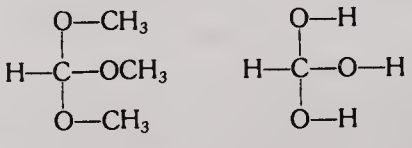
Lab notebook	(1)
Flaming an apparatus	(E31.3)
Reflux	(0.5)
Stirring	(0.4)
Drying gases	(2.3)
Heating	(0.5)
Simple distillation	(7.2)
Vacuum distillation	(7.11)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Boiling points	(3.5)
Refractive index	(13.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
GLC	(11.3)
Storing	(0.11)
Labeling	(0.13)

New Techniques and Principles:

Preparation of alkoxide with potassium metal

INTRODUCTION

The Williamson synthesis is named for Alexander Williamson (1824–1904), professor for nearly 40 years at the University College in London. He was appointed to his position as professor of practical chemistry in 1849 and his first few years of research were remarkably productive. It was during this period, in 1850, that he presented his paper on preparation of ethers to the British Association at Edenburgh. He not only developed the synthesis that bears his name, but also was the first to assign the correct structure to acetone and the first to synthesize ortho esters. An ortho ester is really an ether like trimethoxymethane (I), and can be synthesized in a manner similar to the Williamson synthesis. The ortho ethers are so called because



(I) (II)

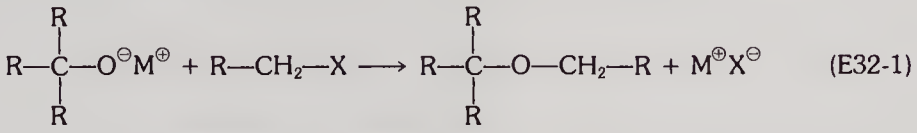
they were thought to be esters of ortho acids, like orthoformic acid (II). The ortho acids are unstable hydrates of carboxylic acids and normally can not be isolated. Professor

Williamson was known as an excellent teacher, and tried to instill in his students the desire and ability to think productively. About laboratory procedures, he would tell them, "If you know clearly what you want to do, there is always a way of doing it."

In this experiment you will prepare benzyl isopentyl ether, which has a powerful, fruity odor and is sometimes used as an ingredient of perfumes, especially for soap.

E32.1 DISCUSSION OF THE SYNTHESIS

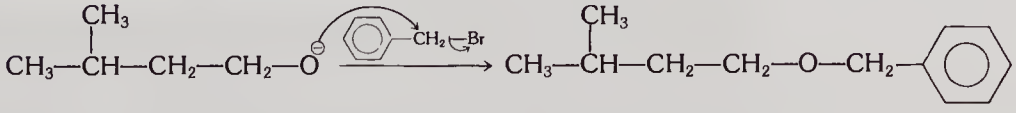
The reaction is an S_N2 reaction of a primary alkyl halide (haloalkane) with an alkoxide or aryloxide nucleophile. The alkyl halide must be primary but the alkoxide can be made from a primary, secondary, or tertiary alcohol. The general reaction is



(E32-1)

wherein R is an alkyl or aryl group, X is Cl, Br, or I or other good leaving group, and M is sodium or potassium. The reason that the alkyl halide must be primary is because as branching on the halogenated carbon increases, elimination to yield an alkene becomes prominent.

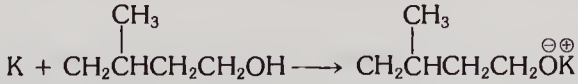
The mechanism of the reaction is simply the one step S_N2 displacement of bromide by isopentoxide:



(E32-2)

By looking at the structure of the product, you can see that there are two possible combinations to make the ether: isopentoxide plus benzyl halide or benzyloxide plus isopentyl halide. However, if you were to use the latter combination, formation of ether would be in competition with production of some alkene, whereas no alkene can form if you use isopentoxide plus benzyl halide.

To prepare potassium isopentoxide you add small pieces of potassium to the isopentyl alcohol:



(E32-3)

You can use either sodium or potassium, but because potassium has a lower ionization energy, it reacts faster.

E32.2 EXPERIMENTAL PART

Preparation of potassium isopentoxide. Firmly attach to a ringstand a 100-ml round-bottom flask fitted with water-cooled reflux condenser. Be sure that the condenser that you use does not have supports at the bottom for column packing. Put a magnetic stirring bar in the flask. At the top of the condenser attach a drying tube containing desiccant. Carry the assembly to a flame-permit area and gently flame the apparatus as described in Experiment 31. Allow the apparatus to cool to room temperature. Temporarily remove the drying tube and pour down through the condenser 15 ml of *dry* isopentyl alcohol (isoamyl alcohol, IUPAC 3-methyl-1-butanol) and 10 ml of dry toluene. Replace the drying tube, put a magnetic stirrer beneath the flask, and start the stirrer. Next, put about 20 ml of mineral oil in a 50-ml beaker and weigh it. Using the density of potassium, estimate the volume that weighs 2.9 g. Using a flat spatula, cut off the appropriate size

piece from the stockroom supply and with tongs or forceps quickly transfer it into your beaker of mineral oil. Weigh the beaker again and obtain the mass of potassium by difference. Adjust the amount of potassium by either removing some or adding to it until you have 2.9 g of it under the mineral oil in the beaker. Now, holding the potassium under the oil with your tongs or forceps, cut the sample into about 10 pieces with your spatula. Dip each piece into a beaker of ligroine to rinse off the mineral oil, then add it through the condenser. First put in one very small piece to determine the violence of the reaction. Having satisfied yourself in this regard, add the remainder at a rate that keeps the reaction well under control. If a piece of potassium sticks to the side of the condenser and does not fall into the flask, push it down with a spatula or stirring rod. Put the ligroine and mineral oil into their assigned recovery containers. If necessary to hasten the reaction rate, heat the mixture under gentle reflux until *absolutely all* of the potassium has reacted. Then cool the mixture to room temperature.

Keep a beaker of i-pentyl alcohol nearby in which to soak tongs, spatula, etc. to dispose of tiny potassium scraps.

Halogenated compounds can react explosively with alkali metals.

Check with your instructor as to where flame-permit areas are located and the time allowed for flaming.

Be certain to cool the apparatus to room temperature before adding the alcohol.

Be careful not to break the beaker while cutting the potassium into pieces.

Add the potassium to the alcohol piece by piece. Moderate the reaction with an ice-water bath if necessary.

It is a good idea to wear rubber gloves while working with potassium.

Set a shield between yourself and the reaction apparatus.

Preparation of benzyl isoamyl ether. Weigh 6.3 g of benzyl chloride (*alpha*-chlorotoluene) and cautiously add it down the condenser into the alkoxide mixture. Mix the reactants thoroughly and, after the initial boiling has subsided, heat the mixture on a steam or hot water bath for 1 hr. Allow the mixture to cool to room temperature. △

Work with benzyl chloride in a hood only. Do not inhale its vapors and keep it off your skin. It is an alkylating agent and potentially a carcinogen. It is a potent lachrymator.

Workup. Add 30 ml of water down the condenser and agitate the apparatus to dissolve the precipitate. Pour the mixture into a separatory funnel and drain down the aqueous layer. Thoroughly wash the organic layer with 50 ml of water, then dry the organic layer over anhydrous magnesium sulfate. Gravity filter the solution into a small distilling flask, add a boiling chip, and distill off the toluene (110 °C) and the isopentyl alcohol (130 °C) at atmospheric pressure, using a heating mantle or oil bath as heat source. As soon as alcohol ceases to distill, cool the flask to room temperature and assemble the flask into a vacuum distillation apparatus. Distill in vacuo, collecting as product the fraction that comes over at the temperature determined by use of the temperature-pressure nomogram of Figure 7.15. The boiling point of the product ether is 236–237 °C at 748 torr and 117–119 °C at 19 torr.

Analysis. As directed by your instructor, obtain an IR spectrum, GLC chromatogram, and refractive index of the product. The refractive index is reported to be 1.4810–1.4850 at 25 °C. Correct the percent yield based on quantitative GLC analysis.

Writing the discussion. Based on the analysis you performed, discuss the product identity and purity. Discuss also the percent yield, relating it to the various steps in the procedure, and make suggestions for increasing it.

E32.3 EXERCISES

Prelaboratory

1. Why is it necessary to use dry reagents and a dry apparatus for these reactions?
2. Why is potassium kept under mineral oil while cutting it and waiting to use it?
3. What is the density of potassium? About how many milliliters of it have to be cut from the stockroom piece to make up 2.9 g? Show your calculations.
4. Make a labeled sketch of the equipment setup for preparation of the potassium isopentoxide.
5. What is the byproduct precipitate that is dissolved by adding 30 ml of water to the product mixture?
6. What is the IUPAC name for isoamyl alcohol?
7. Make a flow diagram for this experiment, noting at each step all of the reactants and products present.

Postlaboratory

1. Write a mechanism that explains how isopentyl bromide reacts with benzyloxide to make an alkene.
2. Name the product ether of Experiment 32 by the IUPAC system of nomenclature; by the oxa system.
3. Write a formula for and give an IUPAC name to the elimination byproduct of the reaction of sodium methoxide and 1-bromobutane.
4. Show the products that would be formed by reaction of (a) potassium 2-methyl-2-butoxide and 2-bromopropane; (b) sodium ethoxide and chlorobenzene at room temperature; (c) sodium phenoxide and bromoethane.

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1. Tilden, W. A. *Famous Chemists;* George Routledge and Sons, Ltd.: London, 1921.
2. *The Givaudan Index,* 2nd ed.; Givaudan-Delawanna: New York, 1961.
3. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; pp 669–671.
4. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; pp 184–191.

EXPERIMENT 33 FRIEDEL-CRAFTS ACYLATION

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.2)
Adding reagents	(0.8)
Stirring	(0.4)
Cooling	(0.5)
Heating	(0.5)
Liquid-liquid extraction	(6.2)
Extraction of acids	(6.1)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Vacuum filtration	(4.3)
Distillation	(7.2)

Microdistillation	(7.18)
Storing	(0.12)
Labeling	(0.13)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
UV	(14.4)
Wet qualitative tests	(Q8.4, Q9.3)
Boiling points	(3.5)

INTRODUCTION

In 1877, a French chemist, Charles Friedel, and an American chemist, James Crafts, collaborated in discovering a process for attaching alkyl and acyl substituents to aromatic compounds. Such processes, now known as Friedel-Crafts alkylations or acylations, respectively, are still widely used.

Charles Friedel (1832–1899) was successor to Wurtz at the Sorbonne in Paris. He was the first person to make 2-propanol by reduction of propanone, and to report, along with Crafts, the process of transesterification. He was also one of the pioneers of organosilicon chemistry.

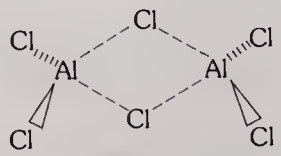
James Mason Crafts (1839–1917) was a student of Bunsen and of Wurtz. He became a chemistry professor first at Cornell and then at Massachusetts Institute of Technology. He resigned his post in 1874 and returned to Wurtz' laboratory, where he remained for 17 years, largely in collaboration with Friedel. He returned to M.I.T. in 1891 as chemistry professor, and rose to department head in 1895 and to president of M.I.T. in 1897.

Friedel-Crafts acylations are important and useful reactions in aromatic chemistry. They circumvent some of the problems associated with the aromatic alkylations, namely (1) multiple alkylations caused by ring activation from the first attached alkyl group, (2) rearrangements of the alkyl group, and (3) inability to subsequently attach other substituents to the ring in the *meta* position. The product of a Friedel-Crafts acylation is an aromatic ketone.

In this experiment, you will prepare a ketone most commonly called *p*-methoxyacetophenone, although it is also known by the trivial name, acetanisole. It is quite unusual (perhaps for good reason!) to hear it given its systematic name, 1-(4-methoxyphenyl)ethanone. Acetanisole, a natural ingredient of castoreum and other plants, has a flowery odor which is useful in mimosa, acacia, new-mown hay, and other floral perfumes. It is also used in soap perfumery.

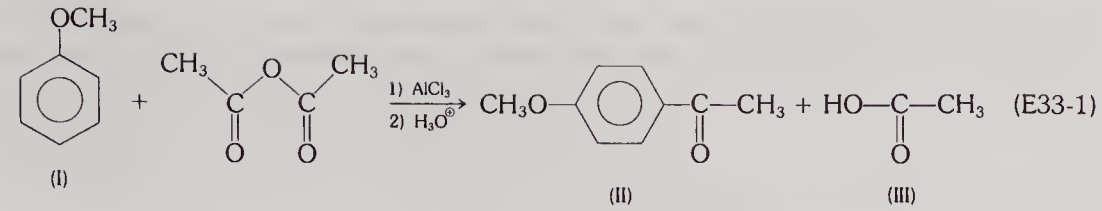
E33.1 DISCUSSION OF THE REACTION

Although $AlCl_3$ is the most commonly used catalyst in Friedel-Crafts reactions, a number of other catalysts like BF_3 and $SnCl_4$ can be used. Such catalysts possess empty *p* orbitals at the valence level and act as Lewis acids. Even though aluminum chloride is usually shown with the formula $AlCl_3$ (the form in which it exists in the solid state) its structure in nonpolar solvents such as benzene is dimeric with formula Al_2Cl_6; the formation of the dimer is due to the tendency of aluminum to complete its octet.



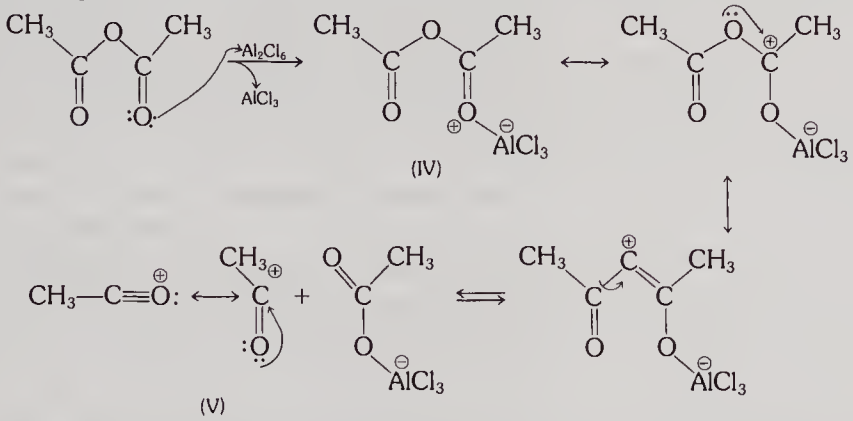
The configuration of chlorides about each aluminum is roughly tetrahedral.

You will prepare acetanisole (II) by reaction of anisole (I) with acetic anhydride in the presence of aluminum chloride as the catalyst:



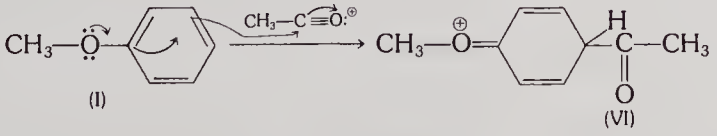
(E33-1)

The reaction begins as acetic anhydride's carbonyl oxygen undergoes a sufficiently energetic, correctly oriented collision with aluminum of the catalyst, producing the Lewis acid-base complex (IV):



(E33-2)

The resonance-stabilized complex exists in equilibrium with a small amount of acylium ion (V). Acylium, stabilized by resonance as well as by hyperconjugation, is of course highly electrophilic and relatively easily forms a bond when it reacts with the electron-dense ring of anisole (I):

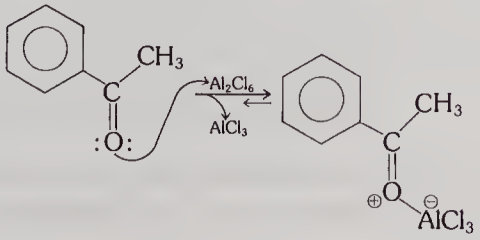


(E33-3)

The benzenonium ion (VI) subsequently loses the proton attached to its sp^3 ring carbon and becomes a molecule of product.

The major product of the reaction should be the *para* isomer for the following reasons. Although it is possible for the *ortho* isomer to be a product also, it is less likely than *para* on two accounts: First, the position *ortho* to methoxy experiences an inductive deactivation by oxygen and second, methoxy sterically inhibits *ortho* collisions. Once *p*-methoxyacetophenone is produced, it is less likely than anisole to react with an acylium ion because the newly attached keto function deactivates the ring by resonance and induction and because it sterically inhibits further collisions. Keeping the reaction temperature low also helps to prevent multiple acylations.

Friedel-Crafts acylations are commonly carried out with either acid chlorides or acid anhydrides, but there are advantages in using anhydrides. They are more readily available in good purity, are somewhat easier to work with because the reaction is not as violent, yield few byproducts, and produce product mixtures from which the ketone products can be removed in high purity by a single distillation. The major disadvantage is that aluminum chloride is required in greater quantity. Whereas an *alkyl*ation requires about 0.1 mole of $AlCl_3$ for each mole of alkyl halide, an acid chloride *acyl*ation needs 1.1 moles of $AlCl_3$ per mole of acyl chloride because the product ketone strongly complexes with catalyst, thereby removing it from the reaction arena:



(E33-4)

Acylation with an anhydride requires 2.1 moles of $AlCl_3$ per mole of anhydride because the catalyst also becomes bound to the byproduct acetic acid (III) in equation E33-1.

Although molecular rearrangements can be a problem in Friedel-Crafts alkylations, they do not occur during acylations because the acylium ion is more stable than any alkyl cation that could form from it by a 1,2-hydride shift.

E33.2 THE TECHNIQUES

Weighing $AlCl_3$. Because of the fuming of aluminum chloride in moist air, you must weigh it rapidly and put it into a tightly covered container immediately. Furthermore, you should weigh it in a hood in order to protect the laboratory personnel from the fumes of HCl. Leave the reagent jar open no longer than necessary.

Bottles of anhydrous aluminum chloride which have been closed for a while sometimes have a high internal pressure due to release of HCl gas. Wrap a dry cloth around the region of the lid and open with care.

Weigh aluminum chloride in a hood only.

Do not allow anhydrous aluminum chloride to come into contact with water. A dangerous exotherm will result.

The dropping funnel. You can make a separatory funnel function as a dropping funnel by leaving the stopper off the top. Protect the contents of the funnel from moisture by affixing a drying tube containing coarse granules of desiccant. Adding a small amount of some indicator Drierite is handy because its color turns from blue to pink when hydrated. Keep the drying tube stoppered at both ends when not in use. Put hydrated Drierite in a recovery container so that it can be heated in an oven and made anhydrous again.

The HBr trap. You can keep HBr evolved during the Friedel-Crafts reaction out of the atmosphere by conducting the HBr into a container of water. Make the trap from a 250-ml Erlenmeyer flask fitted with a *two-hole* stopper. Put a glass tube in one hole and leave the other open to prevent pressure buildup within the flask. The tube must not extend beneath the surface of the water because change in pressure occurring between additions of acetic anhydride might draw water into the reaction vessel to react exothermically and perhaps violently with the anhydride and aluminum chloride therein. The HBr will be largely taken up by the water in the trap, yielding hydrobromic acid. At the end of the reaction the acid can be put in a recovery container for use in other experiments in which acid washes are required.

Make certain that the HBr trap in use is open to the atmosphere so that pressure does not build up in the apparatus.

Keep the inlet tube above the liquid in the trap so water does not back up into anhydrous reactant and cause a dangerous exotherm.

E33.3 EXPERIMENTAL PART

Apparatus. Leaving room for heating and cooling baths beneath, clamp a 25-ml round-bottom flask to a ringstand and insert into its neck a Claisen head. Put a small dropping funnel directly above the flask and an upright condenser in the offset arm of the Claisen head. Put drying tubes on the separatory funnel and at the top of the condenser. All parts must be dry and clamped to the ringstand. Attach a gas trap to the top of the condenser and charge it with 10% aq NaOH.

Clamp all components of the reaction assembly solidly in place so that the dangerous reactants will not spill onto you or into each other and violently react.

Bottles of anhydrous aluminum chloride which have been closed for a while sometimes have a high internal pressure due to release of HCl gas. The lid areas should be wrapped in a dry cloth and opened with care.

Weigh the aluminum chloride in a hood.

Aluminum chloride is a strong acid and must not come in contact with skin and eyes. Do not inhale the dust or fumes that arise from it.

Preparation of acetanisole. Remove the flask from the ringstand and put 1.35 g of anisole (methyl phenyl ether, IUPAC methoxybenzene) into it along with 10 ml of methylene chloride (IUPAC dichloromethane). Carefully and rapidly weigh 3.6 g of anhydrous $AlCl_3$ into a dry vial and cap it. Insert a dry powder funnel into the flask and add the $AlCl_3$ in small portions, agitating the flask after each addition and if necessary cooling the flask in a cold water bath to keep the contents from boiling. After addition is complete, cool the flask to room temperature and, being careful that the joint to the Claisen head is tight, put 1.25 g of acetic anhydride (IUPAC ethanoic anhydride) into the dropping funnel.

At a rate of about one drop every 3 s, add the acetic anhydride through the dropping funnel directly into the agitated liquid. Stir continuously with a magnetic stirrer or carefully agitate the entire assembly so as to induce a rapid, swirling motion of the liquid in the reaction flask. If the exotherm causes boiling, decrease the rate of anhydride addition and/or cool the reaction flask with the cold water bath. You will save time if you cool the mixture rather than decrease addition rate. When all of the anhydride has been added and the reaction is obviously no longer vigorous, heat the flask (still part of the total reaction assembly) on a 50 °C water bath for about 30 min to complete the reaction.

Work behind a safety shield during addition of the acetic anhydride to protect yourself from a suddenly violent reaction.

Slow addition and constant agitation are necessary during the acylation in order to avoid sudden exotherms and a violent reaction.

Remove the water bath, disassemble the apparatus, and discard the liquid from the acid trap down the drain. While the mixture is still warm, slowly and *cautiously* pour the contents into a 100-ml or larger beaker containing 10 ml of concentrated hydrochloric acid and about 12 g of crushed ice. Add 8 ml of methylene chloride to the mixture. If any precipitate (basic aluminum salts) remains after thorough mixing, add enough more concentrated hydrochloric acid to dissolve it. Do not use too much ice since it will make separations difficult or delay your work while you wait for ice to melt.

The addition of acylation reaction mixture to the iced-concentrated hydrochloric acid must be approached cautiously. This is VIOLENTLY EXOTHERMIC and might froth over. Work behind a shield if possible!

Workup. Pour the mixture into a separatory funnel and allow the two layers to separate. Drain off the lower layer and save it. Extract the aqueous layer with 5 ml of methylene chloride, drain it, and combine it with the lower layer already collected. Discard the aqueous layer down the drain. Wash the combined organic layers with 10% aqueous sodium hydroxide until the *washings* are alkaline on litmus (probably about 5 ml will be required). Wash the organic layer with 5 ml of water, put it in a small Erlenmeyer flask, and dry it over an anhydrous salt selected from Table 2.1. Filter the dried solution into a distillation flask of appropriate size. △ Distill off methylene chloride and put it in a recovery container. Continue to distill the product using a micro apparatus with small flask and without water-cooled condenser. Use a small, tared beaker as receiver. Allow the solid to crystallize; then put it in a Hirsch funnel and wash it with a small amount of cold hexane. Obtain the percent yield and submit the product in a labeled vial to your instructor. If the product will not crystallize, redistill it.

Analysis. As directed by your instructor, obtain a melting point, IR, NMR, and UV spectra, an iodoform test, and a 2,4-dinitrophenylhydrazone derivative melting point.

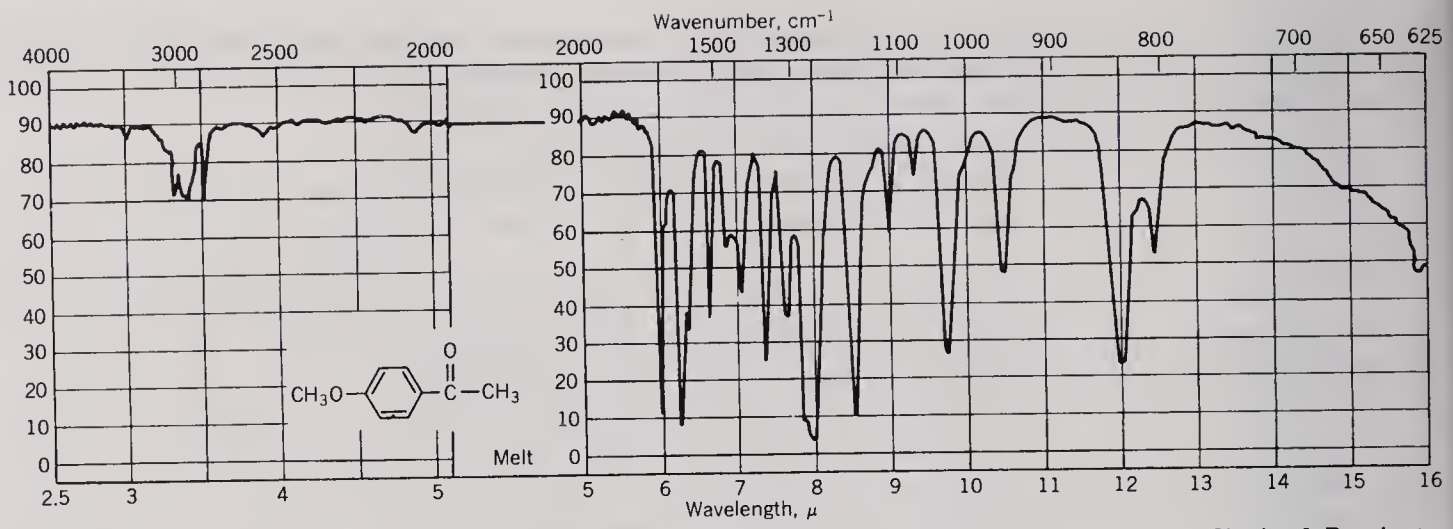


FIGURE E33.1 IR spectrum of *p*-methoxyacetophenone. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

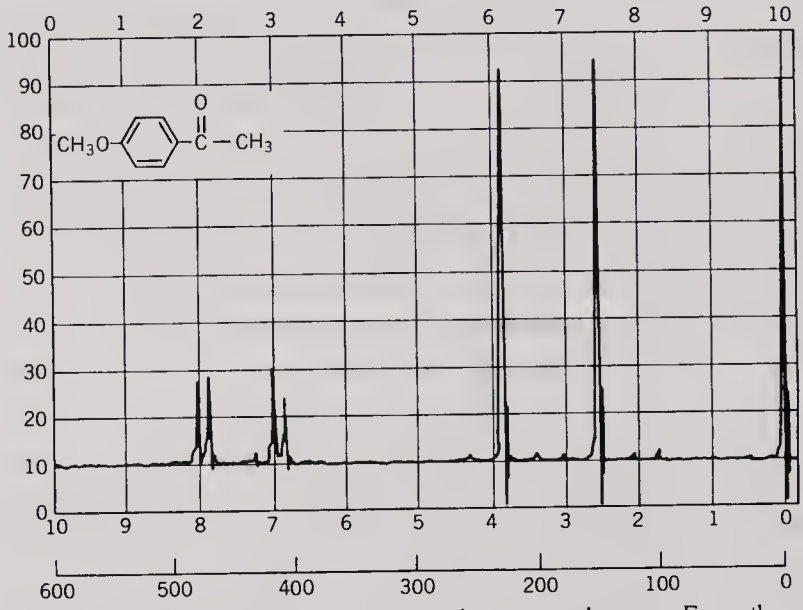


FIGURE E33.2 NMR spectrum of *p*-methoxyacetophenone. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Compare your IR and NMR spectra with those of Figures E33.1 and E33.2. The UV spectrum of *p*-methoxyacetophenone in methanol shows maxima at 270 nm (e 16,100) and 217 nm (e 11,600).

Writing the discussion. You should include a discussion of your percent yield; that is, why you did or did not obtain the desired yield; the identity of your product as established by melting point and other tests performed; the purity of your product as evidenced by color, melting point, and refractive index.

E33.4 EXERCISES

Prelaboratory

1. Why is it so important that the aluminum chloride be kept away from moisture? What gas would be evolved? Write an equation to illustrate your comments.
2. How is the ethanoic anhydride kept from contact with moisture in the air during the reaction?
3. After the aqueous layer is extracted with methylene chloride to remove the remaining organics, in which layer will the organics be, top or bottom?

4. Prepare a flowchart indicating how you will perform the series of separatory funnel operations, taking care that each layer gets where it needs to go throughout.
5. In the interest of efficient time use, when is a good time to (a) get the 50 °C water ready for the heating of the reaction mixture? (b) To get the crushed ice ready?
6. Review operational hazards for heating reactants (0.5), filtration (4.3), and distillation (7.2).

Postlaboratory

1. What would be the product(s) of the Friedel-Crafts acylation using benzene and the mixed anhydride of acetic and propionic acid? Write a mechanism that accounts for the products.
2. Draw a resonance hybrid for the acylium ion (V) in equation E33-2 which includes hyperconjugation as well as resonance.
3. Draw resonance structures that show how the keto function of *p*-methoxyacetophenone deactivates the ring to further electrophilic attack.
4. Explain why acylium ions do not rearrange by drawing resonance and hyperconjugation structures demonstrating that propionyl cation is more stable than the cation formed by its 1,2-hydride shift.
5. Recognizing that dichloromethane can react in a Friedel-Crafts alkylation to yield *bis* (4-methoxyphenyl)methane, explain on the basis of carbocation stabilities and reaction rates why methylene chloride can be used as a solvent in Experiment 33.

REFERENCES

1. *The Givaudan Index,* 2nd ed.; Givaudan-Delawanna: New York, 1961.
2. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; pp 729–733.
3. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; pp 218–225.

EXPERIMENT 34 THE CANNIZZARO REACTION

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Simple distillation	(7.2)
Melting points	(3.2)
Boiling points	(3.5)
Testing pH	(0.11)
Suction filtration	(4.3)
Recrystallization	(5.3)
Storing	(0.12)
Labeling	(0.13)
GLC	(11.3)
UV	(14.4)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Refractive index	(13)
Wet Analysis	(Q8.2, Q9.1, Q8.5, Q9.4)

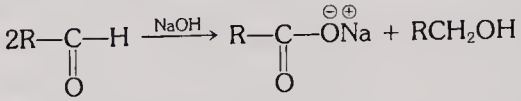
New Principle

Bisulfite addition compound

INTRODUCTION

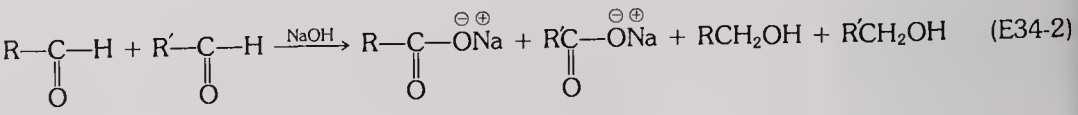
A Cannizzaro reaction is the auto-oxidation-reduction of an aldehyde in the presence of strong base. It was named for the Sicilian chemistry professor, Stanislao Cannizzaro, who discovered it in 1853. In 1841 he entered the University of Palermo as a medical student and became involved in biological research. Realizing the necessity for a better understanding of chemistry, in 1845 he went to the University of Pisa to work under Rafael Piria, the leading Italian chemist of the day. By 1847 he had decided to devote himself to chemistry. Although he is noted for the Cannizzaro reaction and for having named the OH group hydroxy, his major fame rests on his notable clear and logical publication designed to correct many scientific misconceptions of the day and to systematize many chemical relationships.

When a carbonyl compound with *alpha*-hydrogens is subjected to treatment with dilute base, it can undergo an aldol condensation (please see Experiment 15). But when there are no *alpha*-hydrogens on an aldehyde to react with base, a **Cannizzaro reaction** can be made to occur as in the following generalized reaction:



(E34-1)

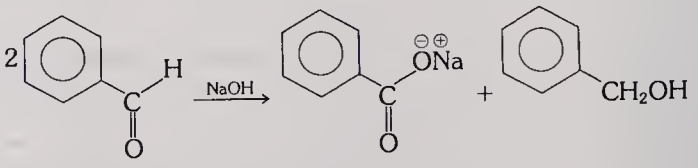
A combination of two different aldehydes can also be made to undergo a Cannizzaro reaction, but a more complex mixture of products is obtained in what is called a **crossed Cannizzaro reaction:**



(E34-2)

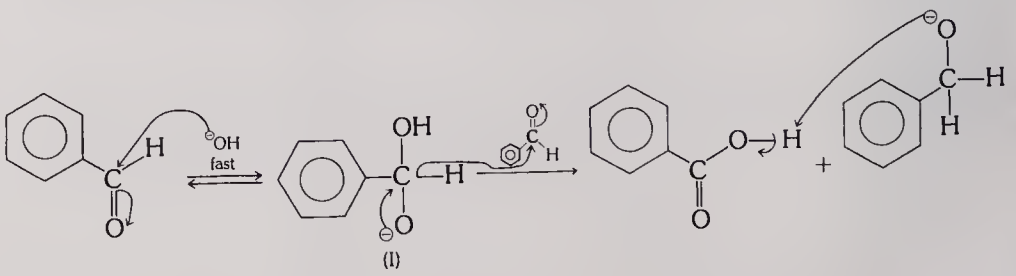
E34.1 DISCUSSION

When benzaldehyde (IUPAC benzenecarbonal) undergoes treatment with strong base, it produces the salt of benzoic acid (IUPAC benzenecarboxylic acid) and benzyl alcohol (IUPAC phenylmethanol):

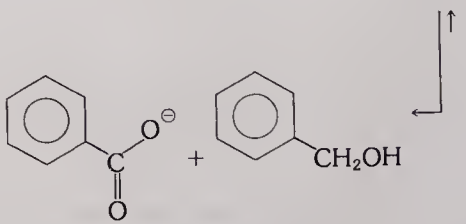


(E34-3)

The mechanism of the reaction is as follows:



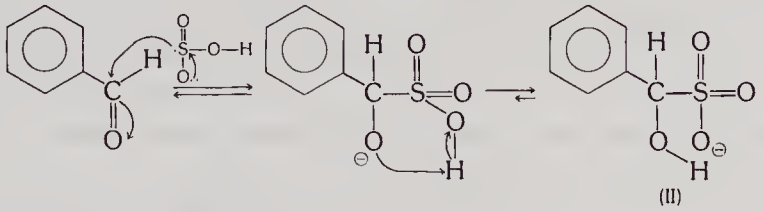
(E34-4)



It begins with a readily reversible collision of hydroxide ion with carbonyl carbon to produce the monosodium salt of the *gem*-diol (I). The rate-determining step involves an intermolecular hydride transfer, produced when the aldehydic hydrogen of (I) undergoes a properly oriented collision with the carbonyl carbon of a second molecule of benzaldehyde. The final step occurs as the very strong conjugate base of benzyl alcohol (pK_a 18) takes a proton from benzoic acid (pk_a 4). Obviously, the equilibrium is far in the direction shown.

The extraction of the product mixture with ether separates the benzyl alcohol and unreacted benzaldehyde from the ether-insoluble sodium salt of benzoic acid.

The sodium bisulfite washes of the ether extract remove unreacted benzaldehyde from benzyl alcohol by forming a bisulfite addition compound with the aldehyde:



(E34-5)

The resulting bisulfite compound (II) is soluble in water because of its ionic character. Hence it can be removed in the aqueous layer. Two extractions are advisable because the reaction is reversible, and not all of the aldehyde is converted at once to the addition compound.

E34.2 EXPERIMENTAL PART

The Cannizzaro reaction. Put 5.3 g of benzaldehyde into a 50-ml Erlenmeyer flask. Dissolve 5 g of sodium hydroxide pellets in 5 ml of water. Allow the solution to cool, then pour it into the flask containing the benzaldehyde. Stopper the flask securely and shake it vigorously until a long-lasting emulsion is formed. Set the mixture aside while you set up the distillation apparatus for the isolation of benzyl alcohol.

It is advisable to wear rubber gloves when working with sodium hydroxide pellets and with concentrated hydrochloric acid.

Isolation of benzyl alcohol. Add just enough water to the Erlenmeyer flask so that, with shaking, all crystalline deposits dissolve. Pour the solution into a separatory funnel and extract it with three successive 10-ml portions of ether (IUPAC ethoxyethane). Drain off the lower aqueous layer into a large beaker and save it for workup to obtain the benzoic acid.

Wash the ether layer with two 5-ml portions of 20% aqueous sodium bisulfite; then with 5 ml of water. Discard the aqueous washes.

Avoid switching electrical devices on or off in the vicinity of ether vapors.

Dry the ether layer over anhydrous sodium sulfate. △ Filter or decant the dried solution into a small distilling flask. Using simple distillation, distill off the ether and put it in a recovery bottle. Continue distilling and collect the benzyl alcohol, which has a boiling point of 205 °C. As directed by your instructor, get a GLC chromatogram; IR and NMR spectra; the refractive index; and wet analysis tests. Submit the product in a labeled vial to your instructor. △△

Isolation of benzoic acid. Add about 15 ml of water and about 10 g of crushed ice to the beaker containing the aqueous layer from the ether extractions of the product mixture. Slowly add, with vigorous stirring, concentrated hydrochloric acid until the pH of the liquid is 1 or 2. Collect the precipitate in a small Büchner funnel with suction and rinse it with ice-cold water. △ Recrystallize the precipitated benzoic acid from water.

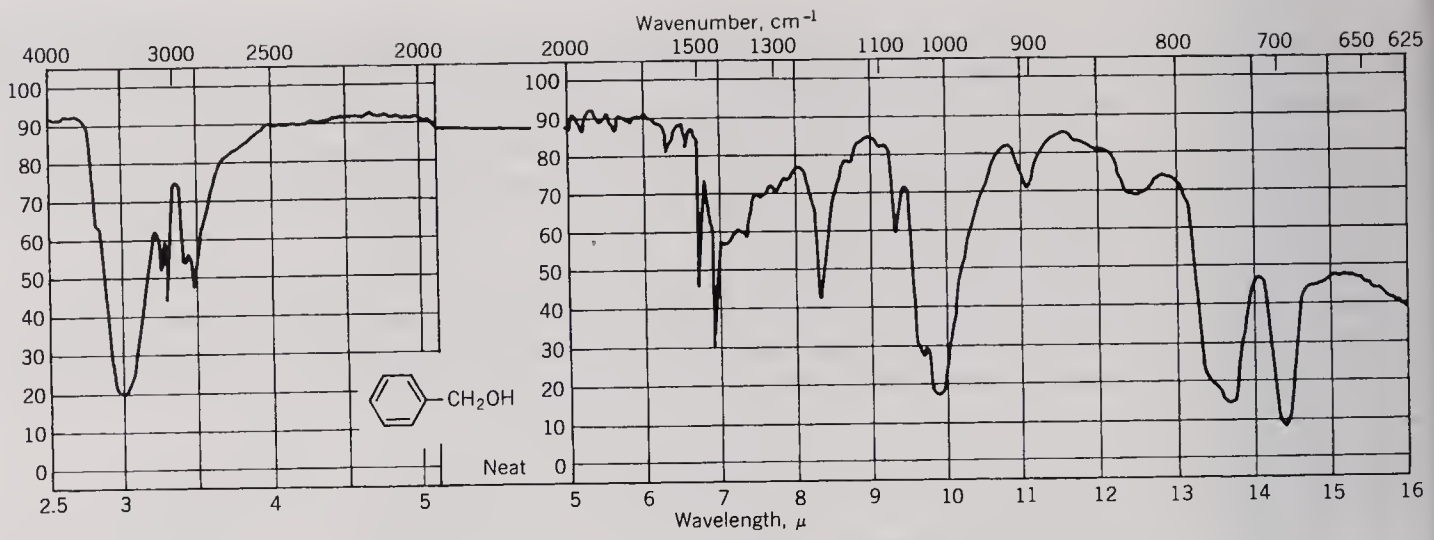


FIGURE E34.1 IR spectrum of benzyl alcohol. From the Aldrich Library of IR Spectra, Edition 3, Charles J. Pouchert.

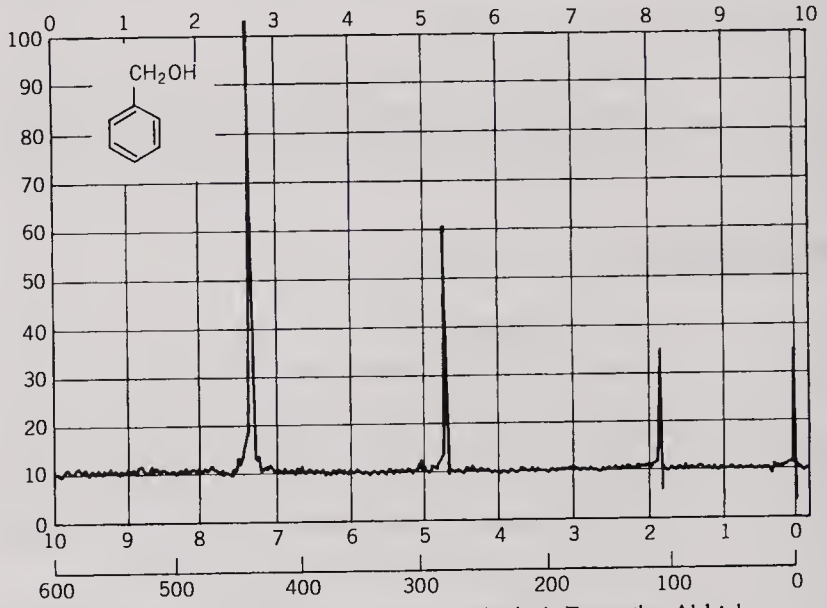


FIGURE E34.2 NMR spectrum of benzyl alcohol. From the Aldrich Library of NMR Spectra, Edition 2, Charles J. Pouchert.

Dry the crystals by an appropriate method and as directed by your instructor obtain a melting point; results of wet analysis; and UV, IR, and NMR spectra. Submit the product in a labeled container to your instructor. △△ See Figures 16.18 and E18.1 for NMR and IR spectra, respectively, for benzoic acid. The UV spectrum in methanol shows maxima at 279 nm (ε 729), 272 nm (ε 893), and 228 nm (ε 11,900).

Writing the discussion. Discuss the yields of acid and alcohol relative to each other (why were they, or why were they not equal?) and to your technique of synthesis and workup. Discuss their identity and purity based on the analyses performed. Compare your spectra to those of Figures 34.1 and 34.2.

E34.3 EXERCISES

Prelaboratory

1. The molecular weight of benzaldehyde is 106.12 g/mole and its density is 1.05 g/ml. How many milliliters will you measure out for this reaction?
2. Which grade of ether will you use for the extraction of the product mixture, technical or anhydrous? Explain.

3. Make a flow diagram of the product mixture workup.
4. Will you use an air, or water, condenser for the ether distillation? For the benzyl alcohol distillation? Explain.
5. What is the purpose of the addition of concentrated hydrochloric acid to the aqueous layer from the separatory funnel? Write the equation that illustrates the process.
6. Review hazards associated with extraction (6.2), distillation (7.2), suction filtration (4.3), and recrystallization (5.3).

Postlaboratory

1. From a theoretical standpoint, can all aldehyde be removed from alcohol by converting the aldehyde into a bisulfite addition compound and washing? Explain.
2. Show the products from the reaction of benzaldehyde with formaldehyde and strong, concentrated base. What kind of a reaction is this?
3. Write the mechanism that shows the reaction of methanal (formaldehyde) in the presence of strong, concentrated base.
4. Discuss a necessary modification in the reaction portion of this experiment if the reactant is 4-methylbenzaldehyde rather than benzaldehyde. Explain with resonance-hyperconjugation structures or their hybrid.

REFERENCES

1. *Dictionary of Scientific Biography;* Gillespie, C. C., Ed.; Scribner's: New York, 1971; Vol. III.
2. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p. 711.

EXPERIMENT 35 THE SANDMEYER REACTION

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Cooling	(0.5)
Diazotization	(E30)
Heating	(0.5)
Direct steam distillation	(7.15)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Boiling points	(3.5)
Storing	(0.12)
Labeling	(0.13)
GLC	(11.3)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Refractive index	(13)
Wet analysis	(Q7.1, Q7.2)

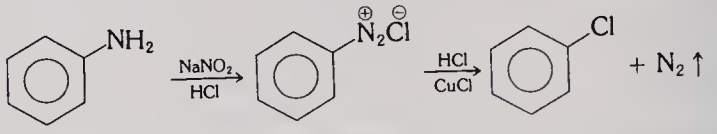
INTRODUCTION

When copper (I) chloride or copper (I) bromide is the catalyst, replacement of the nitrogens in an aryl diazonium salt with chlorine or bromine is known as a **Sandmeyer reaction.**

The Sandmeyer reaction is named for its discoverer, the Swiss chemist Traugott Sandmeyer. He was born in 1854 at Wettingen in Aargau. In 1888, when he was 28, he became an assistant to Victor Meyer and later to Arthur Hantsch, professors at Zürich Polytechnic. In 1888 he began work as an industrial chemist for J. R. Geigd, manufacturers of dyestuffs in Basle, Switzerland. In 1899, while involved in the synthesis of indigo, he discovered the reaction that bears his name.

E35.1 DISCUSSION OF THE PREPARATION

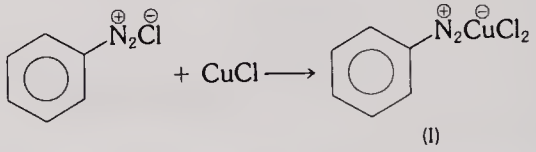
Aniline (IUPAC benzenamine) can be converted to chlorobenzene as follows:



(E35-1)

The diazotization step is discussed in Experiment 30. The second step, the Sandmeyer reaction, is generally considered to proceed by a carbocation process, but the mechanism is not known for certain.

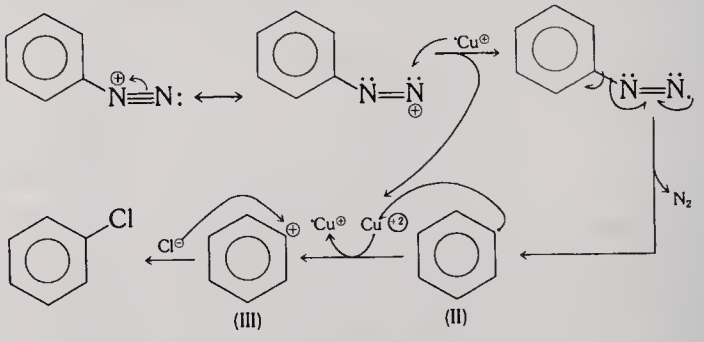
When an aqueous solution of copper(I) chloride is added to benzenediazonium chloride, a voluminous, white double salt precipitates:



(E35-2)

The double salt (I) decomposes as the temperature rises above 15 °C; the higher the temperature, the faster it decomposes to yield chlorobenzene and nitrogen gas. The solution is warmed gradually in order to prevent rapid evolution of nitrogen gas and concomitant foaming.

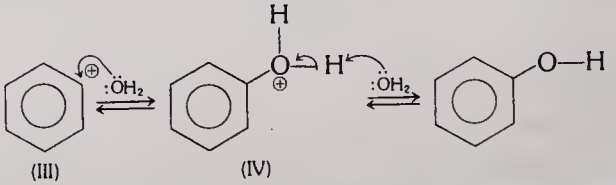
From a mechanistic viewpoint, the catalysis by copper(I) might proceed as follows:



(E35-3)

In the first step, copper (I) gives up its electron, thereby becoming copper(II). As a result, the diazonium salt becomes neutral, and nitrogen is lost. This leaves a phenyl-free radical (II) which on collision with copper(II) ion reduces it again to copper(I). The loss of the electron by phenyl-free radical generates the very unstable phenyl cation (III), which collides with chloride ion and forms product.

A byproduct that is always found in Sandmeyer reactions is phenol:



(E35-4)

To avoid forming large amounts of byproducts in a Sandmeyer reaction, it is important to add the diazonium salt solution to the copper(I) solution and not vice versa. In this

experiment considerable amounts of phenol (IUPAC also benzenol) and azobenzene (IUPAC diphenyldiazine) along with biphenyl (IUPAC phenylbenzene) would be produced.

E35.2 EXPERIMENTAL PART

Diazotization of aniline. Put 25 ml of water in a 250-ml Erlenmeyer flask and add 12 ml of concentrated HC1. Swirl the mixture and add, with constant swirling, 3.5 g of aniline. Cool the mixture to 5 °C in an ice-salt bath.

Prepare a solution of 3.0 g of sodium nitrite dissolved in 12 ml of water. Cool it to 5 °C. Add the sodium nitrate solution to the aniline solution, with swirling and cooling, at a rate so that the temperature does not rise above 10 °C. Keep the mixture in the ice bath until you are ready to use it. Precipitate might be present, but it will go into solution during the Sandmeyer reaction.

Sandmeyer preparation of chlorobenzene. Dissolve 3.8 g of copper(I) chloride in 12 ml of concentrated HC1 and 5 ml of water in a 250-ml Erlenmeyer flask. Cool the solution to 5 °C in the ice-salt bath.

With constant agitation of the cold copper(I) solution, add the benzenediazonium chloride solution slowly to it. Keep the mixture below 20 °C during addition. Allow the mixture of precipitate and solution to stand at room temperature for 10 min; then slowly warm it on a steam bath, occasionally swirling the mixture to prevent excessive sudden foaming. Heat it on the steam bath until formation of nitrogen gas is no longer evident.

Rubber gloves are advisable when working with concentrated HC1. Avoid heating the reaction mixture so rapidly that sudden foaming ejects acidic solution from the flask.

Using a heating mantle or oil bath as a heat source, steam distill the mixture by the direct process. Collect 40 ml of distillate. Put it in a separatory funnel and add 10 ml of 6*M* aqueous NaOH. Mix the phases thoroughly, then remove the aqueous layer and discard it. Wash the organic layer with 5 ml of water. Dry the solution over anhydrous calcium chloride.

Filter or decant the liquid into a small distilling flask and distill it. The boiling point of the product is 132 °C.

Analyze the product, as directed by your instructor, by GLC, refractive index, IR, NMR, and wet analysis for chlorine (Part III). Compare the spectra of product with standard spectra or with spectra of known chlorobenzene from the stockroom.

Turn in your product in a labeled vial.

Writing the discussion. Discuss the yield, trying to ascertain where losses occurred during the reaction and workup. Discuss the purity and identity of the sample based on the analysis performed.

E35.3 EXERCISES

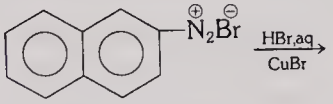
Prelaboratory

1. Why must the mixture be kept cold while preparing the diazonium salt?
2. What visible evidence will you have that the Sandmeyer reaction is taking place?
3. Look up the density of chlorobenzene. Will the density of aqueous NaOH be greater than 1? How will you tell which layer in the separatory funnel is the aqueous phase?
4. Will the condenser for steam distillation be air-cooled, or water-cooled? For the final distillation? Explain.
5. In the interest of saving time, when is a good time to set up the steam distillation apparatus?

6. Review hazards associated with diazotization (Experiment 30), heating reactants (0.5), steam distillation (7.15), and extraction (6.2).

Postlaboratory

1. Complete the equation, showing the major product and byproducts:



2. A student added a mixture of copper(I) bromide, concentrated HBr, and water to a benzenediazonium bromide solution and obtained the expected Sandmeyer product along with considerable amounts of benzenol, diphenyldiazine, and phenylbenzene. Criticize the student's procedure. Draw the structures of the Sandmeyer product and the three byproducts.
3. Show mechanistically how diphenyldiazine and phenylbenzene could be produced during the Sandmeyer reaction to make chlorobenzene.

REFERENCES

1. *A New Dictionary of Chemistry*, 3rd ed.; MacKenzie, L., Ed.; Interscience: New York, 1961.
2. Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longman: London, 1956; p 600.

XV ORGANIC REDOX

Many organic reactions involve oxidation-reduction systems, and balancing equations for such reactions is not always easy by inspection, just as in inorganic chemistry.

The concept of organic redox is like that of inorganic redox, but involves two significant variations: First, the concept of oxidation number loses much of its significance; and second, nearly all organic redox involves hydrogen. To illustrate, notice that the oxidation numbers of carbon in ethane, ethene, and ethyne are respectively -3, -2, and -1, even though the structural formulas show that carbon in all three compounds has a valence of 4. Because of organic redox involvement with hydrogen, oxidation is conveniently defined as loss of hydrogen and reduction is defined as gain of hydrogen. Therefore, a reasonable approach to balancing organic redox equations is a half-reaction method in which hydrogens are the balancing medium just as electrons are for inorganic chemistry. The balancing hydrogens will be given the symbol H*. This symbol represents all kinds of hydrogens, no matter what their form, that is, H^+, H^-, $H^\cdot$, H_2, or H attached to a compound.

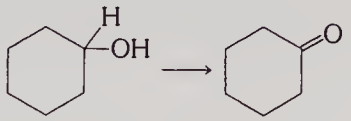
In order to balance organic redox equations, you will find the following sequential rules to be helpful:

1. Write an equation for the main reactants in each half-reaction.
2. Balance charges by using H^+ in acid solutions and HO^- in basic solution.
3. Balance O atoms with H_2O.
4. Balance all kinds of hydrogens with H*.

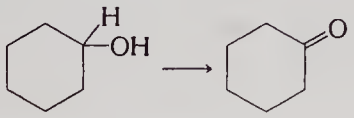
5. Multiply each half-reaction by a number which will make the number of H*s equal in the two half-reactions (use the lowest common multiple).
6. Add together the two half-reactions and consolidate the terms. Notice that the H* terms cancel out.

As an example, let us consider the acidic oxidation of cyclohexanol to cyclohexanone, using chromium (VI) oxide as the oxidizer:

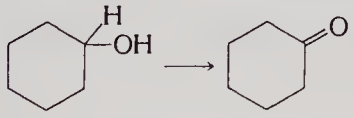
1. Write the half-reactions:
   a. reduction: $CrO_3 \longrightarrow Cr^{3+}$
   b. Oxidation:



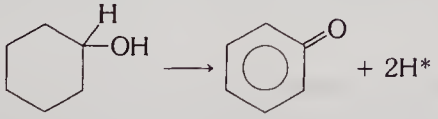
2. Balance charges with H^+:
   a. $CrO_3 + 3H^+ \longrightarrow Cr^{3+}$
   b.



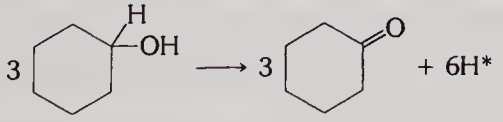
3. Balance O with H_2O:
   a. $CrO_3 + 3H^+ \longrightarrow Cr^{3+} + 3H_2O$
   b.



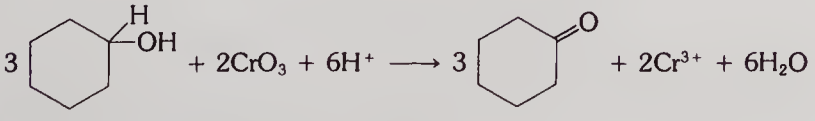
4. Balance all kinds of hydrogens with H*:
   a. $CrO_3 + 3H^+ + 3H^* \longrightarrow Cr^{3+} + 3H_2O$
   b.



5. Make the number of H*'s equal:
   a. $2CrO_3 + 6H^+ + 6H^* \longrightarrow 2Cr^{3+} + 6H_2O$
   b.



6. Add the half-reactions:



EXPERIMENT 36 OXIDATION OF BENZYL ALCOHOL

Time Required: 3–4 hr

Review Techniques and Principles:

Lab notebook	(1)
Heating and reflux	(0.5)
Filtering with filter aid	(4.5)
Vacuum filtration	(4.3)
Testing pH	(0.11)

Recrystallization	(5.3)
Drying solids	(2.1)
Melting points	(3.3)
IR	(15.3, 15.4)
Storing	(0.12)
Labeling	(0.13)
Wet analysis	(Q8.5, Q9.4)

New Technique:

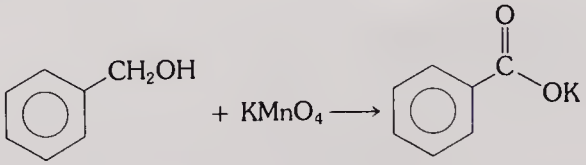
Testing for unreacted permanganate

INTRODUCTION

Benzyl alcohol (IUPAC phenylmethanol) is a local anesthetic and is sometimes used topically to treat itches. You can make a simple anti-itching lotion by combining equal parts of benzyl alcohol, ethanol, and water. Benzoic acid has been widely used as a food preservative, most often as its sodium salt. Benzoic acid has also been used topically to treat ringworm of the scalp and similar skin problems.

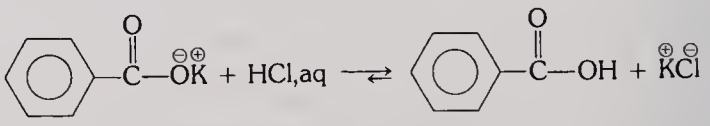
E36.1 DISCUSSION OF THE OXIDATION

Benzyl alcohol is very easily oxidized to benzoate ion by an oxidizing agent like potassium permanganate:



(E36-1)

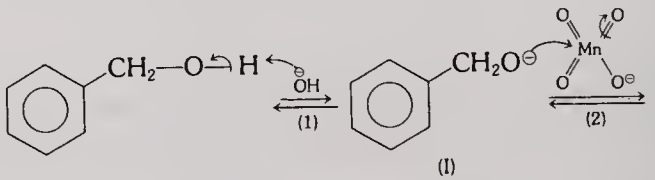
The oxidation of easily oxidized alcohols occurs smoothly with alkaline permanganate solutions, the driving force for the reaction being reduction of permanganate ion. Potassium is a spectator ion throughout the process. After oxidation, benzoate is easily converted to benzoic acid by addition of a mineral acid:

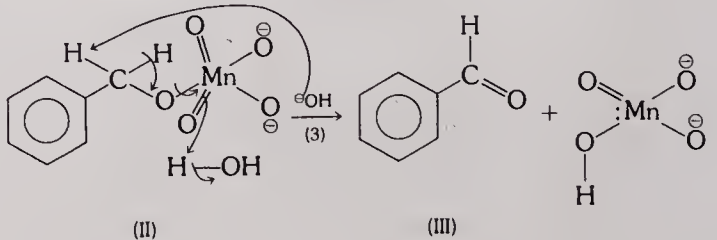


(E36-2)

The equilibrium is far in the direction of the acid because the benzoate ion is a much stronger base than chloride.

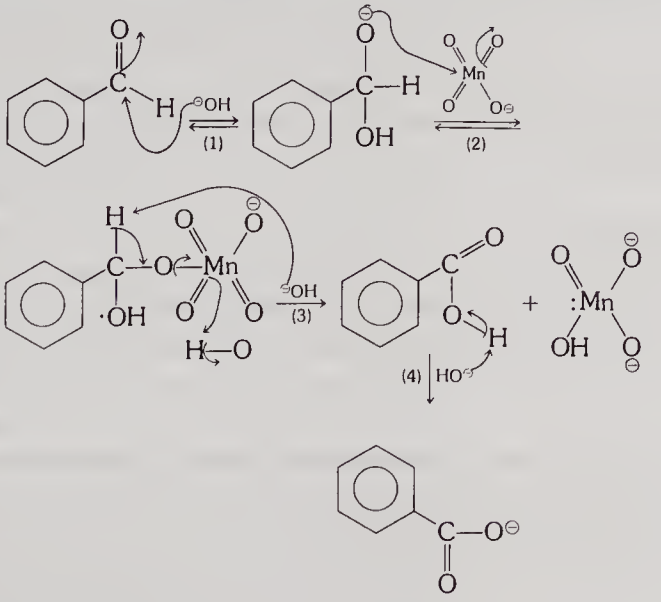
The mechanism of the reaction might be as follows:





(E36-3)

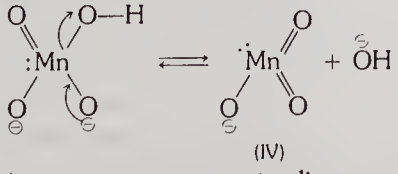
In the first step, equilibrium production of small amounts of the salt of benzyl alcohol (I) makes the alcohol more nucleophilic. This is a catalytic step, with hydroxide as the catalyst. Because of the salt's negative charge, its bond-making ability is enhanced, and the required force of collision for bond-making between salt and manganese is reduced. In other words, the activation energy in step 2 is lower for the alcoholate ion than it would be for the alcohol itself. Redox occurs in step 3. Notice that the removal of a proton from the benzylic carbon in (II) generates an electron pair which forms the *pi* orbital of the incipient double bond between carbon and oxygen. In order to maintain an octet around oxygen, the electron pair bond between benzylic oxygen and manganese breaks and the reduction of manganese occurs as it accepts the electron pair. Manganese(VII) is reduced to manganese(V). Benzaldehyde (IUPAC Benzenecarbonal) is the organic product (III), which is even more easily oxidized than the alcohol, and is further oxidized to the carboxylic acid in a second series of reactions paralleling the first. However, a hydration of the aldehyde probably occurs prior to oxidation as seen in step 1:



(E36-4)

Notice the use and regeneration of the hydroxide catalyst in step 3. In the acid-base step 4, hydroxide converts the acid to its conjugate base, a salt. Notice that in series E36-4 the redox step involves removal of a proton from a carbon of the organic species.

Manganese(V) ion seen as byproducts in equations E36-3 and E36-4 loses hydroxide and becomes the more stable, green manganate ion [structure (IV)]:



(IV)

(E36-5)

In an auto-oxidation-reduction, green manganate disproportionates to become purple permanganate and the chocolate brown manganese(IV) oxide precipitate which forms during permanganate oxidation reactions:

$$MnO_3^{-1} \longrightarrow MnO_4^{-1} + MnO_2\downarrow \qquad \text{(E36-6)}$$

As the phenylmethanol oxidizes, the fine, brown, MnO_2 precipitate forms. Strong heating of such mixtures tends to give rise to hot spots within the mixture, especially as the precipitate becomes heavier. Because these hot spots can give rise to violent bumping, reflux must be gentle.

Sometimes small excess amounts of purple permanganate ion remain after a reaction is complete. Because this ion would stain the final product pink it is necessary to remove it by reducing it to MnO_2 with sulfite or bisulfite ion:

$$2MnO_4^{-1} + 3SO_3^{-2} + H_2O \longrightarrow 2MnO_2\downarrow + 3SO_4^{-2} + 2OH^{-1} \qquad \text{(E36-7)}$$

E36.2 TESTING FOR UNREACTED PERMANGANATE

To test the reaction mixture for unreacted permanganate, put a drop on a piece of filter paper. If the brown manganese oxide spot develops a purple (permanganate ion) or green (manganate ion) ring around it some oxidizer is still unreacted. To destroy the excess oxidizer, add a small amount of solid sodium sulfite or sodium bisulfite. Stir the mixture thoroughly; then repeat the test. Use this approach until there is no colored ring around the brown spot.

E36.3 EXPERIMENTAL PART

Benzoic acid preparation. Dissolve 3 g of sodium hydroxide pellets in 200 ml of water in a 500-ml three-neck round-bottom flask. Add 2.2 g of benzyl alcohol (IUPAC phenylmethanol). Attach a water-cooled reflux condenser to one neck and stopper the other two. Stir the mixture magnetically.

Weigh out the stoichiometric amount of potassium permanganate that will react with the benzyl alcohol. With a spatula, add the permanganate through one of the side necks over a period of about 5 min. After the addition is complete, put the stopper back in the neck and reflux the mixture gently for 30 min. Then cool the mixture to room temperature.

Do not proceed until you have asked your instructor if you calculated the correct amount of $KMnO_4$ to use.

It is a good idea to wear rubber gloves while working with the sodium hydroxide pellets, potassium permanganate, and concentrated hydrochloric acid.

Powerful oxidizers can cause violent explosions in contact with many dry organic compounds. Do not let the permanganate come in contact with the benzyl alcohol before it is mixed with water.

Workup. Make an aqueous filter aid slurry and prepare a filter with it in a Büchner funnel. Put a nickel-size filter paper disc over part of the diatomaceous earth in the funnel. Test the reaction mixture for unreacted permanganate and heat it with sodium bisulfite if necessary; then, with water aspirator on, pour the mixture onto the filter paper spot in the Büchner funnel. Do not allow the filter to suck dry and crack. Repeat the filtration if necessary, through the same filter if possible, until the filtrate is nearly clear and colorless. Put the filter cake into the assigned container and pour the filtrate into a large beaker. △ Carefully add concentrated hydrochloric acid until the pH of the liquid is about 2. Stir thoroughly while adding the acid. Next, cool the filtrate to about 20 °C or lower. Put a chunk or two of ice in if you wish.

Using a Hirsch funnel, collect the precipitate and wash it with a small amount of cold water. Discard the filtrate down the drain. △△ Recrystallize the filter cake in a minimal amount of water. △△ Dry the crystals by a method appropriate to your time schedule. Turn in the crystals in a labeled vial.

Analysis. Obtain a melting point of the product and IR and NMR spectra of the starting material and product. Compare the spectra of product with Figures 16.18 and E18.1. Also perform wet analysis tests for carboxylic acids (Part III).

Writing the discussion. Consider the following points for discussion in your report: Look in the IR spectrum of your product for the appearance of a strong absorption at 1600–1800 cm^{-1}. To what functional group does this belong? What does its presence or absence in your IR spectrum indicate? Compare the positions of O—H absorptions of starting material and of product, and explain. Compare the spectrum of the known benzoic acid sample with the spectrum of your sample. Does your sample appear (1) to be the same; (2) to be free of extraneous IR absorptions which indicate lack of purity?

Does this presence or absence of extraneous peaks follow what you would expect from the sharpness of the melting point?

E36.4 EXERCISES

Prelaboratory

1. Balance redox equation E36-1 and calculate to two significant figures the amount of $KMnO_4$ to use in oxidizing 2.2 g of benzyl alcohol. Show all calculations clearly labeled. Why calculate to only two significant figures? Check this value with your instructor before proceding to the experimental work.
2. Look in a handbook and determine whether 2.2 g of benzyl alcohol is soluble in 200 ml of water. Is there likely to be some immiscibility under the conditions of the reaction? Does this mean that all of the benzyl alcohol will not react, or will it dissolve as benzoic acid is formed and the equilibrium shifts in that direction?
3. At the end of the oxidation reaction, what is the product? Is the product in the precipitate or in solution? Under what conditions is it likely to be in the filtrate? In the precipitate? Considering that $K_a = 10^{-4}$ for benzoic acid, what is likely to be the effect of excess hydroxide?
4. When is a good time to prepare the filter aid filter so as to make good use of time?
5. Why must the final mixture be acidified? Why must the aqueous portion of the final mixture be clearly acidic? Why is the mixture cooled to 20 °C before filtering?
6. Review hazards related to heating reactants (0.5), vacuum filtration (4.3), recrystallization (5.3).

Postlaboratory

1. Write a balanced equation for the alkaline permanganate oxidation of 2-propanol.
2. Write a detailed mechanism for the permanganate oxidation of isopropyl alcohol. Will a second oxidation of a geminal diol occur after the first oxidative step in this case? Why?
3. Balance equation E36-6.

REFERENCE TO RELATED PROCEDURE

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; pp 520, 672.

EXPERIMENT 37 OXIDATION OF *p*-METHYLBENZALDEHYDE

Time Required: 3 hr

Review Techniques and Principles:

To be provided by student

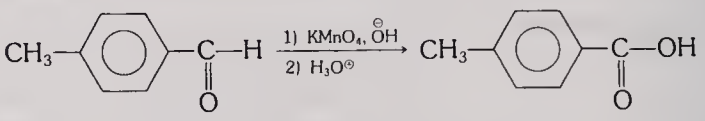
INTRODUCTION

Although one usually consults the chemical literature to find recipes for chemical transformations, it is not unusual that the practicing chemist must devise a procedure by analogy to past experience with similar processes. In this experiment you will design your own procedure for oxidation of *p*-methylbenzaldehyde to *p*-methylbenzoic acid, using potassium permanganate as the oxidizer and Experiment 36 as a guide.

This experiment yields one of the chemical intermediates used in the synthesis of the mosquito repellent, *N*,*N*-diethyl-*p*-methylbenzamide (Experiment 25).

E37.1 DISCUSSION OF THE PREPARATION

The overall, unbalanced equation for the reaction is



(E37-1)

Notice the two major differences between this equation and E36-1: First, there is a methyl group in the *para* ring position, and second, the substrate is an aldehyde rather than an alcohol. So, ask yourself the question, "How might these differences alter the procedure with which I am already familiar?" You will recall that you can very easily oxidize aldehydes to carboxylic acids. In fact, this oxidation is easier than the reaction to prepare the aldehyde by oxidation of the corresponding alcohol. Aldehydes even oxidize by exposure to oxygen in the air, and for this reason previously opened reagent bottles of aldehydes often contain some of the corresponding carboxylic acid. Therefore, you can presume that the presence of carbonyl itself rather than hydroxyl should present no difficulty unless it is one of keeping the reaction under control. The effect of a *para*-methyl group should be to donate electrons by induction and hyperconjugation, making the carbonyl region somewhat more negative than it was for the benzaldehyde intermediate in Experiment 36. So, you must ask yourself several questions: "Is the additional negative character sufficient to prevent formation of the geminal diol that precedes oxidation to the carboxylic acid?"; "Will the *para*-methyl group oxidize in addition to the aldehyde function?"; "How easily does the methyl group of toluene oxidize?"; "Will the electron resonance and inductive effect of carbonyl oxygen increase the acidity and oxidizability of the methyl group?"; "Which of these various effects is (are) most important?"; "What is the overall effect of the *two* functional groups on solubilities, reaction rates, and workup procedures?"; "What modifications in procedure might be necessary or desirable?"

E37.2 EXPERIMENTAL PART

Procedure. By analogy with the procedure used in Experiment 36, devise a method for oxidizing 10.0 g of *p*-methylbenzaldehyde (use 2.0 g if you are not going to make the insect repellent in Experiment 25). Use $KMnO_4$ as the oxidizer and do not make major deviations. Start with a good flow diagram. Next, write a balanced chemical equation and calculate the amounts of reactants required. Finally, write a detailed procedure with short sentence instructions in numerical order, arranged neatly in appropriate blocks related to the various operations to be carried out. Decide what analyses should be performed for establishing the identity and purity of your product. The literature value for the product melting point is 180 °C. Ask if your instructor wants to review the procedure before you begin the laboratory work.

Review the safety precautions for Experiment 36; and write additional precautions if necessary.

If you feel uncomfortable about what to expect of your reaction, work behind a safety shield.

Do not proceed until you have asked your instructor if you calculated the correct amount of $KMnO_4$ to use.

Writing the discussion. Compare your method to the one described in Experiment 36. Discuss its success in terms of identity of product, yield, and purity, and make suggestions for improvement.

E37.3 EXERCISES

Prelaboratory

1. Write the stoichiometric equation for the oxidation.
2. Calculate the amount of oxidizer to use with 10.0 g (or 2.0 g) of 4-methylbenzenecarbonal. Check this amount with your instructor
3. Calculate the theoretical yield of product.
4. List the equipment you will need for this experiment.
5. List the various review techniques and principles used in this experiment.
6. Review the hazards associated with the various review techniques.

Postlaboratory

1. Write a balanced redox equation for the oxidation of *p*-methylbenzaldehyde by oxygen in the air.
2. Write a mechanism for oxidation of benzaldehyde by chromic oxide and sulfuric acid.
3. If the hydroxide solution is added to 4-methylbenzenecarbonal, would a Cannizzaro reaction occur? If it did, would it affect the yield of final product? Explain.

Acknowledgment
The writer thanks Julie Ostrander, William Villaire, and Ali Zand for laboratory experimentation leading to this experiment.

EXPERIMENT 38 REDUCTION OF BENZALDEHYDE

Time Required: 3–4 hrs

Review Techniques and Principles:

Lab notebook	(1)
Glassware	(0.3)
Mixing	(0.4)
Cooling	(0.5)
Simple distillation	(7.2)
Liquid-liquid extraction	(6.2)
Drying liquids	(2.2)
Gravity filtration	(4.2)
Heating	(0.5)
Vacuum distillation	(7.11)
GLC	(11.13)
IR	(15.3, 15.4)
NMR	(16.4, 16.5)
Storing	(0.12)
Labeling	(0.13)
Organic qual	(Q8.2, Q9.1)

INTRODUCTION

Inorganic hydrides like lithium aluminum hydride, $LiAlH_4$, and sodium borohydride, $NaBH_4$, are very important reducing agents of carbonyl compounds. These reducing agents are especially useful for reducing expensive substrates and those sensitive to catalytic reduction at other than carbonyl sites.

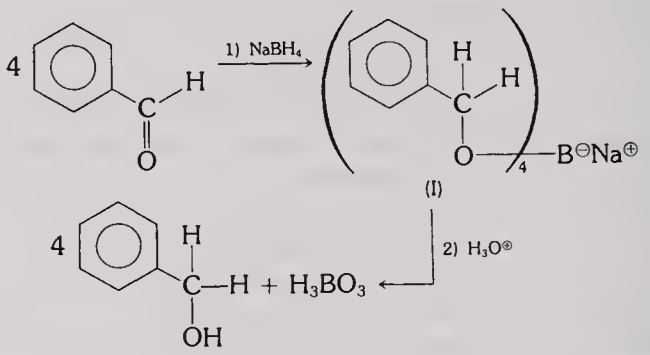
Lithium aluminum hydride is handled like a Grignard reagent because its highly

reactive nature makes it sensitive to atmospheric oxygen, carbon dioxide, and moisture. It reacts with carbonyls of aldehydes, ketones, carboxylic acids, esters, and other carboxylic acid derivatives.

Sodium borohydride is a milder reducing agent than lithium aluminum hydride, reducing aldehydes and ketones, but not acids or esters. It reacts slowly enough with water in neutral or alkaline solution that a reduction that is reasonably rapid can be carried out in aqueous medium without appreciable hydrolysis of the reagent.

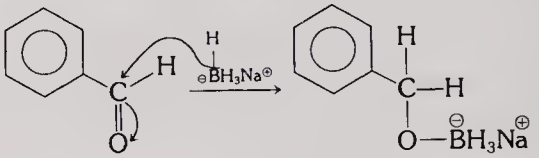
E38.1 DISCUSSION OF THE REDUCTION

Reduction using sodium borohydride is a two-step process:



(E38-1)

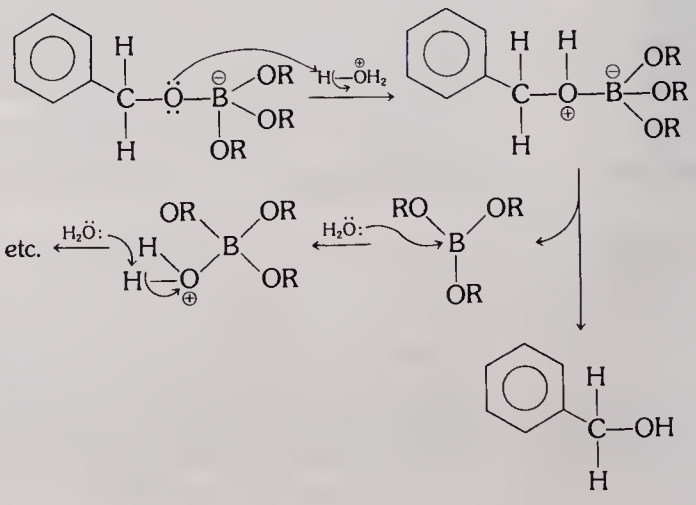
In the mechanism of the reduction, the key step is reaction of hydride with carbonyl carbon and its subsequent transfer:



(E38-2)

As the hydride ion transfers, the carbon-oxygen π bond breaks and forms a bond to boron. This process is repeated three more times, producing intermediate (I) shown in equation E38-1. The probability of attaching four alcoholate groups to boron is not high in a relatively short period; so, a slight molar excess of the reducing agent is employed. Notice that the intermolecular hydride transfer is similar to that found in the Cannizzaro reaction (Experiment 34).

In the second step of the process, hydrochloric acid is added to break up the intermediate boron salt (I):



(E38-3)

In this equation only one benzyl group has been shown, the other three being designated by the usual symbol, R. As hydrochloric acid releases all of the benzylate groups as benzyl alcohol (I), boric acid, H_3BO_3, is produced as a byproduct.

E38.2 EXPERIMENTAL PART

Reduction of benzaldehyde. Put 10 ml of 95% ethanol in a 50-ml Erlenmeyer flask and add 0.72 g of sodium borohydride. Swirl the mixture to effect dissolution and then place a thermometer in the flask. Using an eyedropper or Pasteur pipet, add 4.2 g of benzaldehyde (IUPAC benzenecarbonal). Holding the thermometer so it does not rattle about in the flask and break, swirl the contents of the flask constantly. Watch the temperature so that it stays between 40 and 50 °C, if necessary, cooling the reaction mixture from time to time in an ice-water bath. After addition of benzaldehyde is completed, allow the mixture to stand at room temperature for 15 min. Then add 5 ml of 6*M* hydrochloric acid dropwise with swirling.

Because of the caustic character of sodium borohydride it is advisable to wear gloves.

Workup. Pour the reaction mixture into a round-bottom flask and distill off the ethanol to the point that two liquid phases are apparent. Put the ethanol into its recovery container. Pour the two liquid phases into a separatory funnel. Rinse the flask with 8 ml of ether (IUPAC ethoxyethane) and add the rinse to the separatory funnel. Agitate the funnel gently to get all of the product into the ether, drain off the lower layer, pour out the ether layer, and put the lower layer back into the funnel. Extract twice more with 8-ml portions of ether. Combine all three ether extracts and dry them over anhydrous magnesium sulfate. Filter or decant the ether into a 50-ml round-bottom flask. △△ Distill off the ether on a steam or hot water bath and put it in a recovery container. △△

Assemble the flask into a vacuum distillation apparatus and distill in vacuo, using an oil bath or heating mantle as heat source. △△ The boiling point of the product is 93 °C at 10 torr. Put the product in a labeled vial and submit it to your instructor.

Analysis. Obtain GLC, IR, and NMR, and organic qualitative analyses, as directed by your instructor.

Writing the discussion. Discuss the identity and purity of the product as determined by the analytical tests performed. Discuss the percent yield, factors contributing to it, and possible methods to improve it. Compare your spectra with Figures E34.1 and E34.2.

E38.3 EXERCISES

Prelaboratory

1. What experimental evidence leads you to suspect that the reduction is exothermic?
2. What is the purpose of adding the 6*M* hydrochloric acid? Is the acid used in stoichiometric amount? Why?
3. What inorganic byproduct does the lower layer in the separatory funnel contain?
4. What organic material is being extracted into the ether?
5. How will you know at what temperature to collect product if the pressure is not 10 torr?
6. Will you use an air-cooled, or liquid-cooled, condenser for condensing ether? For condensing the product? Explain.

7. Review hazards associated with distillation (7.2), extraction (6.2), and vacuum distillation (7.11).

Postlaboratory

1. *Stu Dent* planned a sodium borohydride reduction of acetophenone by analogy with that of Experiment 38. After the reduction step he planned to add hot hydrochloric acid to speed up the rate of hydrolysis. *Red Uction* told him he did not think that would be a good idea. With whom do you agree? Explain.
2. What would be the product of complete sodium borohydride reduction of 2,4-pentanedione? How many moles of sodium borohydride would be used for 0.200 mole of the dione?
3. Complete equation E38-3, showing in detail how four molecules of product are obtained and how $B(OH)_3$ (boric acid) is a byproduct.

REFERENCES

1. Vogel, A. I. *Practical Organic Chemistry,* 3rd ed.; Longman: London, 1956; p 881.
2. Mohrig, J. R.; Neckers, D. C. *Laboratory Experiments in Organic Chemistry,* 2nd ed.; Van Nostrand: New York, 1973; p 88.
3. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory;* Wiley: New York, 1986; p 71.

XVI

KINETICS AND EQUILIBRIA

How fast a chemical reaction proceeds and how far it goes to completion are subjects of considerable interest to the practicing chemist. In the chemical industry, time is money, and the amount of product obtained in a given time is an important economic consideration.

KINETICS

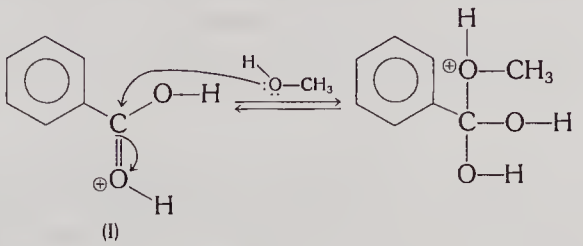
The study of rate processes is called **kinetics.** The measurement of rates of chemical reactions is important to the chemist in providing information about reactions pathways and to the industrial chemist for control of optimum reaction conditions.

You undoubtedly recall that there are three rate factors: *collision frequency* factor, *orientation* (probability) factor, and *energy* factor. In organic chemistry, the last of these is ordinarily the most important.

For new electron pair bonds to be made and for old bonds to break, there must be *collisions* between molecules; and the more often the collisions occur, the greater the likelihood that bonds will be broken and/or made. One way to make collisions more frequent is to increase the concentration of the reactants because if they are close together they have only to travel a short distance before colliding with each other. Collision frequency can also be increased by raising the reaction temperature, thereby giving reactant molecules energy to move faster and collide more often. Although collisions are necessary for chemical reactions, they are not in themselves sufficient. Orientation and collision energy must also be considered.

The parts of molecules that collide with each other must be the reactive parts, that is, the functional groups like halide, hydroxyl, and carbonyl. In other words, the *orien-*

tation of the reactant molecules must be correct. For example, during the esterification of benzoic acid, methanol oxygen must collide with the carboxyl carbon:



(I) (XVI-1)

It is nonproductive for the methanol oxygen to collide with any other part of the protonated benzoic acid molecule (I). Notice in the example that an oxygen-carbon σ bond was *made* during the collision, and that a carbon-oxygen π bond was *broken* during the collision.

The third and critical factor to be considered is whether the properly oriented collision occurs with enough *energy* so that bond breaking and making can take place. A weak, properly oriented collision would result in methanol's rebounding from the acid.

The amount of energy required to break the old bond and make a new one is the activation energy, E_{act}, for the reaction. It is represented by the energy difference between the reactants and the transition state, as depicted in Figure XVI.1. The way molecules are usually given the energy required to pass through the transition state of the rate-determining step is to heat the reactants: the faster they move, the greater the force of collision.

The rate of a reaction is often expressed in terms of its rate constant, k. The **rate constant** is the ratio of reaction rate to the product of reactant concentrations as they appear in the rate expression, and the larger the rate constant, the faster the reaction.

$$k = \frac{\text{rate}}{\text{concentration terms}} \qquad \text{(XVI-2)}$$

EQUILIBRIUM

Chemical equilibrium in a reaction mixture is that state wherein forward and reverse rates are equal and the concentrations of reactants and products remain unchanged. The implication in this definition is that an equilibrium reaction does not go to completion, but rather proceeds in both directions simultaneously. The dynamic character of such reactions is emphasized by examining the relationship between the rate constants in the forward and reverse directions. It is interesting that understanding of equilibria originally came via studies of reaction rates. Let us consider the general one-step reaction

$$A + B \rightleftharpoons C + D \qquad \text{(XVI-3)}$$

The rates (V) of the forward (f) and reverse (r) reactions can be given by

$$V_f = k_f[A][B] \qquad \text{(XVI-4)}$$

$$V_r = k_r[C][D] \qquad \text{(XVI-5)}$$

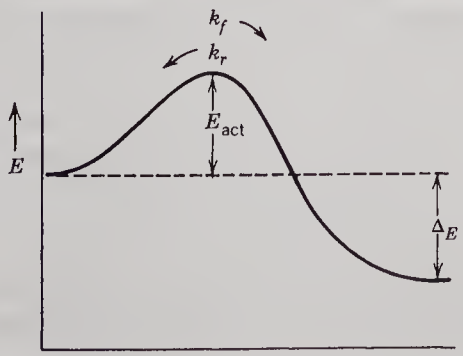


FIGURE XVI.1 Energy curve for exothermic chemical reaction.

At equilibrium the rates of the reactions are equal, and the equations can be combined:

$$k_f[A][B] = k_r[C][D] \qquad \text{(XVI-6)}$$

Rearrangement gives

$$K_{eq} = \frac{k_f}{k_r} = \frac{[C][D]}{[A][B]} \qquad \text{(XVI-7)}$$

wherein K_{eq} is the equilibrium constant. We see that this is a mathematical statement of the definition given at the beginning of this section.

The position of equilibrium determines the maximum amount of product that can be obtained under given conditions unless we shift the equilibrium by some method such as removing one of the products by distillation. Notice the exothermic change in energy, ΔH, on the energy curve of Figure XVI.1. This exotherm is related to the position of equilibrium: the greater the exotherm, the farther the reaction proceeds to the right before equilibrium is established. Another way to describe this situation is to say that the greater the value of the forward rate constant relative to the reverse rate constant, the greater is the exotherm.

EXPERIMENT 39 SOLVOLYSIS OF 2-CHLORO-2-METHYLPROPANE

Time Required: 2–4 hr

Review Techniques and Principles

Lab notebook	(1)
Stirring	(0.4)
Heating	(0.5)
Thermometer	(3.1)

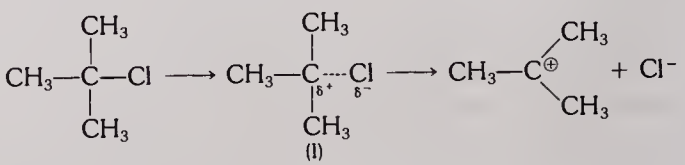
New Techniques and Principles

Kinetics measurements

Under the conditions used for this experiment, the solvolyses of 2-chloro-2-methylpropane (*t*-butyl chloride) and 2-chloro-2-methylbutane (*t*-pentyl chloride) proceed by an S_N1 reaction. S_N1 conditions are summarized here, but for details you should consult your lecture textbook. Before you study this experiment, you should also read Section XVII.

E39.1 THE S_N1 REACTION

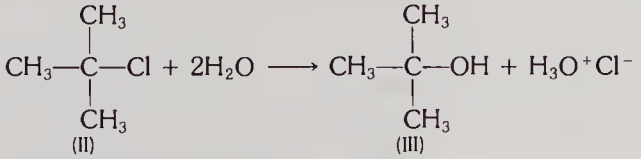
S_N1 means "substitution, nucleophilic, unimolecular." In other words, the reaction is a nucleophilic substitution reaction in which the rate-determining step involves a transition state (I) containing only one molecule necessarily undergoing covalency change:



(E39-1)

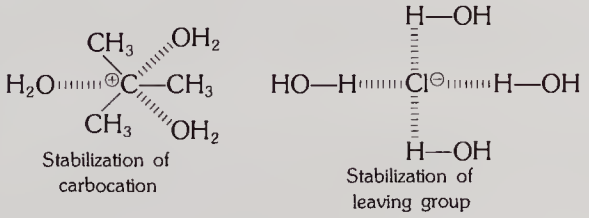
The term *solvolysis* is a combination of the words "solvent" and "lysis" (unbinding or loosening) and refers to the role of solvent in breaking the bond between carbon and

leaving group. The solvent in this experiment is water, and solvolysis of 2-chloro-2-methylpropane (II) yields 2-methyl-2-propanol (III).



(E39-2)

The two prime requisites of an S_N1 reaction are first, that the substrate molecule be able to form a reasonably stable carbocation (carbonium ion) and second, that the solvent be capable of helping to remove the leaving group and then to stabilize both carbocation and leaving group. This the solvent does by solvating the cation through use of dipole-dipole interactions and by solvating the anion by hydrogen-bonding, the strongest of the dipole-dipole interactions:



Although we can imagine that any polar solvent molecule is able to stabilize carbocation and anion, it should be obvious that the greatest stabilization results with the most polar solvents. Because normally the strongest dipoles are those of the H—O, H—N and H—F bonds, the most effective S_N1 solvents are protic.

E39.2 S_N1 KINETICS

The rate of an S_N1 reaction is most strongly influenced by the following factors, all of which you will have an opportunity to investigate in this experiment.

Solvent. Not only does solvent help to determine whether an S_N reaction will be S_N1 or S_N2, but it also influences the rate of the S_N1 reaction. The ability of the solvent to loosen and break the bond between carbocation and leaving group depends on its polarity and protic nature: the better the hydrogen-bonding capability, the faster the reaction.

Temperature. As temperature is increased, the rate of a reaction increases for two reasons: first, the reactants collide more often, and second, they collide more forcefully. Very roughly, one can expect that for each 10 C° rise in temperature the reaction rate will double.

Concentration. As you have already seen in Section XVI, increasing concentration of the substrate (the substance on which the nucleophile acts) increases the rate.

Substrate. The substrate molecule is divided into two parts: the hydrocarbon portion and the leaving group. The rate of an S_N1 reaction increases as the stability of the intermediate carbocation increases; the cation stability is of course dependent on resonance and hyperconjugation. Because the bond to the leaving group is being broken in the transition state for the rate-determining step, the rate is different with different leaving groups. The best leaving groups are those that are least basic because the less basic the group is, the less it is attracted to a positive site. Another way to look at it is that the best leaving groups are the weak conjugate bases of strong Brønsted acids.

Rate Equations Because only the substrate is involved in the transition state of the rate-determining step, the rate (V) of an S_N1 reaction is independent of nucleophile concentration, and is directly proportional to that of the substrate alone:

$$V \propto [RCl] \tag{E39-3}$$

That is, if we double the substrate concentration, we cause the rate of reaction, V, to be double. If we measure time in seconds and concentration in moles per liter, the units of rate are moles per liter $\times$ seconds. So, the rate relates to how fast the concentration is changing per second. Introduction of a proportionality constant makes it possible to write

$$V = k[RCl] \tag{E39-4}$$

Constant k, the *rate constant*, applies only to the given reaction under specified conditions of temperature and solvent. It is an important value for comparing reactions that are similar to each other.

Because the concentration term is constantly changing we must rely on calculus, writing the rate equation in derivative form:

$$\frac{d[RCl]}{dt} = -k[RCl] \tag{E39-5}$$

The negative sign is used because as the reaction proceeds, the concentration of reactant is decreasing. What this derivative equation tells us is that in an infinitely small period of time, dt, there is an infinitely small decrease in substrate concentration, $d[RCl]$. Rearrangement gives the differential equation

$$\frac{-d[RCl]}{[RCl]} = k\,dt \tag{E39-6}$$

This equation can be integrated, that is, it can be made to relate the change in concentration to a longer period of time than the infinitely small dt:

$$-\int_{[RCl]_0}^{[RCl]} \frac{d[RCl]}{[RCl]_0} = k\int_0^t dt \tag{E39-7}$$

The symbol $\int$ means "integrate"; it and the other symbols around it are called an *integral*. We shall integrate the right-hand integral from time zero (when the reaction begins) to time t (the time somewhat later); and we shall integrate the left-hand integral from the concentration at time zero, $[RCl]_0$, to the concentration which will be present at time t:

$$-\ln \frac{[RCl]}{[RCl]_0} = kt \tag{E39-8}$$

This integrated equation gives a natural logarithmic relationship of the concentration ratio. We can rewrite this equation by changing to base 10 logarithms, and by inverting the concentration ratio to get rid of the negative sign:

$$2.303 \log_{10} \frac{[RCl]_0}{[RCl]} = kt \tag{E39-9}$$

There is more than one way to obtain rate constants. In this experiment, we shall calculate the value of the rate constant, k, by measuring the time, t, required for a 10.0% reduction in the initial concentration of substrate, $[RCl]_0$. At time t 90.0% of the substrate will still remain, and the concentration [RCl] at time t will be

$$[RCl] = 0.900[RCl]_0 \tag{E39-10}$$

By substituting the right-hand side of equation E39-10 into equation E39-9, we get

$$2.303 \log_{10} \frac{[RCl]_0}{0.900[RCl]_0} = kt \tag{E39-11}$$

Cancelling like terms, performing the mathematical operations, and rearranging gives the very simple relationship

$$k = \frac{0.104}{t} \qquad \text{(E39-12)}$$

As you can see, the rate constant units for an S_N1 reaction are sec^{-1}.

E39.3 THE TECHNIQUE

In this experiment you will determine rate constants for several variations of the S_N1 process. The procedure will be to mix a tenfold excess of substrate with dilute aqueous sodium hydroxide in the presence of an indicator. The hydroxide ion will neutralize the hydronium ion byproduct shown in equation E39-2, changing the indicator color. You will note the time, *t*, required for the color change and use it in equation E39-12 to calculate *k*.

The reason that acetone is used to dissolve the alkyl halide is so that when the reactants are mixed, there will be no time lag while alkyl halide is dissolving and is not completely available for reaction. The amount of acetone is relatively small and has a negligible effect on the course of the reaction.

The sodium hydroxide used to neutralize the byproduct hydronium ion is present in small quantity relative to the water; hence its activity as a nucleophile is small. Even if some hydroxide did behave as a nucleophile, there would be no change in time *t*. The amount of elimination by way of E1 reaction should be very small because the concentration of hydroxide is small and the temperature relatively low.

Only a few comments about laboratory technique are required. However, they are very important to the success of a kinetics experiment.

A thermostated, constant temperature bath is ordinarily used for kinetics studies because small temperature variations can lead to relatively large errors in *k*. In this experiment, you will be using a rather crude bath, and must try to maintain the temperature as constant as possible. This will not be difficult at room temperature, but at other temperatures, it will require that you monitor the bath temperature constantly, adding small amounts of hot or cold water to the bath if necessary. This is particularly critical at elevated temperatures because reaction times will be shorter. The actual temperatures of the water bath are not critical. But the temperature for each trial within a set must be the same and must be known as accurately as possible.

The amount of base added is crucial to your experimental success because it is the amount of base present that determines how far the reaction progresses before the indicator changes color. Therefore you should pipet the volume of aqueous sodium hydroxide very carefully.

E39.4 EXPERIMENTAL PART

Ask your instructor which of the following described variations you should perform, and whether and to what extent you should combine this experiment with Experiment 40.

During the entire experiment you will have a partner who will watch a stopwatch or watch with sweep second hand. Record the time in seconds.

Make a table for data collection with column headings for substrate name, substrate concentration, base concentration, solvent name, time, rate constant, and comments.

General procedure. Using a 1.0-ml graduated pipet, transfer 0.30 ml of 0.10*M* aqueous NaOH into each of three clean 25-ml Erlenmeyer flasks; then add 6.7 ml of solvent from a 10-ml graduated cylinder. Add one drop of bromphenol blue indicator solution to each flask, stopper the flasks, and label them "A."

Using a 10.0-ml graduated pipet, transfer 3.0 ml of a 0.10*M* acetone (IUPAC propanone) solution of substrate into each of three clean 25-ml Erlenmeyer flasks; then stopper the flasks and label them "B."

Never suck solutions into a pipet with your mouth. Use a rubber bulb.

Fill a pneumatic trough or similar container to within 3 cm of the top with room temperature water. Clamp the two sets of flasks onto two or three ringstands. Adjust the flask height on the ringstands so that they are immersed in the water to the lower part of the flask neck. Record the temperature of the water to the nearest 0.1 °C if possible. The temperature used is not critical as long as you know what the temperature is. Swirl the contents of the flasks occasionally over a period of 5 min to ensure that they are at the temperature of the water bath. Keep the stoppers on the flasks until just before use. (If a large container is not available, two 1000-ml beakers can be used. Put an "A" flask in one and a "B" flask in the other. This arrangement is quite satisfactory, but the temperatures are not as easily regulated, and it takes longer.)

Now remove one "B" flask from the bath, wipe water from the flask with a sponge or towel, and pour its contents into an "A" flask. Tell your partner, "Begin timing" at the moment of pouring. Keeping the combined solution in the constant temperature bath, swirl it for about 10 s to ensure good mixing. At the instant the solution changes from blue to yellow, tell your partner, "Stop." Check the reactant mixture temperature a few times during the experiment, making corrections and/or noting temperature variations. If there is an unavoidable temperature change from beginning to end, use the arithmetic mean.

Repeat the process twice more with the other two samples from each set. Put the flask contents in an acetone (IUPAC propanone) recovery container. Rinse the flasks with water, and then with a little acetone, putting the rinses in the recovery container. Allow the flasks to air dry. Calculate the rate constant from equation E39-12 and report the rate constant as the average of the values. If you use the computer for analysis you will need only to input raw data without any prior calculations.

Variations in experimentation

1. Use distilled water as solvent, 2-chloro-2-methylpropane (*tert*-butyl chloride) as substrate, and ambient bath temperature.
2. Use the same solvent and substrate at a temperature about 10 °C higher than before.
3. Use 25% *aq* methanol as solvent, same substrate, and ambient bath temperature.
4. Use distilled water as solvent, 2-chloro-2-methylbutane (*tert*-pentyl chloride) as substrate, and ambient bath temperature.
5. Use distilled water as solvent, 2-bromo-2-methylpropane (*tert*-butyl bromide) as substrate, and ambient bath temperature.
6. Use distilled water as solvent, 2-bromobutane (*sec*-butyl bromide) as substrate, and ambient bath temperature.
7. Use the same solvent, substrate, and temperature as in 1, but use a 0.2*M* concentration of substrate.

Computer analysis. If your chemistry department has the right kind of personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR,* and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations.

Writing the discussion. Discuss the relative values of the rate constants for the various trials, proposing theoretical explanations.

E39.5 EXERCISES

Prelaboratory

1. What unit of time will you record for your measurements?
2. Look at equation E39-4. What are the units for the rate constant in an S_N1 reaction as based on the unit of time you will be using?

3. Based on consideration of the intermediate carbocation, explain why you think any elimination, which also proceeds by the carbocation mechanism should or should not change the rate determination during this kinetic study.
4. Why is sodium hydroxide put into the reaction mixture?
5. What is the function of the acetone in this reaction?
6. Propose a reason for wiping water from the propanone-haloalkane flask before pouring the solution into the second flask?
7. Where should flask "A" be after mixing the two reaction solutions?

Postlaboratory

1. *Ali Quat,* studying the kinetics of solvolysis, expected that the S_N1 rates of reaction for 2-methyl-2-chlorobutane and 5-butyl-5-chlorononane should be the same because they are both tertiary substrates. What do you think he actually found? Explain.
2. Starting with the transition state for the S_N1 reaction of *t*-pentyl chloride, draw a structural arrangement (like those in Section E39.1) that shows how solvent helps to separate carbocation from leaving group.
3. What was a possible alkene byproduct of the sovolysis reaction with *tert*-butyl chloride? With *sec*-butyl bromide? Explain whether its production would have affected your data (think in terms of the rate-limiting step of the process).
4. Using the rate constant you determined for *tert*-butyl chloride at ambient temperature, calculate the rate of the reaction in moles per liter × second for a 0.25*M* concentration.

REFERENCE

1. Mohrig, J. R.; Neckers, D. C. *Laboratory Experiments in Organic Chemistry,* 2nd ed.; Van Nostrand: New York, 1973; p 90.

EXPERIMENT 40 DETERMINATION OF ACTIVATION ENERGY

Time Required: 2–2½ hr

Review Techniques and Principles

Lab notebook	(1)
Stirring	(0.4)
Heating and cooling	(0.5)
Thermometer	(3.1)
Kinetics measurements	(E45.3, E45.4)

E40.1 ACTIVATION ENERGY

Activation energy is that energy which must be supplied to overcome steric effects and to begin breaking old bonds. It is the amount of energy that is required to change the substrate into the activated complex (transition state). It is the distance between the energy positions of substrate and transition state as shown on the energy curve of Figure E40.2. Activation energy is generally given the symbols $\Delta H‡$, ΔH^*, or E_{act} (see Figure E40.1); or $\Delta G‡$ and ΔG^* if free energies are being considered.

The activation energy is related to the rate constant by the Arrhenius equation:

$$k = Ae^{-E_{act}/RT} \qquad \text{(E40-1)}$$

which can be expressed in logarithmic form as

$$\ln k = \left(\frac{-E_{act}}{R}\right)\left(\frac{1}{T}\right) + \ln A \qquad \text{(E40-2)}$$

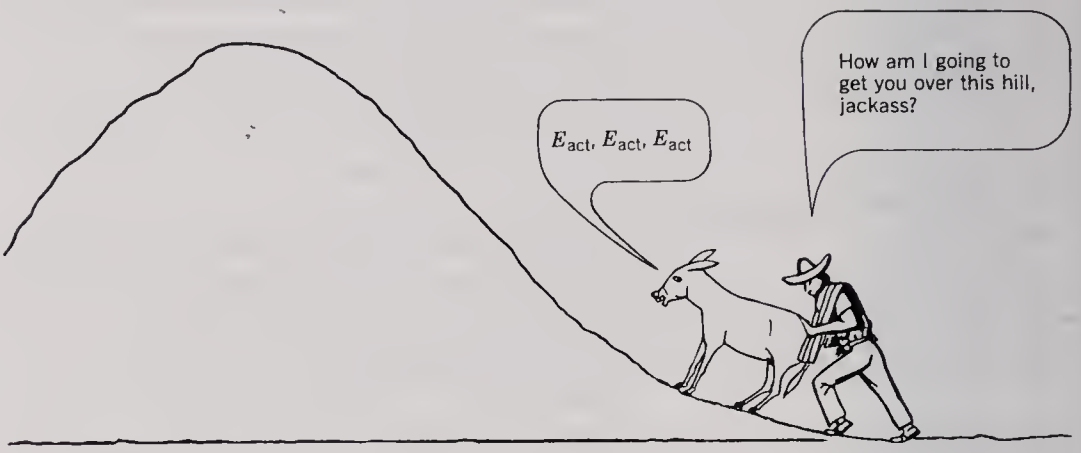


FIGURE E40.1 Most processes require energy of activation.

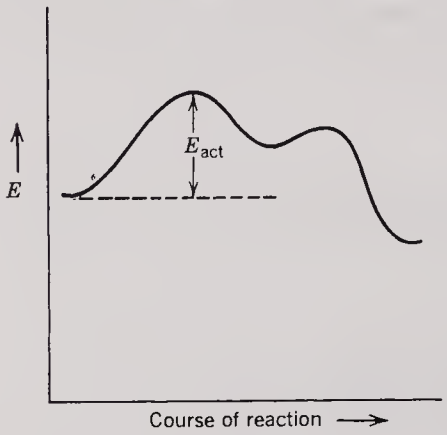


FIGURE E40.2 Typical S_N1 energy curve.

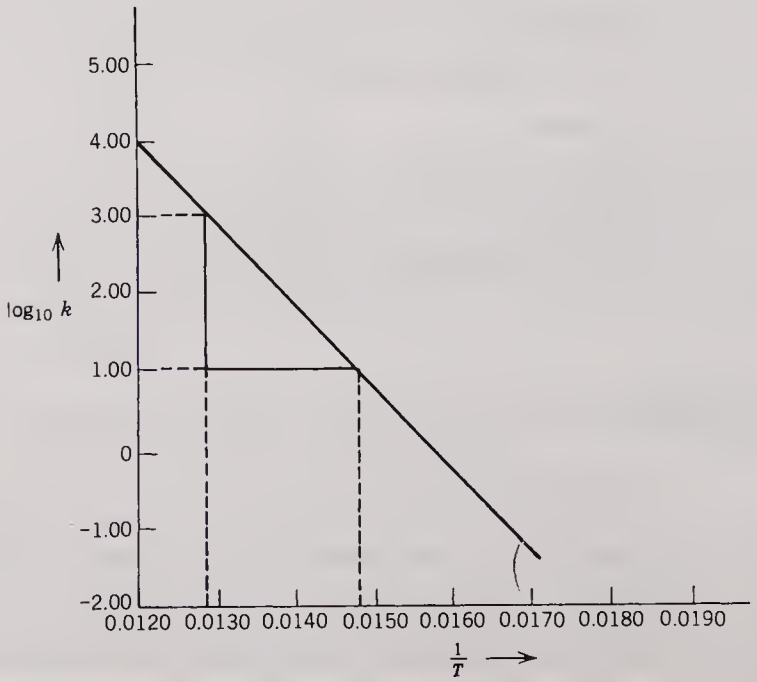


FIGURE E40.3 Plot for determining activation energy.

wherein R is the universal gas law constant 1.99 cal/mole × °K, T is the Kelvin temperature, and A is a constant related to the frequency of molecular collisions and the geometry for alignment of molecules in the transition state. We can rewrite this equation by changing to base 10 logarithms as

$$\log_{10} k = \left(\frac{-E_{act}}{2.303R}\right)\left(\frac{1}{T}\right) + \log_{10} A \qquad \text{(E40-3)}$$

Notice that equation E40-3 has the form of an equation for a straight line, $y = mx + b$, wherein m is the slope of the line and b is the intercept. In equation E40-3, the slope is $-E_{act}/2.303R$ and the intercept is log A. The negative sign associated with the slope tells us that the plotted line of the equation runs from upper left to lower right, as seen in Figure E40.3.

From equation E40-3 you see that we can find the activation energy for any given reaction by determining its rate constant at two or more temperatures, making a plot of log k *versus* $1/T$, measuring the slope, and calculating the activation energy from

$$-E_{act} = 2.303\text{R} \times \text{(measured slope of line)} \qquad \text{(E40-4)}$$

Because the measured slope of the line is negative, the solved value for E_{act} will be positive.

E40.2 EXPERIMENTAL PART

Ask your instructor what substrates, solvents, concentrations, and temperatures you should use, or whether you are to make your own selections.

Procedure. Use the same methods as described for Experiment 39, but use three water bath temperatures: room temperature, 10 C° above room temperature, and 10 C° below room temperature. Use ice to control the temperature of the cold water bath.

Data treatment. Using equation E40-12 and the average time values at each temperature, solve for the rate constant at each temperature. Obtain the activation energy by plotting $\log_{10} k$ as the ordinate and $1/T$ as the abscissa as shown in Figure E40.2. Report the activation energy in kcal/mole.

Computer analysis. If your chemistry department has an appropriate personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR,* and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations.

Writing the discussion. The following suggestions all pertain to this experiment, but not all of them are appropriate for discussion. Select what seem to be the four most appropriate items for your discussion: discussion of kinetics, why effects of NaOH were minimal during this experiment, how E_{act} was determined, discussion of how temperature affects the rate constants that you determined, discussion of a plot of k versus °C relative to loss of accuracy, how precisely you were able to make your measurements and how that affected your final results, why the slope of equations E40-2 and E40-3 are negative, why NaOH was used in the reaction, the method of determining k, what you would do differently to make the procedure work better another time. The selection depends, of course, on the question, "Can I draw conclusions relative to the suggested topic based on what *I* discovered during this experiment?"

E40.3 EXERCISES

Prelaboratory

1. Review the prelab exercises for Experiment 45.
2. Make a table in your notebook for data collection, arranging the three individual and average reaction times; initial, final, and average °C temperature; T; $1/T$; and log k in the most logical sequence for use as you work. If you use the computer for analysis, you will need only individual reaction times, and initial and final temperatures.
3. What term of equation E40-2 is the slope?
4. What does the negative sign of the slope tell us to expect from the plot of log k *versus* $1/T$?
5. Once a plot of log k *versus* $1/T$ is prepared, how will you find E_{act}?

Postlaboratory

1. Using the rate constants, k, that you determined at the three centigrade temperatures, make a plot of k as the abscissa and temperature as the ordinate from 0 to 50 °C. Draw a smooth curve through the three points. Determine from the plot what centigrade temperature change results in a doubling of the rate.
2. Using equation E39-4, rationalize the use in exercise 1 above of k rather than the rate itself.
3. Using the °C *versus* k plot from exercise 1 above and the rate equation E39-4, determine the rate in moles per liter × second of 2-chloro-2-methylpropane hydrolysis at (a) a temperature of 20 °C and a concentration of 0.10*M* 2-chloro-2-methylpropane; (b) a temperature of 40 °C and a concentration of 0.25*M* 2-chloro-2-methylpropane. Note the utility of the plot in determining rates at all temperatures and concentrations.

EXPERIMENT 41 KINETIC AND EQUILIBRIUM CONTROL OF SEMICARBAZONE FORMATION

Time Required: 2–3 hr

Review Techniques and Principles:

Lab notebook	(1)
Activation energy	(Experiment 40)
Mixing	(0.4)
Heating	(0.5)
Reflux	(0.5)
Cooling	(0.5)
Vacuum filtration	(4.3)
Drying solids	(2.1)
Melting points	(3.3)
Storing	(0.12)
Labeling	(0.13)

E41.1 DISCUSSION

When the ratio of products formed depends on the rates of the reactions at a given temperature, the process is said to be under kinetic control, or rate control. An example of rate-controlled processes is the competition of o, *p*, and *m* positions on toluene for

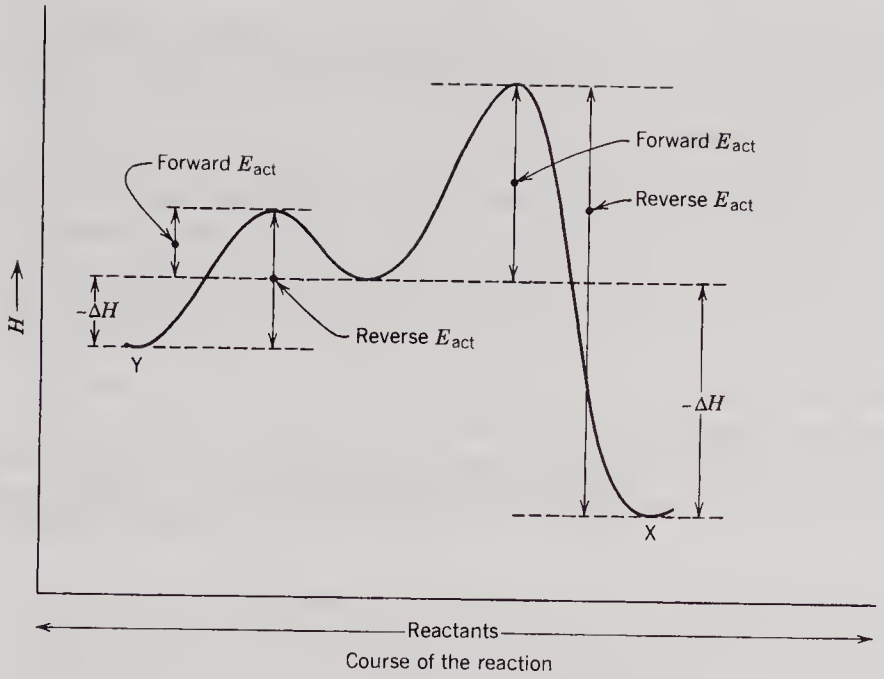
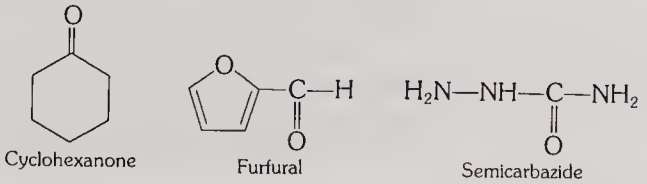


FIGURE E41.1 Energy curves for kinetic versus equilibrium processes.

nitronium ion. When the ratio of products depends on the position of equilibrium, the process is said to be under equilibrium control.

In general, but not always, an organic reaction that has a low activation energy is not very exothermic; and an organic reaction that has a high activation energy is quite exothermic. This is the situation that applies in the competing reactions of cyclohexanone and furfural (IUPAC 2-oxolecarbonal) with semicarbazide.

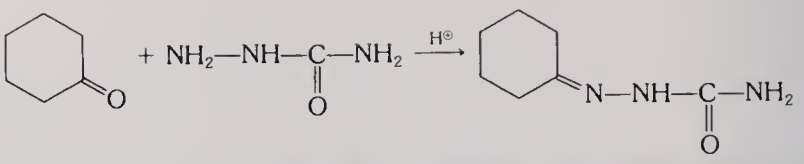


The overall energy curves look like those in Figure E41.1. Notice that the more exothermic reaction is depicted with the higher activation energy. X and Y on the figure are the semicarbazones of cyclohexanone and furfural, but which is which is left for you to discover by experimentation. Actually, Figure E41.1 is only an overall representation of the energy curves since the formation of a semicarbazone involves many intermediate steps, and hence requires a many-humped curve.

The curves of Figure E41.1 teach that at a low temperature the semicarbazide is more likely to react to form Y than X. This is because there is not enough energy in the system to provide very many collisions forceful enough to overcome the higher activation energy to form X. The rate will be faster in the direction of Y and more Y will be formed in a given time. Hence at lower temperatures the reaction is rate controlled.

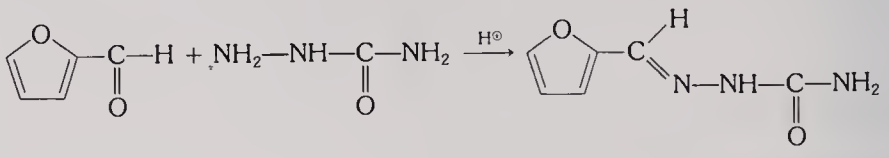
On the other hand, if the temperature is high, the major product will be X. This is because at the higher temperature collisions are energetic enough for more molecules to overcome the required higher activation energy. If the temperature is not too high, the force of collisions will not be sufficient to cause reversal of X formation because the activation energy of the reverse process is even higher. However, the energy in the system is quite adequate to cause reversal of Y to carbonyl compound and semicarbazide. Notice that the curve shows that Y forms faster than X but that it also reverts more quickly at a higher temperature to reactants again. At the high temperature, then, this reaction is equilibrium controlled.

The reactions of cyclohexanone and furfural with semicarbazide are shown in equations E41-1 and E41-2, respectively.



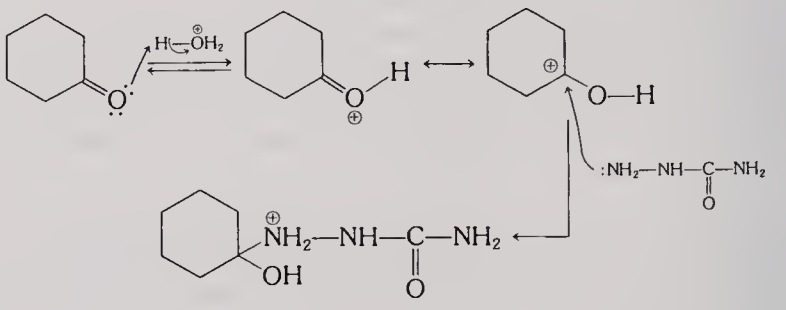
(E41-1)

The products are the semicarbazones and are called cyclohexanone semicarbazone and furfural semicarbazone. Their melting points are 166 and 202 °C, respectively.



(E41-2)

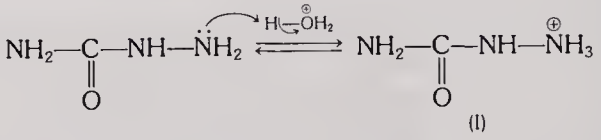
In the reaction mechanism, the nonbonding electrons of nitrogen farthest from the carbonyl of semicarbazide must form a bond from nitrogen to carbonyl carbon of the aldehyde or ketone. This bond formation is facilitated by acid catalysis:



(E41-3)

Remember, it is easier to make a bond when the charges or partial charges on atoms to be bonded together are as opposite as possible (reactions between opposite ions are practically instantaneous).

The pH of the reaction mixture must be carefully controlled. That is why potassium monohydrogen phosphate is present as a buffer. If too many hydrogen ions are present in the reaction mixture, too much of the semicarbazide will be converted to the protonated, non-nucleophilic form (I):



(E41-4)

The protonated nitrogen no longer has any nonbonding electrons with which to form a bond upon collision with the carbonyl carbon of the aldehyde or ketone. On the other hand, the mixture cannot be too basic because in the absence of protons, the carbonyl carbon of the aldehyde or ketone is not positive enough to facilitate bond formation to nitrogen, as shown in the second step of E41-3.

E41.2 EXPERIMENTAL PART

Preparation of solutions. Put into a 125-ml Erlenmeyer flask 50 ml of water, 2.2 g (0.030 mole) of semicarbazide hydrochloride, and 4.4 g of potassium monohydrogen phosphate. Add 5 ml of 95% ethanol. Swirl the mixture and put half in a 100-ml round-bottom flask. △

Put into a large test tube 3.0 ml (0.030 mole) of cyclohexanone, 2.4 ml (0.030 mole) of freshly distilled furfural, and 15 ml of 95% ethanol. Swirl the mixture and divide it into three equal parts, one in each of three test tubes. Put a boiling chip in one test tube.

Competition between cyclohexanone and furfural or semicarbazide at near 100 °C. Set the round-bottom flask containing the aqueous semicarbazide solution on a steam or hot water bath. Attach a water-cooled reflux condenser, put in a boiling chip, and heat the mixture until the water bath is at 80 °C. Heat the ethanolic solution in the test tube with the boiling chip until it begins to boil. Lift the condenser momentarily and add the hot contents of the test tube to the flask. Reflux the mixture for 15 min. Cool the solution to room temperature and then in an ice bath for about 10 min. Collect the crystals in a Hirsch funnel and wash them with a small amount of water. Suck them as dry as possible, spread them out in a beaker, and dry them in a 50 °C oven. Obtain the melting point. Label the product A. △△

If the water bath is heated to more than 80 °C, the ethanolic solution added from the test tube might suddenly boil and eject contents from the reaction vessel.

Do not attempt to obtain melting points using an oil bath apparatus. The melting point of one product is too high and attempts to melt it could lead to dangerous overheating of the oil bath.

Competition between cyclohexanone and furfural for semicarbazide at 5 °C. Cool the aqueous semicarbazide solution of the Erlenmeyer flask to 5 °C in a cooling bath. Cool the ethanolic solution of one of the test tubes also to 5 °C. Use separate thermometers or clean a single thermometer between testing the temperatures of the two solutions.

After both solutions are at 5 °C, pour the ethanolic solution into the aqueous solution and swirl the mixture. Allow it to sit at 5 °C for 5 min. Collect the crystals in a Hirsch funnel and wash them with a small amount of ice cold water. Suck them as dry as possible, spread them out in a beaker, and dry them in a 50 °C oven. Obtain the melting point. Label the product B. △△

Attempt at conversion of the A-labeled semicarbazone. Put 0.3 g of the semicarbazone product A, 10 ml of water, and half of the ethanolic contents of the third test tube into a large test tube. Heat the contents on a steam bath or boiling water bath for 5 min. Cool the mixture to room temperature, and then in an ice bath. Collect the crystals in a Hirsch funnel and wash them with a small amount of ice cold water. Dry the crystals and obtain their melting point. △△

Attempt at conversion of the B-labeled semicarbazone. Using 0.3 g of the semicarbazone product labeled B, proceed as described above. △△

Combine all crystals according to melting point and submit them to your instructor in labeled vials.

Writing the discussion. By comparing the melting points of the various products with those given in the discussion section, you can decide which semicarbazide reaction in this experiment involves equilibrium control and which involves kinetic control. Discuss which reaction has the higher activation energy and which reaction is more exothermic. Discuss the relationships between activation energies and the attempted conversion reactions.

E41.3 EXERCISES

Prelaboratory

1. What would happen to the temperature of the near-boiling ethanolic solution in the test tube if it were added to the round-bottom flask through the condenser?
2. What kind of cooling bath will be needed to get the temperature down to 5 °C?
3. Why is it important to have both the semicarbazide and carbonyl compound solutions at the same temperature before combining them?

4. If, during attempted conversion of the semicarbazones, crystals do not readily form during ice bath cooling, do you think the solution might not be saturated? How could you correct this problem?
5. Review hazards associated with heating reactants (0.5) and vacuum filtration (4.3).

Postlaboratory

1. Complete the labeling of all humps and valleys in the energy curves of figure E41.1. Draw structures of transition states and intermediates.
2. Recognizing that Figure E41.1 is not a true representation of the multihump curve that would pertain to semicarbazone formation, discuss which curve best fits the semicarbazide reaction with cyclohexanone.
3. Continue the electron transfer mechanism begun in E41-3 to show the various steps that finally result in hydrazone formation.

REFERENCE

1. Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry,* 4th ed.; Saunders: Philadelphia, 1985; p 406.

XVII

ACIDITY, NEUTRALIZATION, AND SAPONIFICATION

In this section we shall examine concepts of acidity and pH; and determine neutralization equivalents of acids, and saponification equivalents of esters.

The experimentation in this section provides more opportunities for you to ascertain the usefulness of computer analysis of chemical data.

EXPERIMENT 42 ACIDITY CONSTANTS

Time Required: 2 hr

Review Techniques and Principles:

Lab notebook (1)
Stirring (0.4)

New Techniques and Principles:

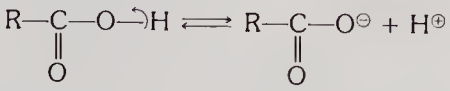
pH meter
Titration curves

Henderson-Hasselbalch equation
Acidity constant determination

E42.1 DISCUSSION OF ACIDITY CONSTANTS

Carboxylic acids are among the strongest organic acids. Still, they are very weak when compared to the strong mineral acids like hydrochloric acid. Whereas the mineral acid is almost 100% ionized in water, a 1*M* aqueous solution of a typical carboxylic acid is only 0.5% ionized, or dissociated.

When we say dissociated, we are referring to the dissociation of the proton from the carboxyl:



(E42-1)

Actually it does not simply dissociate. It is removed by collision with water or some other base, but for simplicity, we shall use the symbol H^+.

The dissociation constant, or acidity constant, K_a, is defined as

$$K_a = \frac{[RCOO^-][H^+]}{[RCOOH]} \tag{E42-2}$$

The bracketed quantities are in moles per liter. Taking the logarithms of E42-2 yields E42-3, which on rearrangement produces E42-4:

$$\log K_a = \log \frac{[RCOO^-]}{[RCOOH]} + \log[H^+] \tag{E42-3}$$

$$\log K_a - \log \frac{[RCOO^-]}{[RCOOH]} = \log[H^+] \tag{E42-4}$$

Taking reciprocals or changing signs gives

$$\log \frac{1}{K_a} + \log \frac{[RCOO^-]}{[RCOOH]} = \log \frac{1}{[H^+]} \tag{E42-5}$$

which can be rewritten as

$$pK_a + \log \frac{[RCOO^-]}{[RCOOH]} = pH \tag{E42-6}$$

because $\log 1/K_a$ is pK_a and $\log 1/[H^+]$ is pH. When anion concentration equals acid concentration, that is, $[RCOO^-] = [RCOOH]$, the ratio is 1/1; since the logarithm of 1 is 0, the pK_a of the acid equals the pH of the medium it is in:

$$pK_a = pH \tag{E42-7}$$

Therefore if the pH is determined when the concentration of anion and acid are equal, the pK_a of the acid will be known. In practice we determine pK_a by titrating an aqueous solution of the acid drawing a titration curve like that of Figure E42.1 to identify the equivalence point. The **titration curve,** a plot of pH versus volume of standard acid or base, graphically shows the change in pH as standard acid or base is added to a solution of organic base or acid. For a monoprotic acid, the **equivalence point** is that point at which the concentration of hydroxide ion added to the solution is equal to the original concentration of organic acid. The equivalence point is an inflection point, that is, a point at which the direction of the curve changes.

The K_a can be calculated by taking the inverse log of the $-pK_a$. For example, if the pK_a is 4.36 the inverse log is 4.4×10^{-5}:

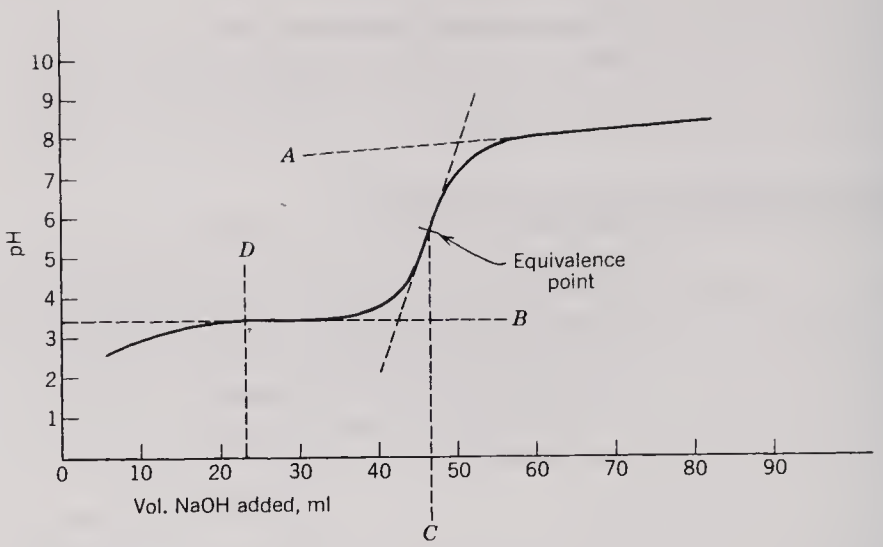


FIGURE E42.1 Titration curve.

$$
\begin{aligned}
-\log K_a = \log \frac{1}{K_a} &= pK_a \\
-\log K_a &= 4.36 \\
\log K_a &= -4.36 \\
K_a &= \text{inverse log } (-4.36) \\
&= \text{inverse log } (.64\text{-}5) \\
&= 4.4 \times 10^{-5}
\end{aligned}
\tag{E42-8}
$$

Another useful equation which can be derived from E42-6 is shown in E42-9, or more generally in E42-10:

$$
\text{pH} - pK_a = \log \frac{[\text{RCOO}^-]}{[\text{RCOOH}]} \tag{E42-9}
$$

$$
\text{pH} - pK_a = \log \frac{[\text{base}]}{[\text{acid}]} \tag{E42-10}
$$

E42-10 is known as the **Henderson-Hasselbalch equation.** We can use it to determine how much mineral acid to add to a solution of an organic acid salt to give nearly complete precipitation of product acid. For example, suppose we have an aqueous solution of sodium *p*-bromobenzoate and want to precipitate it as its water-insoluble acid. If we want only one acid molecule left for every 1000 that precipitate, we can substitute this value and the pK_a value of 4 for *p*-bromobenzoic acid into E42-9:

$$
\begin{aligned}
\text{pH} - 4 &= \log \frac{1}{10^3} \\
\text{pH} &= 4 - \log 10^3 \\
&= 4 - 3 = 1
\end{aligned}
\tag{E42-11}
$$

Solving E42-11 gives a pH of 1, which tells us that mineral acid must be added until the pH of the liquid is 1.

E42.2 THE TECHNIQUES

Titrating with a pH meter. The titration apparatus is illustrated in Figure E42.2. pH meters vary in style, but they all operate in basically the same manner. The following

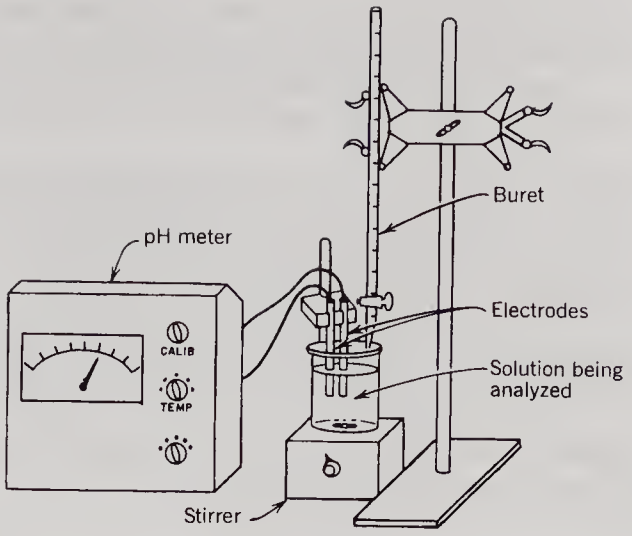


FIGURE E42.2 pH meter set up for titration.

procedure describes use of a Coleman meter, but the directions generally apply to other meters as well.

With the pH meter main switch set on standby, remove the buffer solution bathing the electrodes. Rinse the electrodes thoroughly with distilled water from a squeeze bottle. Draw off drops of water left hanging from the ends of the electrodes by lightly touching the drops with a tissue.

Next, immerse the pH electrodes in a buffer of pH in the region anticipated for the equivalence point and turn the main switch to the pH setting. Check the temperature of the buffer with a thermometer, and set the TEMP knob at that temperature. To calibrate the instrument, set the CALIB knob to the pH of the buffer. Remove the buffer and rinse the electrodes in the same manner as before. Lower the electrodes into the solution of acid to be titrated. The solution should be at the same temperature as the buffer. Set the magnetic stirrer to stir gently.

Read the initial pH of the solution from the meter and record it on a table which includes columns for pH, milliliters of base, and cumulative milliliters of base. Read the pH for every 1 or 2 ml of base. When the pH begins to change more rapidly, record the pH for fractional milliliters of base.

To determine the pK_a of an acid which has marginal solubility in water, ethanol can be added. However, not more than 30 volume% can be added without affecting the valid operation of the pH electrodes.

Distilled water used in titration should be essentially free of carbon dioxide because of the equilibria shown in E42-12, which could affect the value of the equivalence point:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^{\ominus} + H^{\oplus} \rightleftharpoons CO_3^{-2} + 2H^{+1} \qquad \text{(E42-12)}$$

Analysis of data. From the table of collected data, construct a plot of pH on the ordinate and cumulative milliliters of base on the abscissa. Extend the more horizontal and vertical portions of the curve as straight lines *A* and *B*, as shown on Figure E42.1. Measuring between the *A* and *B* along the more vertical line to its midpoint locates the equivalence point for a monoprotic acid. Now draw the perpendicular line *C* to the base and find on the base line the midpoint between *C* and *D*. Draw the vertical line *D* to the titration curve and read the pH at that point. The pK_a of the acid is equal to the pH, as shown in equation E42-7.

E42.3 EXPERIMENTAL PART

Preparation of 0.100M acid. Weigh 5.00 mmoles of propionic acid (IUPAC propanoic acid) into a 50-ml volumetric flask. Add about 25 ml of carbon dioxide-free distilled

water and swirl the mixture to dissolve the acid. Then fill the flask with distilled water to the volume line on the neck of the flask. Mix the contents of the flask thoroughly.

Repeat the preparation using 5.00 mmoles of chloracetic acid (IUPAC chloroethanoic acid), formic acid (IUPAC methanoic acid), or other acid assigned by your instructor.

Titration. Pipet 25.0 ml of the acid solution into a 150-ml beaker. Add 25.0 ml of CO_2-free distilled water. Stir the solution magnetically during the titration. Titrate the solution with 0.100*M* aqueous sodium hydroxide. Put leftover acid solutions in their assigned recovery containers. △△

Analysis. Make a titration curve and determine the equivalence and end points. Determine and report pK_a and K_a.

Writing the discussion. Compare the pK_as of the two acids and rationalize the difference based on chemical structure.

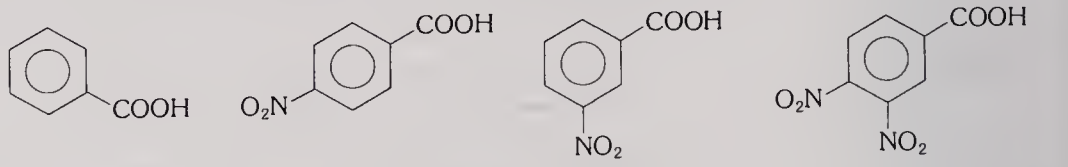
E42.3 EXERCISES

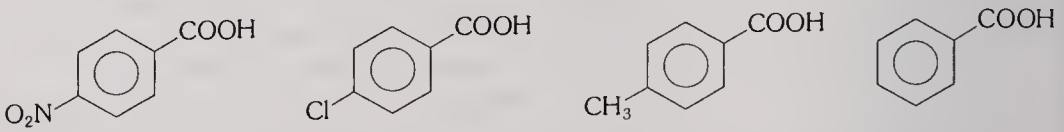
Prelaboratory

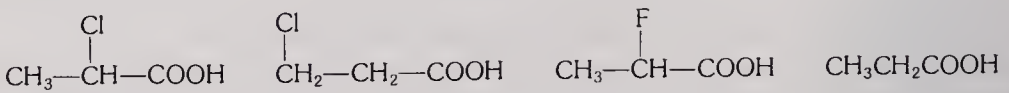
1. Prepare a table in your notebook to be used for recording data.
2. What is the purpose of the 95% ethanol that is sometimes added to solutions?
3. Why should water free of carbon dioxide be used for titrations?

Postlaboratory

1. Arrange the following acids in order of decreasing acidity:

a. 

b. 

c. 

2. What must be the pH of a solution in order to precipitate an acid of $pK_a = 6$ from its salt if you want 10,000 acid molecules for every one anion left?
3. The solubilities of salicylic acid are 0.15 g/100 ml of water at 15 °C and 39.2 g/100 ml of ethanol at 15 °C. The molecular weight is 138 g/mole. Assuming a linear relationship between solubility in alcohol and water, make a plot of solubility *versus* volume% composition of water and ethanol; then determine about what minimum volume of ethanol must be used in order to make 100 ml of a 0.100*M* solution of the acid.

EXPERIMENT 43 NEUTRALIZATION EQUIVALENTS

Time Required: 1 hr

Review Techniques and Principles:

Stirring	(0.4)
Using pH meter	(Exp 49)

New Principles:

Indicator titration end points

E43.1 NEUTRALIZATION EQUIVALENTS

Neutralization equivalent is synonymous with equivalent weight. It is the mass of an acid that gives up a mole of protons. It is called a neutralization equivalent because it represents the amount of acid that is neutralized by an equivalent amount of base. Because carboxylic acids (and some other organic acids) readily donate a proton to a strong base, the equivalent weight is easily determined by titration with a base like sodium hydroxide. After titration, the neutralization equivalent is determined as follows:

$$\left(\frac{\text{acid mass in g}}{\text{base vol in ml}}\right)\left(\frac{1000\text{ ml}}{\text{liter}}\right)\left(\frac{\text{liters of base soln}}{\text{equiv of base}}\right) = \frac{\text{g}}{\text{equiv}} \qquad \text{(E43-1)}$$

Notice that the (liters of base solution)/(equivalents of base) in E43-1 is the inverse of the normality of the base solution.

E43.2 INDICATOR ACTION

To best comprehend this section, you should first be familiar with Section E42.1.

An indicator can be used to determine the **end point,** the point during a titration at which an indicator changes color. Titration with an indicator gives a less reliable value than does titration with a pH meter.

An indicator is a weak acid, HIn, or base, InOH, in which the neutral, molecular form has a different color than the ionic form. It begins to change color when the hydronium ion concentration of its aqueous solution reaches a certain value, and typically continues the change over a range of 1.4 to 2.0 pH units. The particular range depends on the structure of the indicator. Let us consider a specific example. The equilibrium between the neutral acid indicator methyl orange and its conjugate base is

$$\underset{\text{Red}}{\text{HIn}} \rightleftharpoons \underset{\text{Yellow}}{\text{H}^+ + \text{In}^-} \qquad \text{(E43-2)}$$

Because the pH range of methyl orange is 3.1 to 4.4, it is red at pH < 3.1 and yellow at pH > 4.4. In between 3.1 and 4.4, the color is various shades of orange, depending on the relative concentrations of HIn and I^- and their molar absorptivities (see Technique 14). In actual practice during a titration, we are unlikely to see the orange shades because whereas only a 20-fold change in hydronium concentration is required to produce a complete color change in methyl orange, there is typically about a 10,000-fold change in hydronium concentration at the equivalence point. These same principles apply to indicator bases as well as to indicator acids.

As shown in Figure E42.1, the more vertical portion of the titration curve of an organic acid occurs over a range of pH values. To select an appropriate indicator for the titration of a given carboxylic acid, an indicator must have its pH color change *within* the pH range of the acid.

Because indicators are intensely colored (have a high molar absorptivity) only a tiny amount is required to indicate an endpoint. Use of excess indicator leads to erroneous results because the indicator is being titrated as well as the acid in question.

The methods described in this experiment are quite general for any acid. For carboxylic acids that are too insoluble in aqueous ethanol solutions, 95% ethanol can be used, along with bromthymol blue indicator. When organic liquids such as ethanol, methanol, and acetone, with a lower dielectric constant than water, are added to an aqueous solution, the equilibrium conditions are changed. Under such conditions the

ionization constants of weak acids and bases are decreased, and the indicator color-change interval is shifted to higher pH values.

E43.3 EXPERIMENTAL PART

You will be given a sample of formic acid, glacial acetic acid, or propionic acid. Ask your instructor if you are to use one or both methods of determining the endpoint, and which way you are to calculate the neutralization equivalent: by hand, with computer, or both.

Neutralization equivalent via indicator endpoint. Carefully weigh out about 0.2 g of the acid. The exact amount is not critical as long as the mass is known to three significant figures. Put it in a 250-ml Erlenmeyer flask. For acids that have marginal water solubility, add 5–20 ml of ethanol and swirl to dissolve the acid. Next, add 50 ml of water. Add, with swirling, two drops of phenolphthalein indicator solution. Titrate the acid with standard aqueous NaOH with a normality close to 0.100*N* until the solution just barely turns violet and remains violet after swirling. Approach the endpoint by dropwise addition from the buret.

Calculate the neutralization equivalent as described in equation E43-1 and identify the acid. Calculate the percent error.

Neutralization equivalent via pH meter endpoint. Carefully weigh out about 0.2 g of the acid. The exact amount is not critical as long as the mass is accurately known to three significant figures. Set up an apparatus like that described in Experiment 42. Put the acid in the beaker and, if the acid has marginal water-solubility, add 5–20 ml of ethanol. (The listed unknown acids are infinitely miscible with water.) Swirl the mixture to dissolve the acid, then add 50 ml of carbon dioxide-free water. Titrate to the equivalance point with standard aqueous NaOH with a normality close to 0.100*N*. Approach the endpoint by dropwise addition from the buret. You will have reached the endpoint when one or two drops changes the pH by several units.

Calculate the neutralization equivalent, identify the acid, and calculate the percent error.

Computer analysis. If your chemistry department has an appropriate personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR,* and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. You will need only to input raw data. The computer will make all calculations.

Writing the discussion. Declare and discuss the identity of your unknown compound. If both pH meter and indicator methods were used, discuss the relative merits of each that you observed as related to the identification of your unknown. If you used the computer, discuss the merits, if any, of its use for this experiment.

E43.4 EXERCISES

Prelaboratory

1. Why is ethanol added before the water when making up a solution of a slightly water-soluble acid?
2. Why should no more 0.100*M* aqueous NaOH be added than just enough to turn the solution faint violet?
3. Why should no more than two drops of indicator be added?

4. How will you add aqueous NaOH from the buret when approaching the equivalence point?

Postlaboratory

1. The equivalence point in the titration of an acid was 5.22 and the pH range of the more vertical part of the curve was 3.7 to 6.7. Because methyl violet was on the bench top, a student used it as an indicator. Using a table of indicators in a handbook of chemistry and physics, discuss the indicator selection.
2. *Anna Lysis* titrated 0.170 g of a carboxylic acid with 10.0 ml of 0.198*N* NaOH. She calculated the equivalent weight to be 86 g/equivalent, and identified the acid therefore as 2-butenoic acid. Criticize.

EXPERIMENT 44 SAPONIFICATION EQUIVALENTS

Time Required: 2–3 hr

Review Techniques and Principles:

Glassware	(0.3)
Stirring	(0.4)
Reflux	(0.5)
Titration	(E42)

E44.1 DISCUSSION OF SAPONIFICATION EQUIVALENT

Saponification is the base-promoted hydrolysis of an ester:

$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}OCH_3 + OH^{-1} \cdots\cdots\rightarrow CH_3{-}\underset{\underset{O}{\|}}{C}{-}O^{-1} + CH_3OH \qquad \text{(E44-1)}$$

The **saponification equivalent** of the ester is the mass in grams of the ester that reacts with one equivalent of hydroxide. It is the same as the equivalent weight of the ester, that is, the molecular weight of the ester divided by the number of carboxylate functions present.

The procedure is to weigh accurately a known amount of ester, to saponify it with a known volume of potassium hydroxide solution, and to titrate the excess base to a phenolphthalein end point with standardized hydrochloric acid. This titration gives the equivalents of base which were not used up in saponification. A second titration of the basic solution alone gives the equivalents of base present before saponification. The difference between the two represents the equivalents of base which reacted with ester, and therefore also gives the equivalents of ester. The saponification equivalent is given by

$$\begin{aligned} \text{saponification equiv} &= \frac{\text{g ester}}{\text{equiv ester}} \\ &= \frac{\text{g ester}(1000)}{(\text{equiv base})_{\text{before}} - (\text{equiv base})_{\text{after}}} \\ &= \frac{\text{g ester}(1000)}{(V \times N)_{\text{before}} - (V \times N)_{\text{after}}} \end{aligned} \qquad \text{(E44-2)}$$

wherein V and N are the volumes and normality of HCl, respectively, and the volumes are measured in milliliters.

Phenolphthalein can be used as the indicator because it changes color in the pH

range 8–10. The color change range encompassing the end point for titration of a strong base with strong acid but within a range well above that at which carboxylate is titrated. Because the color range is being approached from the high side, it goes from violet to colorless when all hydroxide is titrated.

E44.2 EXPERIMENTAL PART

You will be given 0.5 ml of one of the following esters as an unknown: methyl formate (IUPAC methyl methanoate), diethyl malonate (IUPAC diethyl propanedioate), dimethyl phthalate (IUPAC dimethyl 1,2-benzenecarboxylate), *n*-butyl acetate (IUPAC butyl ethanoate), or methyl benzoate (IUPAC methyl benzenecarboxylate).

Ask your instructor if the alcoholic hydroxide reagents are prepared solutions or whether you should make your own.

Determination of saponification equivalent. Put 2.5 g of crushed potassium hydroxide and 60 ml of 95% ethanol into a 125-ml Erlenmeyer flask and swirl the mixture to dissolve the solid (a small residue of potassium carbonate might remain undissolved). Pour the mixture into a 100-ml graduated cylinder and allow insoluble residue to precipitate over a period of several hours or filter the mixture, using a fast filter paper and suction filtration.

Remember that solid KOH is very caustic.

Pipet 25.0 ml of the ethanolic potassium hydroxide into each of two 125-ml Erlenmeyer flasks, and put the remainder into its assigned recovery container. Into one of the flasks put about 0.2 g of ester. The actual amount does not matter but it must be accurately weighed to three or four significant figures. Attach a reflux condenser to this flask and add a boiling chip. If ground glass joints are used, grease them lightly. Heat the flask on a steam bath for 1½ hr; then check the appearance of its contents. If the saponification mixture still appears to have more than one phase, reflux until it is homogeneous.

It is a good idea to wear rubber gloves and goggles while working with the very caustic ethanolic potassium hydroxide. Never pipet by mouth. Use a rubber bulb for suction.

After reflux, cool the flask and, before the condenser has been removed, rinse the entire interior of the condenser with 25 ml of distilled water. Then remove the condenser. Add a like amount of distilled water to the other flask, add two to three drops of phenolphthalein solution to each, and individually titrate them with standardized aqueous hydrochloric acid about 0.3–0.5*N*. At the end point, the violet color will disappear. When finished, put the alcoholic solutions in the ethanol recovery container.

Using equation E44-2, calculate the saponification equivalent for the ester.

Computer analysis. If your chemistry department has an appropriate personal computer, insert the organic laboratory utility disk into disk drive number one, *CLOSE THE DISK DRIVE DOOR,* and turn on the computer, printer, and screen. Make sure the computer's capitals lock key is down. When the disk stops whirring, follow the instructions that appear on the screen. Unless otherwise directed, make the printer begin printing on a new page. Cut the printout down to the smallest possible size and glue it or tape it on all sides into your notebook. Ask your instructor whether you should submit a printed copy other than the one fastened in your notebook.

Writing the discussion. Discuss your experimental value of the saponification equivalent relative to the true value. Explain the percent error in terms of the accuracy of measurements, the method, and your technical performance. If a computer was used in lieu of, or in addition to your own calculations, discuss the merits, if any, of using the computer.

E44.3 EXERCISES

Prelaboratory

1. Why are the ground glass joints in the reflux apparatus greased?
2. What must be done to the condensers before they are removed from the flasks? Why?
3. What colors will the solution be before and after reaching the endpoint?
4. Why must you never pipet by mouth?

Postlaboratory

1. Calculate the saponification equivalent of (a) glyceryl tristearate and (b) glyceryl dipalmitate. (Look in a handbook of chemistry and physics under stearic acid and palmitic acid.)
2. What is the molecular weight of an ester of a tricarboxylic acid if 0.216 g of it is saponified in 20.0 ml of 0.488*N* KOH, and after saponification 14.2 ml of 0.508*N* HCl is required to neutralize excess base?

XVIII

POLYMERS AND RUBBER

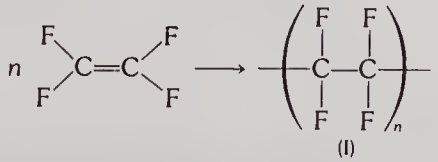
The following discussion is a short review of polymers. To best understand this section you should study the pertinent parts of your lecture text.

Polymers are very large molecules made from the combining of many small ones. Proteins and starches are examples of naturally occurring polymers, in which amino acids and sugars, respectively, are the small molecules from which the polymers are made. There are many synthetic polymers, a few of which will be prepared in this section.

A polymer is made up of many repeating units called **monomers.** An example of a monomer is ethene (ethylene), the monomer for making polyethylene. The combination of two monomers is a dimer, three is a trimer, four is a tetramer, and many is a polymer.

A polymer can be a **homopolymer,** comprised of only one kind of monomer, or it can be a **copolymer,** comprised of two or more different kinds of monomers. Polystyrene and polydimethylsiloxane (Experiment 47) are examples of homopolymers. Polyesters (Experiment 46) and nylons (Experiment 45) are examples of copolymers.

Polymers can be divided into two general classes, depending on their mode of preparation: addition polymers and condensation polymers. **Addition polymers** are made by directly adding one monomer to another without any weight loss. For example, polytetrafluoroethene (Teflon) (I), is an addition polymer:

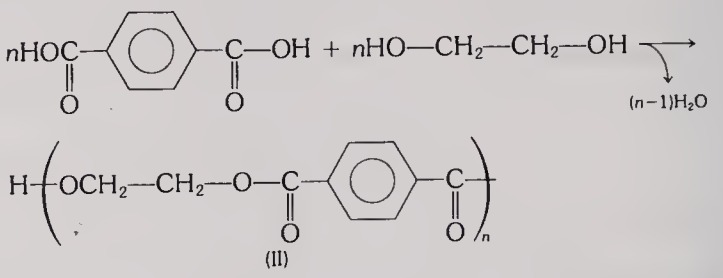


(XVIII-1)

(I)

Condensation polymers are made by a combination of monomers that results in splitting out of a small molecule byproduct. For example, Dacron (II) can be made by

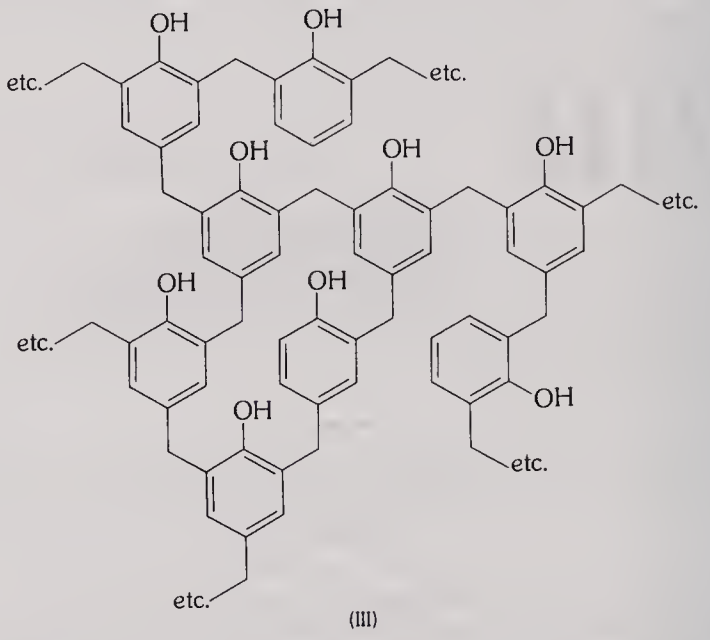
heating 1,4-benzenedicarboxylic acid and 1,2-dihydroxyethane in the presence of a proton catalyst:



(II) (XVIII-2)

Notice the water byproduct which marks the process as condensation polymerization.

Polymers can also be classified as **thermoplastic** or **thermosetting.** Thermoplastic materials are generally linear polymers, like Dacron (II), that can be melted and remolded. Thermosetting polymers, like Bakelite (III), are rigid three-dimensional structures that cannot be softened once polymerization is complete.



(III)

The infusibility of thermosetting polymers is due to **cross-links,** which are bonds, or links, between linear chains.

EXPERIMENT 45 PREPARATION OF NYLON

Time Required: 1–2 hr

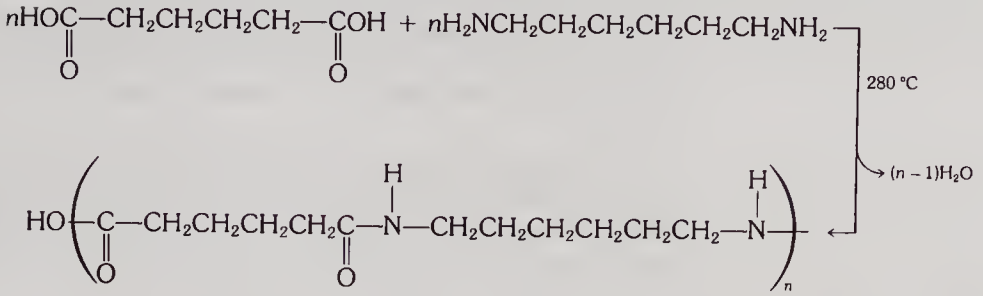
Review Techniques and Principles:

Lab notebook	(1)
Evaporating liquids	(0.6)
Gravity filtration	(4.2)
Heating	(0.5)
IR	(15.3, 15.4)

INTRODUCTION

Nylons are polyamides. That is, an amide is the repeating unit of the polymer. Nylon 66 was the first synthetic polymer that could be suitably made into fibers. It was invented in 1935 as a substitute for silk, a naturally occurring polyamide, a protein.

Nylon 66 is a copolymer made from 1,6-hexanediamine and adipic acid (IUPAC hexandioic acid), the 66 being derived from the numbers of carbons in the monomers. In industry, the monomers are condensed at high pressure and temperature:

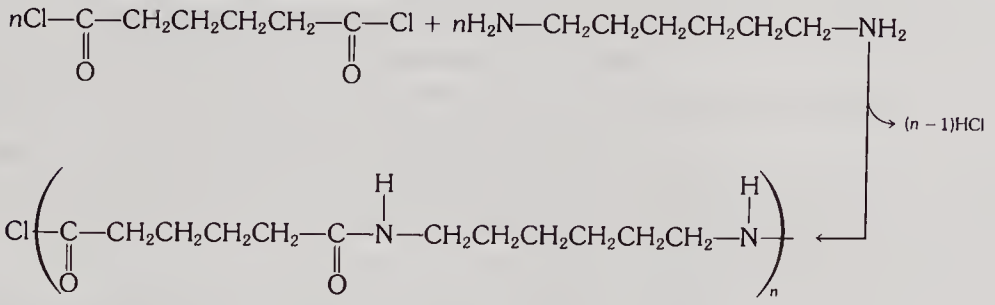


(E45-1)

To avoid the necessity of industrial conditions in this experiment, we shall use the more reactive (and expensive) hexanedioyl chloride rather than the acid itself.

E45.1 DISCUSSION OF THE PREPARATION

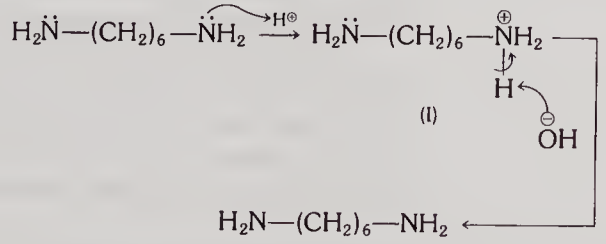
The reaction for preparation of nylon 66 with hexanedioyl chloride is



(E45-2)

The reaction progresses very rapidly, visibly evident as soon as the aqueous solution of amine comes in contact with a hexane solution of acyl halide.

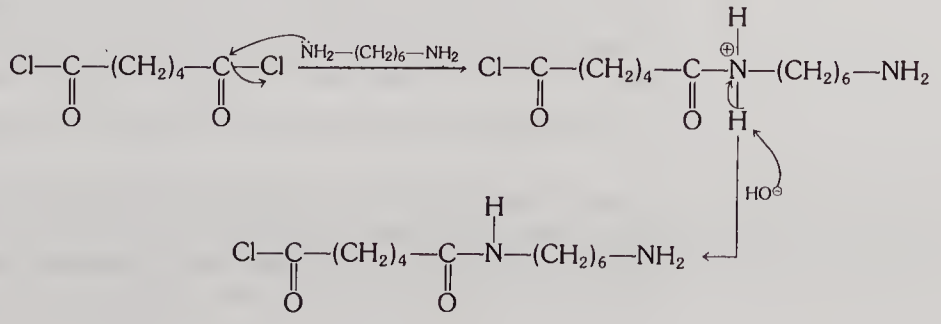
Sodium hydroxide is present to neutralize the HCl byproduct so that the diamine does not act as a Brønsted base and acquire non-nucleophilic nitrogens as in (I):



(E45-3)

Excess amine would accomplish the same purpose as NaOH but is more expensive.

When the nucleophilic nitrogen of the amine reacts with the carbonyl carbon of the acyl chloride, chloride ion is lost, as we see in the first step of sequence E45-4:



(E45-4)

In the second step, a proton is removed by amine or hydroxide thereby forming the first amide link in the polymer chain. Note again how hydroxide functions to scavenge protons.

To prepare the polymer in this experiment, you will cause it to form at the interface between two immiscible liquids, one of which contains the hexanediamine and the other of which contains the hexanedioyl chloride. By reaching down to the interface with a tweezers, you will be able to draw out a fine diameter tube of nylon swollen with solvents. The actual amount of polymer in the strand is quite small, as you will see after evaporating the solvents.

The aqueous acetone (IUPAC propanone) and water washes remove unreacted organic materials and salts from the crude product. You must be careful during drying of the polymer not to overheat it. Nylon decomposes readily at elevated temperatures in the presence of oxygen.

E45.2 EXPERIMENTAL PART

Nylon preparation. Spread several thicknesses of newspaper on the bench. Put 10 ml of 5% aqueous 1,6-hexanediamine (hexamethylenediamine) into a small beaker. With an eyedropper or Pasteur pipet, add 10 drops of 10% aqueous NaOH and mix it by swirling. Tilt the beaker somewhat and pour down the side of the beaker 10 ml of a 5% hexane solution of hexandioyl chloride (adipoyl chloride). The solution must be added slowly to prevent mixing of the two phases.

You will see a polymer film form at the interface between the two phases. Reach through the upper phase with a tweezers, tongs, or wire hook to the interface. Grasp the polymer film in the center and draw it slowly out of the beaker. Put the strand into a second beaker. The strand will form best if you use a new, very clean, unscratched beaker and if the inside of the beaker is wiped *very* lightly with a clean cloth with a trace of silicone stopcock grease on it.

Work in a hood.

It is a good idea to wear rubber gloves while making these preparations. If the crude polymer touches your skin, immediately wash with soap and warm water.

When the strand-making capability of the mixture appears to be finished, mix the two phases thoroughly and decant the hexane layer into a hexane recovery container. Let the remainder of the hexane evaporate; then filter any precipitate from the aqueous phase and discard it. Pour the aqueous phase down the drain.

Thoroughly wash the polymer strand in the beaker four times with 5 ml of 50% aqueous acetone, putting the washings into an acetone recovery container. Then wash the polymer twice with 10 ml of water. Press the strand between paper towels to remove most of the water; then dry it at room temperature or a 50 °C oven. When the polymer is thoroughly dry, weigh it and calculate the yield and percent yield.

Nylon film casting. Put the dry nylon strand in a test tube and add about 10 times its weight of anhydrous methanoic acid (formic acid). Stir it at room temperature or at no more than 40–50 °C. Holding the test tube clasped in your hand will warm it to 37 °C. Pour the viscous solution onto a clean glass plate and allow the solvent to evaporate at room temperature in a hood until the next laboratory period. Remove the film, with a razor blade if necessary, and obtain an IR spectrum. Alternatively, pour the viscous solution onto an IR salt crystal and evaporate the solvent in a vacuum desiccator.

It is advisable to wear rubber gloves while working with anhydrous formic acid.

Nylon thread formation. Using the dry polymer strand or the recovered film cast for IR analysis, put it in a metal spoon or spatula. Heat it *very gently* on a hot plate until it melts; then touch the melt with the tip of a spatula or stirring rod and try to draw it into a thread. This part of the experiment is difficult to do without decomposing the nylon.

You might try this under a stream of nitrogen or helium as an inert atmosphere, or heat the polymer in vacuo until it melts.

Writing the discussion. Discuss the physical properties of the nylon you prepared in relation to its suitability for making clothing. Discuss also the identity as shown by IR analysis.

E45.3 EXERCISES

Prelaboratory

1. Will the upper phase in the beaker be a hexane or aqueous phase? Explain.
2. Why must the hexane solution be slowly added to the aqueous solution? Why is the aqueous solution not added to the hexane solution?
3. What noticeable high-energy IR stretch in the amine should be found at lower energy in the nylon? Explain.

Postlaboratory

1. Continue the mechanism in E45-4 to show how additional amide bonds are formed to make up the polymer.
2. Is nylon a condensation polymer? Explain.
3. Explain why the synthesis of nylon 66 is more feasible in the laboratory with hexanedioyl chloride than with hexanedioc acid.
4. If you were ironing nylon 66 clothing, what temperature must the iron not approach? Is nylon thermoplastic or thermosetting?
5. 2-Azacycloheptanone (caprolactam) can be made into nylon 6 by a ring cleavage at 250 °C in the presence of water. Show the structure of the monomer and polymer.
6. With the hydroxide ion present at the interface, what byproduct of the hexanediamine-hexanedioyl chloride reaction can be formed which would reduce the yield?

Acknowledgment
The writer thanks John Bozzelli of the Dow Chemical Company, Midland, Michigan, for suggesting this experiment and providing experimental information.

EXPERIMENT 46 POLYESTERS, VARNISH, AND PAINT

Time Required: 2–3 hr

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Storing	(0.12)
Labeling	(0.13)
Mortar and pestle	(0.10)
IR	(15.3, 15.4)

INTRODUCTION

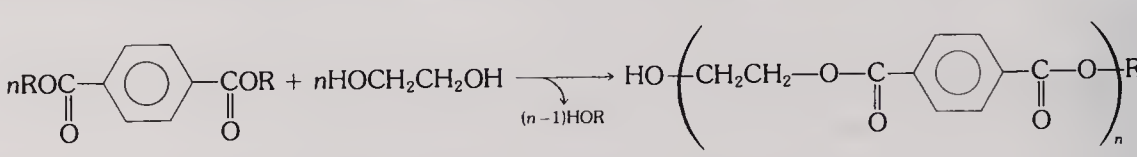
Polyesters are polymers made of repeating ester units. The polyesters have a wide variety of uses, such as in adhesives, textiles, carpets, photographic films, paints and varnishes, plastic tubing, and fiber glass resins. You have heard of the polymers by such names as Dacron, Mylar, and Cronar.

The manufacture of paint and varnish is a very old industrial activity. Originally the raw materials of the industry consisted of natural oils, resins, and mineral pigments, but within the last 40 years the major emphasis has been increasingly on use of synthetic polymers and pigments. A complete discussion of the newer products would require an entire book.

In this experiment you will prepare a usable varnish or paint. The product can be used as a label varnish, to varnish bench tops, or paint ringstands.

E46.1 DISCUSSION OF THE POLYMERIZATION

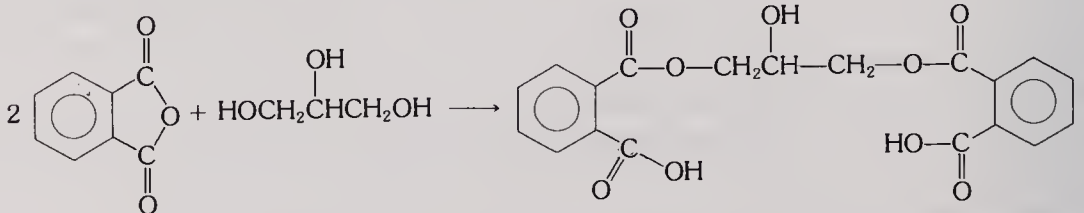
Polyesters are condensation polymers, often prepared by a transesterification in which a polyhydric alcohol takes the place of the monofunctional one. The monofunctional alcohol becomes the small molecular byproduct which is characteristic of condensations like this one between the dialkyl phthalate and ethylene glycol:



(E46-1)

When an alcohol with more than two hydroxy groups is used as one of the monomers, a cross-linked system results, yielding a resinous substance. When glycerine, commonly used as the alcohol, is polymerized with an ester or anhydride of phthalic acid, the product is known as a **glyptal** (gly for glycerine and ptal for phthalic).

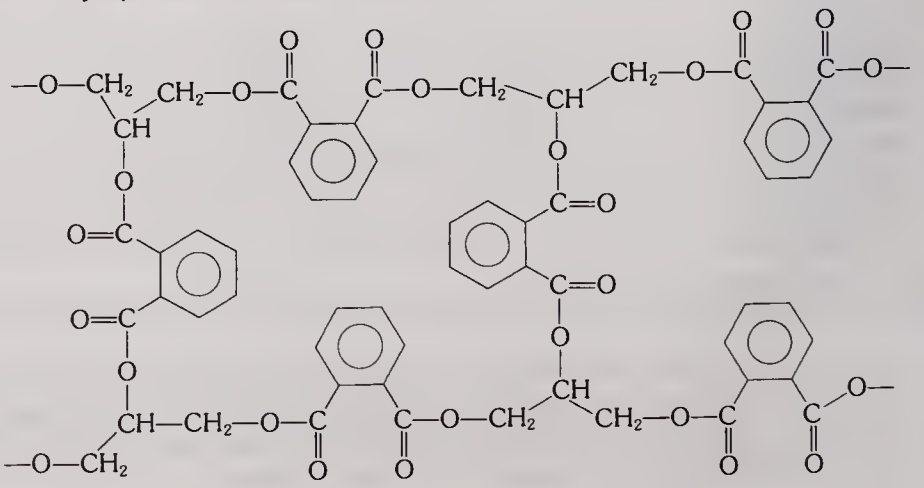
If glycerine and phthalic anhydride are made to condense at a temperature of about 150 °C, the cyclic anhydride system is opened by the primary hydroxyls of the glycol or triol to yield (I):



(E46-2)

(I)

This type of condensation using the primary hydroxyls continues, generating long, linear chains of polyester. In the second stage of the polymerization the direct process of esterification occurs only slowly and, because of a high activation energy, requires a higher temperature. With a greater input of heat, however, further esterification using the secondary hydroxyls produces the crosslinked system,

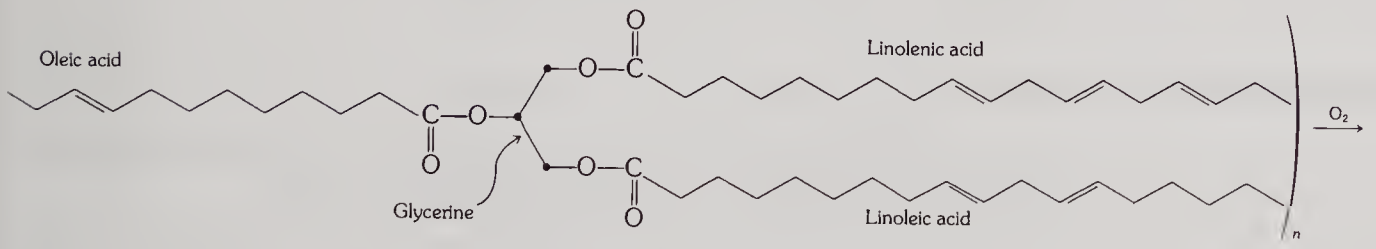


The phthalate cross-links between chains A and B make a polyester which is more rigid than the linear polyester prepared with ethylene glycol in E46-1. A cross-linked polymer is called a **network polymer** or a **resin.** Resins are thermosetting, that is, they do not return to a fluid condition when heated. In this experiment, the resin is kept from becoming too rigid by using ethylene glycol as well as glycerine, thereby limiting the number of cross-links.

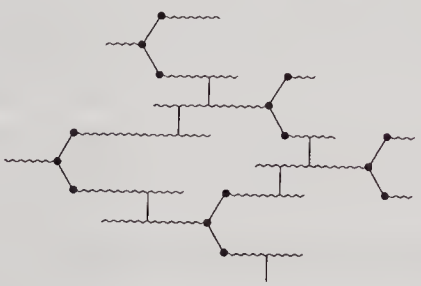
E46.2 PAINT AND VARNISH

Paint is a suspension of pigment particles in a liquid phase called the **vehicle.** When paint is applied to a surface, it dries to a solid film with the pigment held dispersed in a continuous polymeric matrix known as the **binder.** The pigment has a decorative function by providing color, but its presence also improves durability. For exterior paints, the pigment is vital for helping to prevent photodegradation of the binder. The pigment particle size is typically 1 μ in diameter, at which size visible light scattering is very efficient, thereby contributing to the **hiding power** of the pigment. The pigment content of the dried film can be as high as 60% by volume. **Varnish** is simply vehicle without pigment.

Traditionally formulated vehicles based on oils like linseed and soya form the solid dried film by evaporation of solvent and subsequent polymerization. The process depends on oxygen-initiated free radical cross-linking of double bonds found in the fatty acids of the oils:



(E46-3)



Recall that oils are composed of glyceryl esters of the fatty acids. In equation E46-3, the wavy lines on the right side of the arrow represent the hydrocarbon chains shown on the left. Linseed oil is commonly used because it contains 90% unsaturated fatty acids, of which 50% are linolenic with three double bonds. (The more double bonds there are, the more readily cross-linking occurs.) Oils are not as commonly used anymore because by themselves they provide poor water resistance and strength.

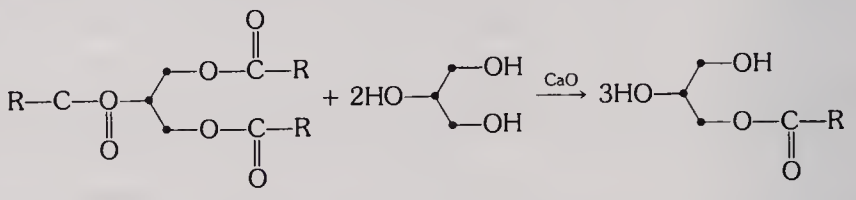
Today it is common for the vehicle to be a solution of a synthetic polymeric resin in an organic solvent, and the paint or varnish hardens simply by loss of organic solvent to the air. An example of this type of formulation is the polyester product you will make in this experiment.

Oleoresinous paints and varnishes are based on mixtures of oils with various natural or synthetic resins, and these formulations give films of greater water resistance and hardness. In some cases the resins chemically react with the oil during preparation of the vehicle and in other cases the resins simply dissolve in the oil and solvent. In either case, cross-linking of the unsaturated oil during and after solvent evaporation leads to the formation of a cross-linked resinous film. Sometimes the unsaturated oils are called

"drying oils." Incorporation of a drying oil into the formulation decreases solvent and water resistance of the dried coating. In the industry, the terms "short oil varnish," "medium oil varnish," and "long oil varnish" are used to designate the "length" of a varnish, that is, the number of gallons of drying oil per 100 lb of resin. A short oil varnish is about 10 gal in length, and a long oil varnish is about 70 gal in length.

How long it takes an oil to "dry" depends on its degree of unsaturation, oxygen supply, temperature, and light, all of which, of course, increase the rate of drying. The rate is decreased by high humidity. The rate can be increased by adding between about 0.05 to 0.2% of cobalt or manganese salts of fatty acids, which act as catalysts. Cobalt is more effective than manganese. Such catalysts can reduce the drying time by as much as 80%.

A very popular combination of polyester resins and unsaturated oils is found in the alkyd resins. The triglyceride oil is first converted to a monoglyceride by calcium oxide-catalyzed transesterification with 2 moles of glycerine:



(E46-4)

The monoglyceride is then polymerized with phthalic anhydride or similar compounds to yield a polyester resin which is capable of further cross-linking after being painted on a surface.

E46.3 EXPERIMENTAL PART

Ask your instructor whether you should make varnish, paint, or some of each by dividing the product; also how much of the oleoresinous varnish to make.

Preparation of the resin. Add to a 50-ml round-bottom flask 4.0 g (0.70 mole) ethylene glycol (IUPAC 1,2-dihydroxyethane), 2.5 g (0.30 mole) glycerine (IUPAC 1,2,3-trihydroxypropane), and 13.5 g (1.0 mole) phthalic anhydride (IUPAC 1,2-benzenedicarboxylic anhydride). Clamp the flask to a ringstand, insert a thermometer into the flask so that the bulb is as far into the liquid as it can go and still be 2–3 mm above the bottom of the flask. Stirring with a stirring rod from time to time, heat the mixture to 110 °C; then stop heating. The exotherm of reaction should carry the temperature to about 150 °C, and you should see water vapor escaping. Test the vapor with cobalt (II) chloride paper. When the temperature no longer rises, heat the mixture to 180 °C and hold it there until no more water vapor appears to be escaping as evidenced visually and by cobalt (II) chloride paper, then heat the mixture to 220 °C. Maintain this temperature until the mixture appears to be thickening; then cool it as rapidly as you can by blowing a slow stream of air on the flask.

Do not stir the mixture with a thermometer. It is a good way to break it and spill mercury.

Remember that melts of 150 °C to 220 °C are much hotter than boiling water. Use a tongs to handle the hot equipment.

Preparation of varnish. When the temperature has dropped to 150 °C, begin stirring in 25 ml of a 60/40 mixture by volume of ice-cold xylene/butanol. Begin with stirring rapidly and adding into the resin 1-ml portions of solvent while stirring. Do not pour cold solvent onto the hot glass. As the temperature of the solution falls, you can add the solvent in larger quantities. Pour the solution into a labeled screw cap vial and cap it loosely; when the temperature of the solution is at room temperature, tighten the cap.

Preparation of oleoresinous varnish. Using all or part of the varnish, add either raw or cooked linseed oil to it in a ratio of 0.2 oil to 1 vehicle by weight. Stir the mixture thoroughly and store it in a labeled, screw cap vial.

Preparation of paint. Using all or part of the varnish, add to it finely ground red iron oxide, lead chromate, or other pigment in a ratio of 1 part pigment to 2 parts vehicle by weight. Grind the pigment with mortar and pestle before adding it to the vehicle. Stir the mixture thoroughly and store it in a labeled, screw cap vial. Before using this paint you must thoroughly remix the pigment with the vehicle.

Inclusion of drier. If you have any cobaltous octanoate or cobaltous fatty carboxylate salts available, separate the oleoresinous varnish into two parts and incorporate 0.1% of the finely powdered salt (use of too much has a deleterious effect). Mix it well and store the solution in a labeled, screw cap vial.

Testing the products. Stir the varnish or paint, and paint a quarter-size spot on the bottom of a clean ringstand base. Check the spot after most of the solvent seems to have evaporated by lightly touching it at its perimeter, and again after around 1, 2, 18, and 24 hr. Note the tack and hardness in each case.

Analysis. Analyze the varnish and oleoresinous varnishes by IR spectroscopy. Paint a salt plate with the varnish and allow the solvent to evaporate. Do not allow the oleoresinous varnish to cure or you might have difficulty removing it from the salt plate. Clean the plate with xylene-butanol.

Cleaning up. Clean up equipment immediately with xylene-butanol washes. Put the washes in an assigned recovery container.

Writing the discussion. Did you observe any effect with the cobalt chloride test paper? Discuss your answers to the following questions. Did IR analysis of the polyester varnish show evidence of O—H stretch, or C=O stretch, of C=C stretch, of ester C—O vibrations? How did tack and hardness of the various test spots compare? How could you circumvent any poor results another time?

E46.4 EXERCISES

Prelaboratory

1. What part of the polymerization occurs during the heating of the reaction mixture to 150 °C?
2. *Al Kyd* heated the resin formulation described in the experimental part to 150 °C, then to 220 °C, and removed the pot from the heat and prepared the varnish. His test spot was still sticky after five days. Describe the experimental error and the theoretical concept that led to this problem.
3. Prof. *Ethel E. Neglykol* suggested that Al's formulation in prelab exercise 2 might be satisfactory for a contact cement. Explain whether you think this is reasonable.
4. Why should the cap on the varnish not be tightened until the mixture is at room temperature?

Postlaboratory

1. Draw the structure of the product from heating butanedioic anhydride with 1,2,3-propanetriol. Is the product a glyptal? an alkyd?
2. Draw the structure of the product that forms when 1,2-benzenecarboxylic anhydride is heated with 1,2-ethanediol. Is the product a glyptal? An alkyd?

3. Define long oil and short oil varnishes in terms of the metric units, liters and kilograms.
4. Explain on the basis of what occurs chemically why it is important to tightly cover a can of paint or varnish containing drying oils. Should small amounts of such paints or varnishes be transferred from large to small cans? Explain.
5. Outline a procedure for preparing the drier, cobaltous octanoate.

REFERENCES

1. *Corrosion Control*, 2nd ed.; Shreir, L. L., Ed.; Newnes-Butterworths: Stoneham, MA, 1976.
2. Young, J. F. *Materials and Processes*, 2nd ed.; Wiley: New York, 1954.
3. Banov, A. *Paints and Coating Handbook*, 2nd ed.; Structures Publishing Co.: Farmington, MI, 1978.
4. Hall, C. *Polymer Materials*, Wiley: New York, 1981.

Acknowledgment
The writer thanks Larry Brown of Dow-Corning Corporation, Midland, Michigan, for suggesting experimental details.

EXPERIMENT 47 PREPARATION OF POLYDIMETHYLSILOXANE

Time Required: 3–4 hr

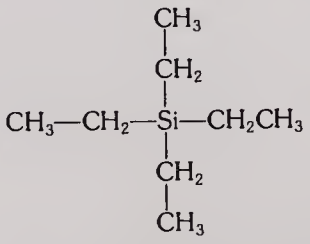
Review Techniques and Principles:

Lab notebook	(1)
Mortar and pestle	(0.10)
Stirring	(0.4)
Heating	(0.5)

INTRODUCTION

Compounds of silicon have been known to man for thousands of years in the form of glasses, cements, and ceramics composed of silicates. Silicates are salts containing silicon and oxygen in anions like SiO_4^{4-}, $Si_2O_7^{6-}$, and $Si_3O_9^{6-}$. Examples of precious silicates are zircon, $ZrSiO_4$, and emerald, $Be_3Al_2Si_6O_{18}$. As you can see, the silicon-oxygen ratio varies widely.

The first organosilicon compound, tetraethylsilane, was prepared in 1863 by Friedel and Crafts, better known for the electrophilic aromatic reactions that bear their names (Experiment 33)



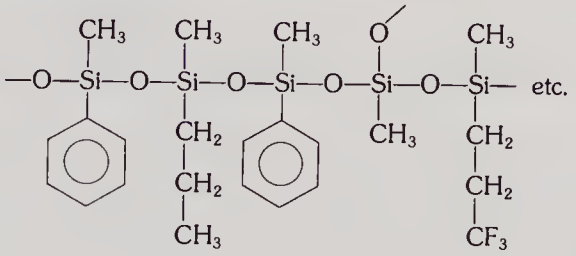
Tetraethylsilane

The foundations of organosilicon chemistry were laid between 1898 and 1939 by Kipping at Nottingham University, and today organosilicon compounds comprise a large industry with applications in science, medicine, aerospace, automotive and electrical

areas, and in building construction. One of the gas chromatograph columns in your laboratory probably has an organosilicon stationary phase. You have almost surely heard about silicone prosthetic devices like artificial finger joints, chins, ears, breasts, or hydrocephalus valves.

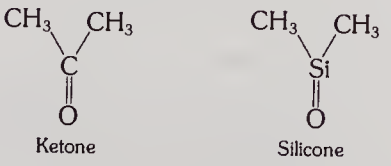
E47.1 SILICONE POLYMERS

A **silicone** is a polysiloxane, a linear or branched polymer with $—(Si—O)_n—$ chains. Because silicon has a valence of four, two more bonds beyond those in the linear chain are available for a variety of alkyls, aryls, or branching:



In this experiment, the linear silicone polymer you prepare will be polydimethylsiloxane, in which all of the alkyl groups are methyl.

The word *silicone* is a misnomer and was applied to the first linear polymers because their empirical formulas led early investigators to believe that the compounds were silicon analogues of ketones:



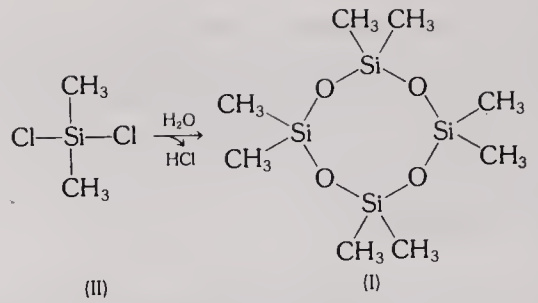
It is now known that silicon cannot make a *p*—*p* pi bond; therefore it cannot make a Si=O double bond. However, silicon does make a *p*—*d* pi bond by accepting into one of its empty *d* orbitals a nonbonding electron pair from a *p* orbital of oxygen:

This sort of electron donation is called **backbonding** and leads to a form of pi bond which is weaker than a *p*—*p* pi bond, and unlike a *p*—*p* pi bond, can be broken during rotation around the Si—O sigma bond. Nevertheless, the backbonding does increase the bond strength along the polymer chain, and results in polymers that have better thermal stability at high temperatures than hydrocarbon polymers.

A second, often times desirable, feature of silicone polymers is their high degree of flexibility and permeability over a wide range of temperatures, resulting from the great mobility of the Si—O linear chains. To a large extent this mobility is due to the wide Si—O bond angle of about 130° which, compared to the C—C tetrahedral bond angle of 109.5°, reduces steric hindrance to rotation.

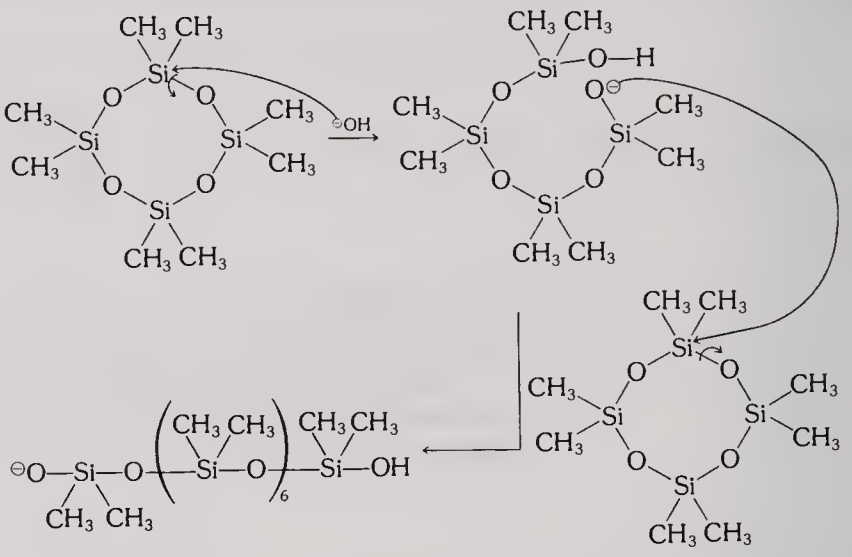
E47.2 DISCUSSION OF THE POLYMERIZATION

In this experiment, you will prepare a dimethyl silicone polymer from octamethylcyclotetrasiloxane (I), a cyclic tetramer. The tetramer, along with other linear and cyclic silicones, was probably synthesized from dichlorodimethylsilane (II):



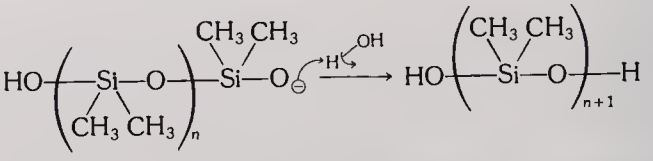
(II) (I) (E47-1)

To effect polymerization of the tetramer you will heat it along with potassium hydroxide. The mechanistic reaction sequence is



(E47-2)

In the first step, hydroxide reacts with silicon, breaking a silicon-oxygen bond in the tetramer. The negatively charged oxygen of the open chain tetramer reacts with silicon of a second tetramer, thereby creating an open chain, negatively charged octamer. This ring-opening process continues until very long chains of polymers have been formed. The chain-forming process is terminated by reaction of the negative oxygen with a water molecule:



(E47-3)

Water is present in small quantities as a natural consequence of exposure to atmospheric moisture. The polydimethylsiloxane polymer (III) with hydroxyls at both ends is said to have hydroxy **end blocking.** As you can readily guess, the more water there is present, the shorter the lengths the polymer chains will be. Before beginning the polymerization, the temperature of the tetramer is brought up to 125 °C to drive out dissolved water because, to obtain a polymer with usable properties, the chains must be long. The high molecular weight, nonliquid silicone product is called a **gum.**

It is very important not to add to much of the promoter potassium hydroxide. Excess hydroxide at a high temperature will cause bonds between silicon and methyl groups to break, resulting in premature cross-linking and a gum with too much "memory." **Memory** is an industrial term meaning that the gum will snap back or shrink rapidly when stretched. If there is too much memory, it will be impossible to work in the filler to make the rubber described in Experiment 48. You should be able to take a 2-cm piece of the gum and pull it like taffy so that it stretches thinner and thinner, then breaks and falls. The final gum that results from the polymerization should be soft and pliable, but not sticky.

E47.3 EXPERIMENTAL PART

If you can, bring from a home a clean, dry metal can of about 5 cm diameter. It will be easier to discard the can when you are finished with the experiment than to clean up a beaker.

Polydimethylsiloxane synthesis. Working rapidly because of the hygroscopic nature of potassium hydroxide, grind a few pellets of it to a fine powder in a mortar with pestle. Put the powder in a small Erlenmeyer flask and immediately set it in an oven at 150 °C. Leave it there for about 20 min, then remove the flask from the oven and attach a drying tube before it cools.

KOH powder is extremely caustic.

Be careful not to get the hot gum or polymer on yourself. 150 °C is much hotter than boiling water.

Weigh into a 20-ml beaker or can 10.0 g of octamethycyclotetrasiloxane. With a finger clamp, suspend the beaker in an oil bath or on a hot plate. Suspend a thermometer in the container so that it does not rest on the bottom. Bring the temperature up to 125 °C and hold it there for 5 min; then add 0.0014 g of dry, powdered potassium hydroxide which has been rapidly but carefully measured on an analytical balance. If the relative humidity at 23 °C (70 °F) is less than 10%, add 0.002 g of 200 centistoke hydroxy end-blocked polydimethylsiloxane. Stir the mixture well for 2 min; then bring the temperature of the mixture up to 150 °C and hold it there. Do not allow the temperature to rise above 150 °C because some tetramer might evaporate and some cross-linking might occur. Stir the mixture continually, or at least every few minutes. At the end of 1 hr at 150 °C, put the can in a 150 °C oven for an additional 2 hr. If no oven is available, leave the container in the bath or on the hot plate and stir it every few minutes. Unless the temperature of a hot plate can be closely regulated at 150 °C, you will have to stir continually to avoid hot spots. By the end of the second hour, the viscosity of the liquid should be so high that it is very difficult to stir. If not, heat it longer. When the polymerization seems to have progressed as far as it will go, cool the product, weigh it, and test it for memory.

Clean up your equipment with toluene. Put the washes in a recovery container.

Writing the discussion. Discuss the percent yield, tackiness, and memory, accounting for and describing methods of improving each.

E47.4 EXERCISES

Prelaboratory

1. What equipment might you want to bring from home that makes cleaning up easier?
2. Why do you think the powdered KOH is put in an oven?
3. Why is the temperature of the tetramer brought up to 125 °C before adding the KOH?
4. Why must you keep the temperature at no more than 150 °C during polymerization?
5. Under what conditions should hydroxy end-blocked polydimethylsiloxane be added?
6. How can you test the gum for memory?

Postlaboratory

1. Write the structure of the polymer that would result from polymerizing octamethylcyclotetrasiloxane along with some hydroxytrimethylsilane.
2. Write a mechanism like that of E47-2 showing how the polymer in exercise 1 would be produced.

3. A resin is a highly cross-linked polymer. A silicone resin can be made by adding trihydroxymethylsilane to the tetramer during polymerization. Draw a structure for a portion of the resin.
4. Explain why carbon and its compounds combine with oxygen to give small molecules like CO_2, whereas silicon and its compounds combine with oxygen to yield polymeric compounds.

REFERENCE

Noll, W. R. *Chemistry and Technology of Silicones;* Academic Press: New York, 1968.

EXPERIMENT 48 SILICONE RUBBER

Time Required: 4 hr

Review Techniques and Principles:

Heating (0.5)

New Techniques and Principles:

Vulcanizing silicone rubber

E48.1 DISCUSSION

A silicone rubber gum is basically a chemical intermediate since most gums eventually are made into some kind of rubber. Silicone fluids, too, can be made into rubber, but the nonrubber use of fluids is more extensive. To make a gum or fluid into rubber it must be filled and vulcanized.

Fillers

Fillers are solids that are added to the gum to give strength and bulk to the rubber. There are two kinds of fillers: extending and reinforcing. We use **extending fillers** to increase bulk, and use **reinforcing fillers** to strengthen the rubber as well as add bulk. It is the reinforcing kind of filler that will be used in this experiment.

Reinforcing fillers consist of extremely finely divided silica (approximately SiO_2), especially made to be used as a filler. The surface area of reinforcing silica can be tremendously large; the filler to be used in this project has a surface area of about 200 m^2/g! And some silica fillers have surface areas up to 400 m^2/g.

On the surface of a reinforcing filler are many hydroxyl groups which, by hydrogen bonds and other dipole-dipole interactions, attach themselves to silicon and oxygen in the polymer. The hydroxyls also make covalent bonds from silicon to oxygen, particularly at the high temperatures used for vulcanization. Figure E48.1 illustrates silica-polymer interactions. In the rubber industry, a thorough mixing of filler, peroxide, and gum is accomplished by using two- or three-roll mills. The metal rollers turn toward each other and force the mixture between them, squeezing all components intimately together.

In a silicone fluid or gum (which is really just a very high molecular weight fluid), molecules are free to move around and past each other, assuming they have sufficient energy. Therefore, we can pour a liquid silicone and knead or press a gum into various shapes. After adding filler, the polymer molecules become much less mobile, being bound to each other by the filler. Even before vulcanization, interaction of silica to silica and silica to polymer is so great that a filled gum considerably stiffens as it sits, producing a condition known in the industry as **crepe hardening.** Because of crepe hardening it will be best for you to work the silica into the gum just before pressing and vulcanizing.

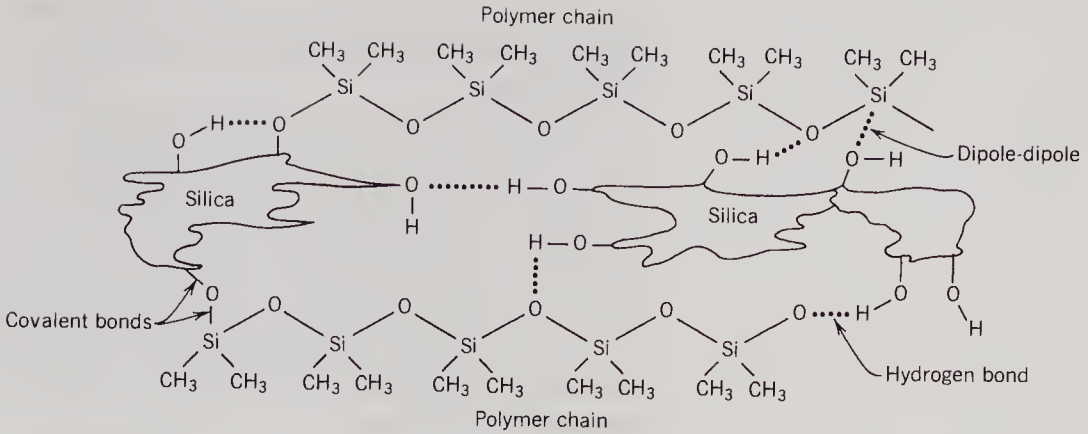
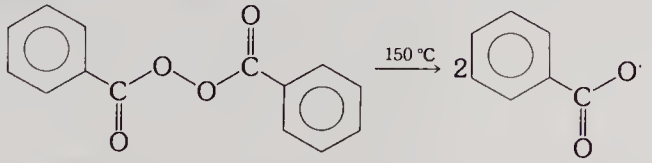


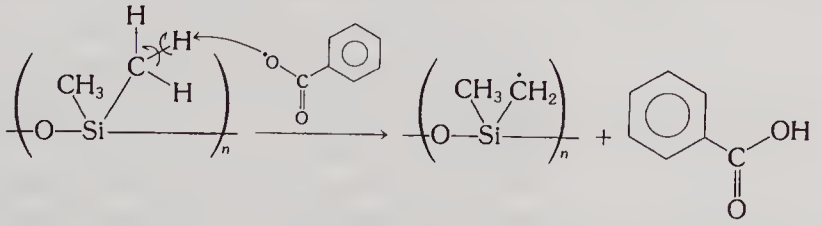
FIGURE E48.1 Silica-polymer interactions.

Vulcanizing Vulcanizing further strengthens the rubber by linking one polymer chain to another. Basically, there are two temperature categories of vulcanization: high temperature and room temperature. Most molded forms of rubber are vulcanized at high temperature. Do-it-yourself products, like bathroom caulk, are room temperature systems, often called **RTV**s. In this project we will use high-temperature vulcanizing with dibenzoyl peroxide as the vulcanizing agent. It is a free radical initiator, which when subjected to the 150 °C temperature of vulcanization (or curing as it is often called in the industry) breaks down homolytically:



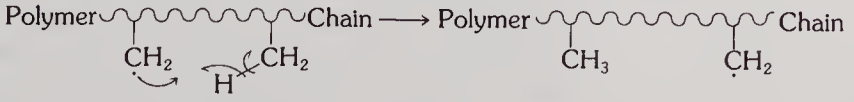
(E48-1)

The benzoyl-free radicals react with hydrogens of the methyl group along the polymer chain, forming methylene-free radicals and benzoic acid as a byproduct:



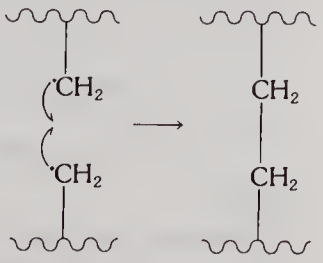
(E48-2)

The free radical character can be transferred along a polymer chain or from one chain to another by collision of sufficient energy and correct orientation:



(E48-3)

When two methylene-free radicals on adjoining chains react, they form a covalent bond joining one polymer chain to the other:



(E48-4)

Such links between chains are termed **cross-links.** After cross-linking, the polymer molecules are chemically bound together and can no longer slip past each other when stress is applied.

After the initial cure, the molded rubber is taken out of the mold and put in the oven at 200 °C for 15–20 hr as a **postcure.** Postcuring completes the vulcanization, and causes the benzoic acid byproduct to diffuse to the surface and sublime away.

If you do not sufficiently mix the peroxide into the silica-filled gum, an empty pocket will form in the rubber during vulcanization wherever a peroxide lump has been left. Volatilization of dimers, trimers, tetramers, and other low molecular weight polymers during vulcanizations is another way that small voids can be created.

To vulcanize the silica-filled gum into a sheet of rubber, you will press the gum between flat metal plates that have been treated with a detergent solution to prevent adhesion of the rubber.

E48.2 EXPERIMENTAL PART

Ask your instructor which of the following experimental sections you should plan to do.

Preparation of silica-filled gum. Weigh your polydimethylsiloxane polymer prepared in Experiment 47. Weigh an amount of Cab-O-Sil LM-7 equal to 10.0% by weight of the polymer. Weigh also an amount of 50% benzoyl peroxide paste equal to 2.0% by weight of the polymer.

Thoroughly clean the hood area bench top where you are going to work by scrubbing it with brush and cleanser, then by rinsing it and drying it completely. Spread a small amount of the filler over about a 10–15 cm diameter area of the bench top so that the bench top is lightly covered. Carefully place the polymer gum on the spread-out filler. Put a little more filler on top of the polymer, and roll the polymer into the filler with a rolling pin. Continue to add filler and roll the mixture until all of the filler is worked into the polymer and the filler appears to be evenly dispersed.

Work in a hood while working with the silica so that it does not get in your lungs and produce silicosis, which could eventually lead to emphysema.

Roll out the polymer-filler mixture to a sheet about 1 mm thick. With a spatula, spread the peroxide paste as evenly as you can over the surface of the sheet. Fold the sheet in half; then roll the mixture thoroughly until the peroxide is *evenly* dispersed throughout.

Do not let benzoyl peroxide paste get on paper or other organic materials. Dry benzoyl peroxide is quite easily detonated by abrasion or heat, but is not as dangerous in paste form.

Vulcanization of silicone rubber. Assemble the press shown in Figure E48.2. Using a small paint brush and a 5% aqueous solution of household detergent coat the surface of the flat metal sheets which will contact the silica-filled gum. Allow the surfaces to dry, then put the gum on the lower sheet. Do not put more gum in the chase than can be contained within it. Put the chase on the sheet and the upper plate over the chase. Press the assembly together with the help of C-clamps and put it into a ventilated 150 °C oven for 15 min. Remove the assembly from the oven, loosen the C-clamps, and remove the sheet of rubber from the chase, cutting it from the chase if necessary. Mark the rubber with your name and return it to the oven for an additional 15–20 hr at 200 °C. △△

If you have time and a large enough sample of gum, work in peroxide but no filler; then vulcanize it.

Test the vulcanized rubber and gum by trying to bend, stretch, or tear a small sample.

Remember that objects removed from a 200 °C oven are very hot. Do not leave these hot objects unattended without a warning sign.

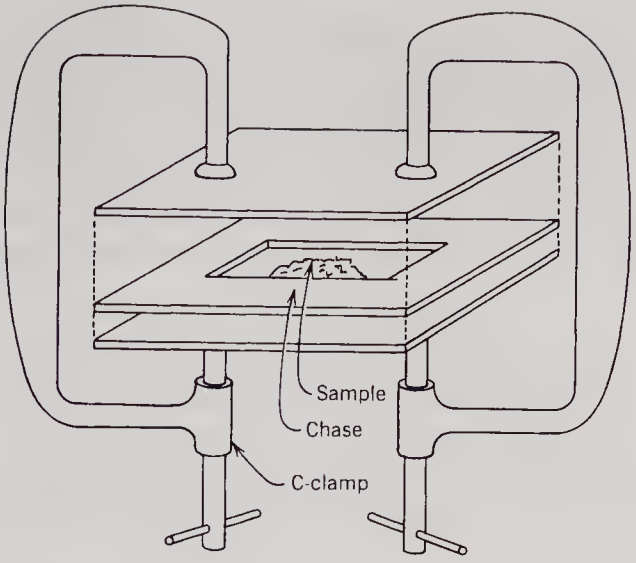


FIGURE E48.2 C-clamp press.

Preparation of GLC septa. Place the sheet of rubber on a flat surface protected by a sheet of pasteboard or similar material. From the rubber sheet cut discs the right size for your GLC instrument. A cork borer works well for cutting the discs.

Writing the discussion. Discuss the quality of the rubber you prepared, relating it to the gum you used, to your technical capabilities, and to the laboratory equipment available for its preparation. Compare the rubber to commercially prepared septa and assess its quality for such a use. Discuss the properties of the vulcanized gum as compared to the vulcanized rubber.

E48.3 EXERCISES

Prelaboratory

1. Why is it important to have the peroxide evenly dispersed in the polymer?
2. What is the purpose of putting detergent on the press plates?

Postlaboratory

1. Suppose you were to mold your silicone rubber into rubber stoppers, which of the following solvents would dissolve in the rubber and escape from the container? Methanol, acetone, hexane, toluene, water.
2. Explain why a silicone rubber gum milled with reinforcing filler might have a limited "shelf life," that is, have a time limit during which it must be used.

XIX

MULTISTEP SYNTHESES

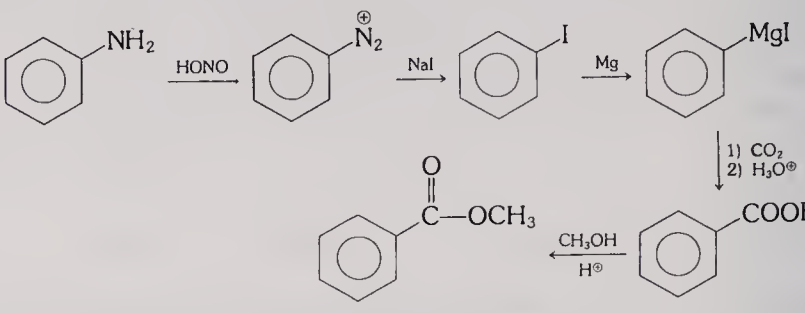
Time Required: 2–4 laboratory periods

Review Techniques and Principles:

Lab notebook	(1)
Chemical literature	(18)
Report writing	(19)

A research chemist is not uncommonly faced with having to synthesize a substance that is not commercially available. Complicated research projects might require as many as 25 or more separate sequential steps, each step providing a chemical intermediate that brings the chemist a little closer to obtaining the final product.

There are a number of experiments in this book that can be put together to make a sequence leading from a simple starting material to a more complex product. For example, if you want to prepare methyl benzenecarboxylate (methyl benzoate) from benzenamine (aniline), you could follow the synthetic sequence

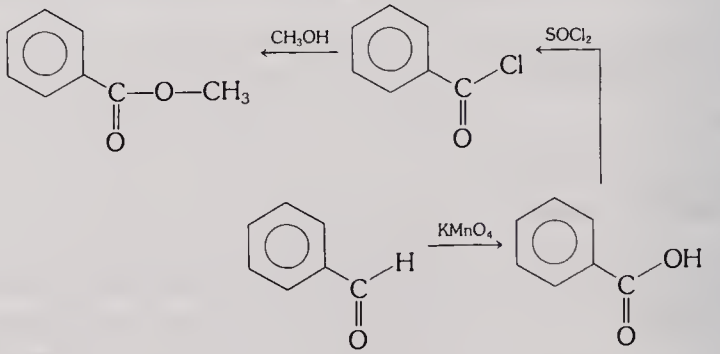


(XIX-1)

You will find procedures for the various steps in Experiments 30, 31, and 21. You can also put together other sequences directly from this book. Imagine the latitude for synthesis that you have if you use all of the known chemical literature!

XIX.1 DESIGNING SYNTHETIC SEQUENCES

Once you know what compound you need to make, you should write equations for possible routes to the product. These routes are the familiar armchair syntheses, or roadmaps, that you probably have practiced writing in conjunction with your lecture course on organic chemistry. You might prefer to do your initial work on roadmaps by starting with the final product and working backward:



(XIX-2)

Once you have some idea about the approach or approaches you might take, you should consult the chemical literature for procedures as specific as you can find. As you search the literautre, the preparations you find may suggest new roadmaps.

You should try to find methods which allow you to use readily available reagents, and which are as inexpensive as possible. Also you need to consider processes that permit you to work with the type of equipment you have at your disposal. Another important consideration is that the yield you can anticipate at each step limits the amount of starting material for the reaction that follows. If you had a series of five reactions, each yielding 70%, the best overall yield you could get for the final product would be only 12%, found by multiplying $0.70 \times 0.70 \times 0.70 \times 0.70 \times 0.70 \times 100$.

You will find that most literature discussions and directions are somewhat more condensed than those to which you have become accustomed in a large part of this book. That is because when you arrive at the point of consulting the chemical literature it is assumed that you have acquired considerable chemical proficiency and knowledge and therefore are capable of reading between the lines. And by this time, no doubt you are!

Most of the chemical literature does not provide information on chemical and operational hazards. So, after consulting the literature and selecting the route to your product, read the literature recipes carefully, trying to imagine all reasonably likely procedural hazards. Record these hazards in your notebook along with chemical hazards gleaned from this book and other sources like those suggested in Appendix C.

XIX.2 EXPERIMENTAL PART

Table XIX.1 lists a number of interesting products you could synthesize in a multistep sequence. There are undoubtedly others in which you might be interested or which your instructor might suggest. Your instructor will tell you how you are to choose your product (it might be assigned), how many synthetic steps are required, and what means you are to use in identifying your intermediate and final products, such as melting point, boiling point, refractive index, UV–VIS, IR, NMR, and GLC.

TABLE XIX.1

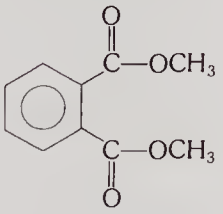
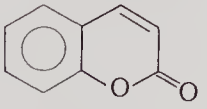
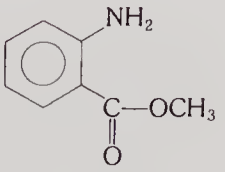
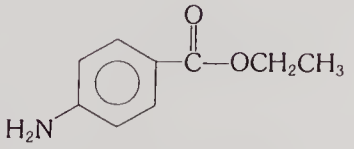
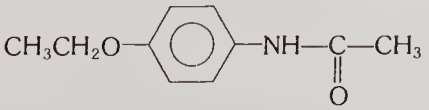
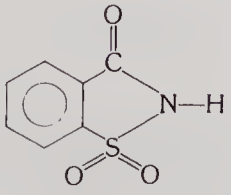
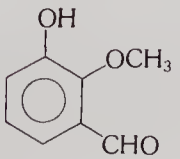
Compound	*Structure*	*Use*
dimethyl phthalate		insect repellent
coumarin		perfume ingredient, odor of new mown hay
methyl anthranilate		artificial grape flavor
benzocaine		topical local anesthetic
phenacetin		analgesic
saccharin		artificial sweetner, as the sodium salt
vanillin		vanilla flavor

TABLE XIX.1 (*Continued*)

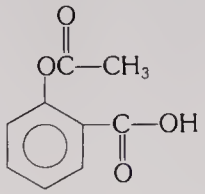
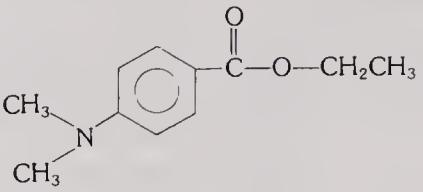
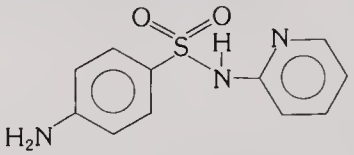
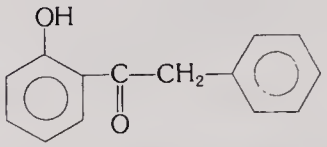
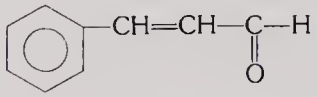
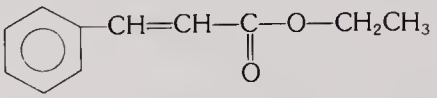
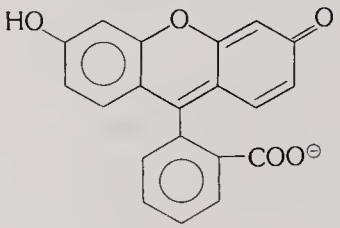
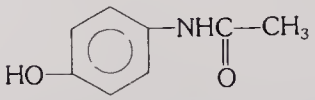
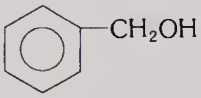
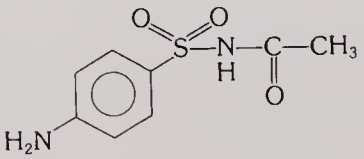
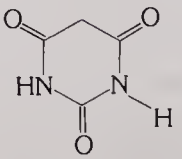
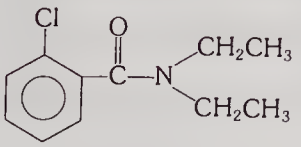
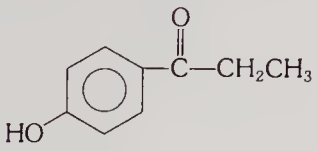
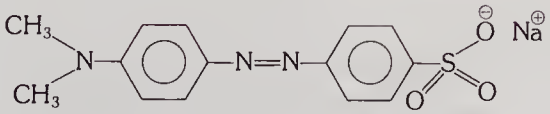
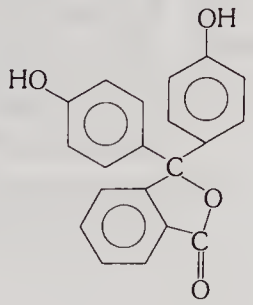
Compound	*Structure*	*Use*
aspirin		before, during, and after exams
ethyl 4-(*N*,*N*-dimethylamino) benzenecarboxylate		sunscreen
sulfapyridine		antibiotic
benzyl salicylate		perfume ingredient, balsam odor
cinnamaldehyde		flavor
ethyl cinnamate		perfume ingredient, balsam-honey odor
fluorescein		fluorescent dye used medically
acetaminophen		analgesic
benzyl alcohol		local anesthetic
sulfacetamide		antibiotic
barbituric acid		parent of the barbiturates

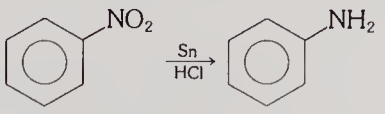
TABLE XIX.1 (*Continued*)

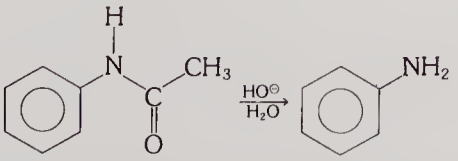
Compound	*Structure*	*Use*
N,N-diethyl-2-chlorobenzamide		insect repellent
4-hydroxypropiophenone		uterine contractant in vet medicine
methyl orange		indicator dye
phenolphthalein		indicator dye

XIX.3 EXERCISES

Prelaboratory

1. What percent final yield would be obtained if a four-step synthetic sequence gave individual yields of 90%, 45%, 60%, and 26%?
2. Compare the two following syntheses of benzenamine with respect to time involved, cost of materials, availability of equipment and reagents, and yield.





3. Estimate the amounts (moles and grams or milliliters) of each reagent you expect will be needed for each step in the synthetic sequence based on the amount expected for product in each step.
4. Outline the work that will need to be accomplished during each laboratory period allotted for the project. Arrange the work so that efficient use of time will be made.
5. Show your instructor your list of safety precautions.

PART III

QUALITATIVE ORGANIC ANALYSIS

QUALITATIVE ORGANIC ANALYSIS

INTRODUCTION

The practicing organic chemist is constantly finding it necessary to determine the identity of unknown substances, perhaps to identify the byproducts of a reaction mixture, or the compounds of an extract of natural origin, or simply to verify the identity of a reaction product.

At one time all organic analysis was wet analysis. That is, determination of compound class or identity depended entirely on test tube reactions. Since the advent of instrumental methods, much less wet analysis is performed. Nevertheless, it is still a very useful tool for quick, simple, test tube classifications and identifications. A few quick tests can often provide valuable information to supplement instrumental evaluations. Furthermore, a lot of what you learn about wet analysis can be modified so that it becomes a preparative procedure. For example, the permanganate test for unsaturation that yields a glycol needs only to be extended by a workup procedure to isolate the product. Also there is something to be said for studying the many organic reactions involved in organic qual.

Entire books have been devoted to organic wet analytical methods, so the scope of Part III is necessarily much more limited. The classes of compounds discussed are confined to alcohols, phenols, aldehydes, ketones, carboxylic acids, esters, and amines. Although the number of compound classes has been limited in this book, it is sufficient to thoroughly acquaint you with the basic procedures. We shall concentrate on identification of single compounds rather than mixtures, although you must keep in mind that a single compound might have more than one functional group.

Characterization and Identification

Qualitative organic analysis is the characterization and identification of organic compounds. **Characterization** or **classification** is the assignment of a compound to a limited number of compound classes, a class of compounds, or a subgroup of compounds within a class. For example, a positive bromine test for unsaturation suggests that the compound tested is an alkyne or an alkene, thereby probably limiting the number of possible compound classes to two. Or, as an example of assigning a compound to a single class, solubility tests showing that a compound is soluble in 5% aqueous sodium hydroxide but not in 5% aqueous sodium bicarbonate suggest that the compound is a phenol. An example of a subgroup classification test is the iodoform test which points to acetaldehyde, methyl ketones, or methyl carbinols. **Identification** is the establishment of a distinct identity for a compound. Identification often involves preparation of a **derivative,** a second compound of known melting point prepared from the first in a simple reaction. Easily prepared, solid derivatives with sharp melting points are particularly important when the compound of interest is a liquid.

Q1 GENERAL PROCEDURE FOR ANALYZING AN UNKNOWN SUBSTANCE

The general procedure is as follows:

1. Make a preliminary examination.
2. Determine basic physical data.

3. Purify or separate the substance from other materials if necessary.
4. Determine the solubility in water, acids, and bases.
5. Perform the ignition test.
6. Test for the elements present.
7. Do the characterization tests.
8. Identify the compound.
   a. Prepare derivatives.
   b. Obtain IR, UV, VIS and NMR spectra, refractive index, and GLC chromatogram.

The individual steps need not always be carried out in exactly the order given. You should use your own judgment about what to do next based on the results obtained up to that point. However, for most analyses this sequence will be quite appropriate. In certain cases, you will be able to skip certain steps because of prior knowledge of the compound. For example, in assigning an unknown, your instructor might tell you the class to which the compound belongs. If you are assigned an unknown within a class of compounds, you can of course omit those steps that are necessary to establish the class of compound. If you are given a general unknown, you will have to first determine with which class of compound you are working.

The unknowns will be taken from the tables of unknowns at the end of this chapter, unless you are otherwise informed by your instructor. Generally speaking, unless reassured by your instructor, you should *TREAT ALL UNKNOWNS AS TOXIC* and work in a hood.

When in doubt about the results of any of the test procedures, *run the same test with a known substance of appropriate structure* to remind yourself what visual evidence you are looking for.

Q2 THE PRELIMINARY EXAMINATION

The preliminary examination includes noting and recording fundamental and easily observed properties such as physical state, color, and odor.

Q2.1 Physical State

The physical state will most often be a solid or a liquid. If the unknown is a solid, you should note whether it appears amorphous or distinctly crystalline; and if crystalline what shape crystals are present (needles, plates, prisms, etc.) and their general size. If the compound is a liquid, you ought to note its relative viscosity, that is, observe whether the liquid flows freely like water or more slowly like syrup.

Q2.2 Color

Record the color of the compound. Most organic compounds are colorless, appearing white if they are solids. If an unknown appears yellowish, tan, or brown, it is probably impure. If the compound itself is colored, you can suspect the presence of conjugated double and/or triple bonds and/or aromatic structures, perhaps along with nitrogen and oxygen within the conjugated system.

Q2.3 Odor

Volatile organic compounds often possess characteristic odors. Many, but not all, aldehydes, ketones, and esters have pleasant fruity odors; aliphatic amines are commonly ammoniacal or fishy smelling, whereas aromatic amines are often disagreeable and nauseatingly foul. The smallest carboxylic acids have sharp odors, whereas some of the larger ones are suggestive of dirty body odors.

Many instructors prefer that you do not smell your assigned unknowns, or will inform you which ones can be safely tested for odor. To test the odor of a compound, hold the container well away from yourself and waft the vapors in your direction with your hand,

continually moving the container closer as required. Use shallow breaths, inhaling into the nose only.

Do not smell an unknown substance for which you have no information regarding toxicity.

Q3 DETERMINATION OF BASIC PHYSICAL DATA

You should obtain the melting point (Technique 3, Section 3.3) of all solids, and the boiling point (Technique 3, Section 3.4) of all liquids. These properties are easy to get and can help you ascertain whether the unknown substance is pure enough for identification. That is, melting and boiling ranges indicate the presence of impurities. Determinations of density (Appendix A, Section A1) and molecular mass (Appendix A, Section A2) can also be helpful.

Q4 PURIFICATION

If you find that the melting point range is greater than 5 C°, you should purify the substance by recrystallization (T5.3) or sublimation (Appendix A, Section A3). If the distillation boiling point suggests that the unknown liquid is impure, you should distill it before proceeding. The distillation boiling point can indicate impurities in two ways: First, the boiling point rises as distillation progresses, and second, a colorless distillate arises from a colored liquid in the pot.

Q5 DETERMINATION OF SOLUBILITY

Discovering the solubility behavior of your unknown is very important. Test the unknown with water, 5% aqueous sodium hydroxide, 5% aqueous sodium hydrogen carbonate, 5% hydrochloric acid, and concentrated sulfuric acid, in that order. Figure Q.1 is a flow

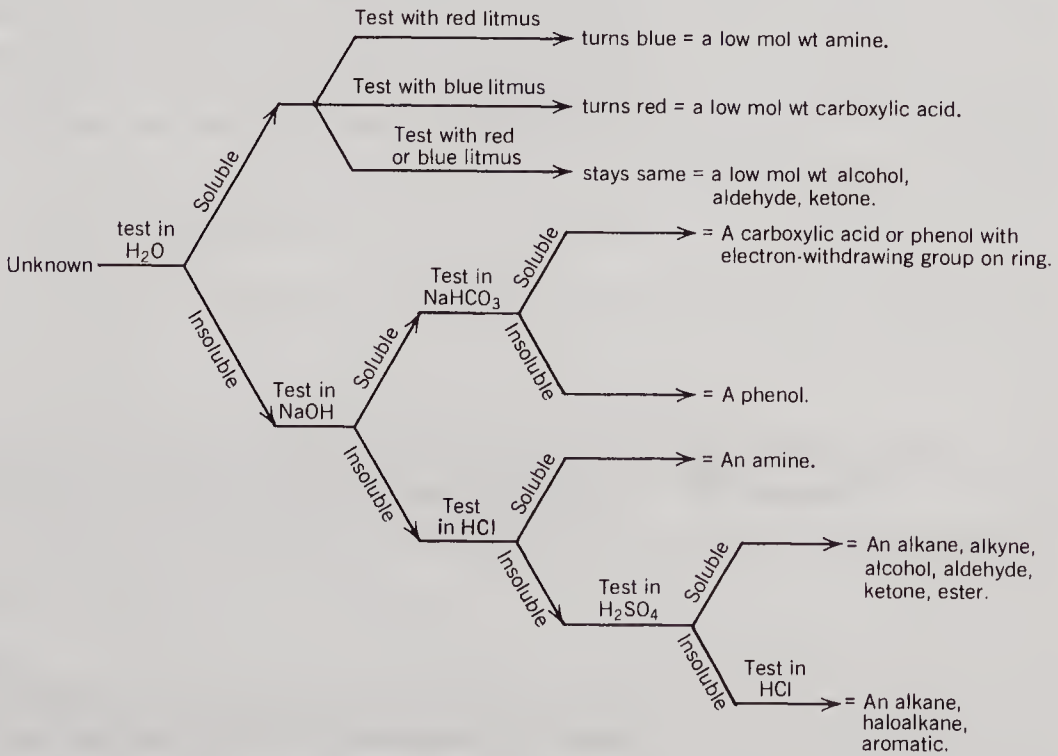


FIGURE Q.1 Flow diagram for solubility determinations.

diagram summarizing the routes to be taken and the conclusions to be drawn from the solubility tests. USE THESE CONCLUSIONS ALONG WITH THOSE FROM ELEMENTAL ANALYSES TO DIRECT YOU TO THE APPROPRIATE CLASSIFICATION TESTS.

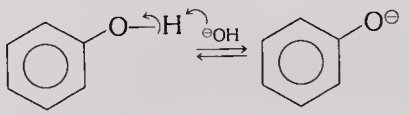
You should keep in mind that solubility is a relative term. When we say "soluble" we generally mean something like dissolving 2 or 3 g of substance in 100 ml of solvent.

Q5.1 Solubility In Water

If a compound is appreciably soluble in water it suggests that there are four or less carbon atoms for each oxygen or nitrogen atom. A ratio of five carbon atoms per oxygen or nitrogen atom usually gives borderline solubility or insolubility. However, remember that branched compounds are more likely to exhibit solubility than straight chain compounds because there are fewer van der Waals interactions among branched hydrocarbons than among straight chain hydrocarbons; hence solvent is able to more easily separate them from each other. Test the water-soluble compounds with litmus paper and compare the results with those outlined in Figure Q.1.

Q5.2 Solubility In Aqueous NaOH

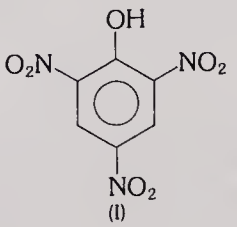
An unknown that dissolves in 1.5*M* sodium hydroxide but not in water must have at least one acidic proton. The acidity constant must be greater than 10^{-15}, the K_a of water. The common compounds that fit into this category are phenols (K_a ca 10^{-10}) and carboxylic acids (aliphatic K_a ca 10^{-5}, aromatic K_a ca 10^{-4}). The reaction is of course the simple Brønsted acid-base reaction:



(Q-1)

Q5.3 Solubility In Aqueous $NaHCO_3$

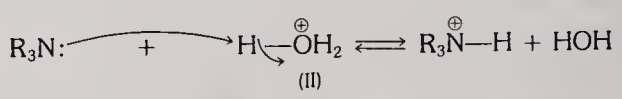
Compounds that dissolve appreciably in 0.6*M* bicarbonate solution have acidity constants that are equal to or greater than 4.3×10^{-7}, the acidity constant of carbonic acid. Therefore, an unknown substance that is soluble in aqueous bicarbonate is generally a carboxylic acid. However, we must remember that phenol-like compounds with electron-withdrawing ring substituents are considerably more acidic than phenol. For example, 2,4,6-trinitrophenol [picric acid, (I)] has an acidity constant of 1.6×10^{-1}, which is about 10,000 times more acidic than acetic acid with a K_a of 1.8×10^{-5}.



(I)

Q5.4 Solubility In Aqueous HCl

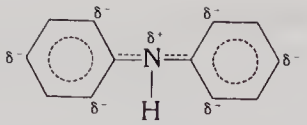
If an unknown substance dissolves in 1.5*M* hydrochloric acid, the chances are pretty good that it is an amine. Primary, secondary, and tertiary amines all dissolve in strong acids because the salt of the amine (II) is water soluble. The reaction is

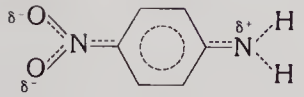


(Q-2)

(II)

However, di- and tri-aryl amines like diphenylamine (III) are not soluble because the electrons on nitrogen are insufficiently basic due to electron delocalization into the rings. Also, for the same reason, aromatic


(III)


(IV)

amines like *p*-nitroaniline (IV) will not dissolve in aqueous acid.

Q5.5 Solubility in Concentrated H_2SO_4

There are a number of compounds that will not dissolve in 5% hydrochloric acid that will dissolve in concentrated sulfuric acid. Compounds that fall into this category are alkenes, alcohols, aldehydes, ketones, and esters. The reason for solubility lies in the attraction of the weakly basic double bond and/or oxygen atoms for the proton of sulfuric acid. If with sulfuric acid the color of the substance changes but it does not appear to dissolve, you should nevertheless classify the compound as soluble.

Procedure for solubility tests. Put 1 ml of the test solution (water, NaOH, $NaHCO_3$, HCl, or H_2SO_4) in a test tube and add a match head size of a powdered solid or one drop of a liquid unknown. Tap or shake the test tube to see if the unknown dissolves. If it does not dissolve, warm the mixture a little, giving the compound several minutes of shaking if necessary before coming to a conclusion. Look carefully for two phases when testing liquids.

Make all necessary solubility tests, following the path on the flowchart of Figure Q.1 to determine what should be done next. You need perform only those tests to which you are led by the previous test.

Always point the test tube away from yourself and others when adding the unknown.

It is advisable to wear rubber gloves when working with concentrated sulfuric acid.

Q6 THE IGNITION TEST

The ignition test consists of igniting a small sample of the unknown and observing the flame and smoke. Highly unsaturated compounds, especially aromatics, burn with a yellow flame and produce a sooty smoke. The soot results from very incomplete combustion of carbon, and the yellow flame is due to heating carbon particles to incandescence. A yellow flame with nonsooty smoke indicates the presence of aliphatic hydrocarbons. If oxygen is present in a compound, the flame appears more colorless (blue) because more complete combustion is occurring and less carbon particles are available to be heated to incandescence. If there is a relatively large amount of oxygen or halogen in the compound, flammability is reduced.

Procedure for the ignition test. Put one or two drops of a liquid or a match head size of a solid on the end of a spatula and hold it above the inner cone of a Bunsen burner flame.

Be sure to work in a flame-permit area of the laboratory.

Keep the sample of unknown well away from the flame. Take only the required amount of sample into the flame-permit area.

Work in a hood so that sooty particles and other pyrolysis products will not be dispersed in the laboratory.

Q7 ELEMENTAL ANALYSIS

The elements other than C and H most commonly found in organic compounds are Br, Cl, I, N, O, P, and S. You can quite easily determine the presence of the halogens,

nitrogen, and sulfur, and methods are described below. Even though oxygen is one of the most common hetero elements, there is no simple way to test for it directly. However, its presence can be inferred by functional analysis as described in Section Q8. As a matter of fact, elemental analysis in general is often unnecessary because functional group analysis is sufficient to indicate the presence of a hetero atom. Nevertheless, elemental analysis is definitely informative and aids in confirmation and in pointing you in the right direction early in your investigation.

Q7.1 Tests for Halogen

There are two very easy tests for detecting the presence of halogens: the Beilstein test and the silver nitrate test. Neither of these tests differentiate well among the various halogens, although AgCl is white, whereas AgBr and AgI are yellow.

The Beilstein Test

The Beilstein test is a fast and simple way to test for the presence of chlorine, bromine, or iodine by igniting the compound on a copper wire. The burning of the compound in the presence of copper oxide on the wire produces a volatile copper halide which gives a transient blue-green flame, which is due to the ease of exciting copper electrons in the presence of halide ions.

The test is quite sensitive to small amounts of halogen, and small amounts of halogen impurities might give a weak positive test; so you must interpret the results with care.

Procedure for the Beilstein test. Using a short length of copper wire with a small loop at the end, scrub the loop end with steel wool and then heat it in a burner flame until the flame is not colored. After cooling the wire, dip the loop directly into the unknown; then place it in the burner flame. If one of the halogens is present, the flame will appear blue-green.

Conduct the Beilstein test only in a flame-permit area.

Keep the sample of unknown well away from the flame. Take only the required amount of sample into the flame-permit area.

Work in a hood so as to confine sooty particles and pyrolysis products.

The Silver Nitrate Test

This test helps you to distinguish between halides that are reactive enough to form carbocations in solution. Benzylic, allylic, and tertiary halides react immediately at room temperature, and secondary and primary halides react rapidly at 100 °C. Aryl and vinyl halides are ordinarily nonreactive. The reaction proceeds via a carbocation intermediate which reacts with solvent to yield an ether:

$$RX + AgNO_3 \longrightarrow AgX\downarrow + \overset{\oplus}{R}\overset{\ominus}{NO_3} \xrightarrow{HOCH_2CH_3} ROCH_2CH_3 \qquad \text{(Q-3)}$$

The visual observation depends on formation of the silver halide precipitate.

Carboxylic acids also form precipitates in ethanolic silver nitrate and can therefore give a false test. However, these precipitates dissolve in the presence of dilute nitric acid, whereas silver halides do not.

Procedure for the silver nitrate test. Put 2 ml of 2% ethanolic silver nitrate in a test tube and add one drop of a liquid unknown or five drops of a concentrated ethanolic solution of a solid unknown. A positive test is formation of a white to gray precipitate. If no precipitate forms within 5 min at room temperature, heat the mixture on a steam bath. Treat all precipitates with two or three drops of 5% nitric acid and agitate the mixture. Pour all solutions containing any form of silver into the silver recovery container.

Q7.2 Sodium Fusion Tests

The sodium fusion tests detect the presence of halogen, nitrogen, and sulfur, and also differentiate among the halogens.

Fusion can be defined as the melting together of two or more substances by application of heat. In a sodium fusion, sodium metal and an organic compound melt together and undergo a redox reaction in which sodium is oxidized and hetero elements are reduced:

$$RX,\ R_3N,\ R_2S \xrightarrow[\Delta]{Na} NaX,\ NaCN,\ Na_2S \qquad \text{(Q-4)}$$

R is alkyl, aryl, or hydrogen. After the fusion reaction you dissolve the ionic compounds in water and perform inorganic qualitative analyses.

You can use either sodium or a 10% sodium-lead alloy for the fusion. Because fusion with sodium alone is characterized by a small explosion or flash of fire in the test tube when the organic compound is added, it is at least moderately hazardous when not carefully performed. Dilution of sodium by lead leads to a less violent process, and it is the sodium-lead alloy procedure that is described below. You can find the sodium-alone method in the first two references at the end of Part III.

Procedure for sodium-lead alloy fusion. Clamp a small dry pyrex test tube vertically on a ring stand, using a clamp with an incombustible liner or none at all (rubber will burn, smoke, or melt at the high-fusion temperature). Put 0.5 g of sodium-lead alloy (as for example, Dri-Na from Baker) in the test tube and heat it with a burner flame until the alloy melts and you observe sodium vapors rising to 1–2 cm above the liquid. Remove the flame and, without permitting the organic substance to touch the sides of the test tube, immediately add two or three drops of a liquid unknown or a two match head size sample of solid directly onto the molten alloy. If you observe no evidence of reaction, heat the mixture gently with the burner flame. After reaction appears complete, heat the bottom of the test tube to a dull red color for 2 min, then allow it to cool to near room temperature. Add 3 ml of distilled water and heat the mixture for about 3 min. Cool the solution, filter it through a small conical filter into a clean test tube, and rinse the filter with 3 ml of distilled water into the same test tube.

Check the test tube for cracks or stars before using it for the fusion.

Check with your instructor for permissible flame-permit areas and times.

Work in a hood if you can.

During the entire operation do not point the test tube toward yourself or anyone else.

Add the organic compound cautiously into the test tube, taking care not to let it touch the test tube walls.

Add distilled water to the fusion mixture with great caution because water reacts violently with any sodium left unreacted after the fusion.

Test for nitrogen. Pour 1 ml of the fusion solution into a clean test tube and check the pH by transferring a drop to pH indicator paper. If the pH is above 13, add *small* drops of 3*M* aqueous H_2SO_4 to the solution until the pH is 13; if the pH is below 13, add *small* drops of 6*M* aqueous NaOH to the solution until the pH is 13. Add two drops of aqueous saturated ferrous ammonium sulfate solution and two drops of 5*M* aqueous potassium fluoride. Boil the solution gently for about 30 s, cool it, and add two drops of 5% aqueous ferric chloride. Next, avoiding excess, add dropwise 3*M* sulfuric acid until the iron hydroxide precipitate *just* dissolves. The test is positive for nitrogen if you observe a deep blue solution or precipitate of potassium ferric ferrocyanide, (Prussian Blue), $KFe[Fe(CN)_6]$. If the solution is green or blue-green, filter it and look for a blue precipitate on the filter paper.

Test for sulfur. Pour 1 ml of the fusion solution into a clean test tube and add 6*M* aqueous acetic acid until it turns blue litmus paper pink. Add aqueous lead(II) acetate. The test is positive for sulfur if you observe a black PbS precipitate.

Test for halogens. Pour 2 ml of the fusion solution into a clean test tube and acidify it with dropwise addition of 6*M* nitric acid until it turns blue litmus paper pink. Boil the solution for 2–3 min to expel H_2S or HCN, the anions of which will interfere with halogen tests. Cool the solution and add a few drops of 0.3*M* aqueous $AgNO_3$. The test for halogen is positive if you observe a *heavy* precipitate, white for AgCl, yellowish for AgBr, and yellow for AgI. If the precipitate is white or yellowish, add 2 ml of concentrated aqueous NH_3 and stir the mixture. AgCl dissolves readily, whereas AgBr dissolves only slightly.

You can obtain a better differentiation among the halogens in the following way. Pour 2 ml of the fusion solution into a clean test tube and acidify it with 3*N* aqueous H_2SO_4 until it turns blue litmus paper pink. Boil the mixture for about 2 min, cool it, and add 0.5 ml of tetrachloromethane (carbon tetrachloride). Add a few drops of dilute aqueous NaClO (laundry bleach). Stopper the test tube, shake it vigorously, then allow the two phases to separate. A light yellow or colorless CCl_4 lower phase indicates chlorine, organe-brown indicates bromine, and violet indicates iodine.

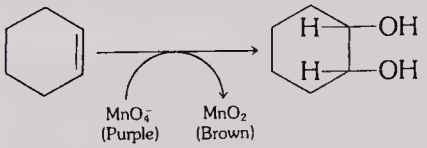
Q8 THE CHARACTERIZATION TESTS

Characterization assigns your unknown to a limited number of compound classes, to a compound class, or to a subgroup within a class by utilizing the following tests. If you have no idea what your compound is, start at the beginning with Section Q8.1 and proceed through the entire series to Q8.7 or until you obtain positive results. If you have some prior knowledge which leads you to believe that you know how to characterize your compound, proceed directly to the appropriate characterization tests.

Q8.1 Characterization of Unsaturated Hydrocarbons

The Baeyer Test

Potassium permanganate is a reagent often used to indicate unsaturation. The purple color of the permanganate gives way to a brown precipitate of manganese (IV) oxide:



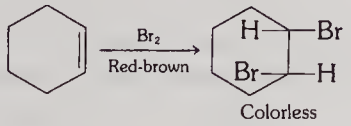
(Q-5)

The appearance of the brown precipitate indicates that the organic compound was oxidized and very often indicates the presence of the unsaturation found in alkenes and alkynes. However, you must approach interpretation of a positive test with thoughtfulness because it can also suggest the presence of other easily oxidized substances like aldehydes, phenols, and aromatic amines. Furthermore, you cannot construe a positive test to indicate the unsaturation of an aromatic structure because aromaticity defies such mild oxidative processes as found in the Baeyer test.

Procedure for the Baeyer test. For water-soluble unknowns, put $\frac{1}{2}$ ml of water into a test tube; for water-insoluble compounds, put $\frac{1}{2}$ ml of 1,4-dioxane or tetrahydrofuran into a test tube. Add two match head sizes of solid unknown, or two drops of liquid unknown; then a room-temperature aqueous alkaline, 1% $KMnO_4$ solution dropwise with agitation until the solution is light purple or until a brown precipitate forms. Formation of a brown precipitate constitutes a positive test.

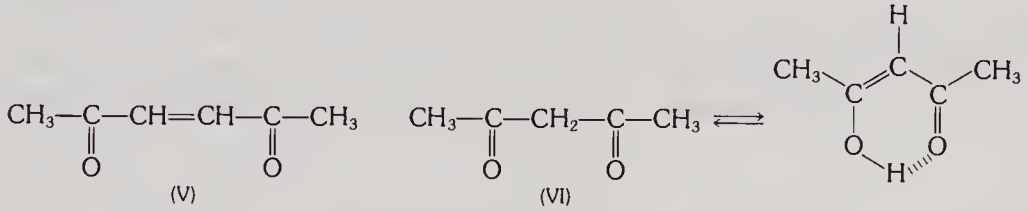
The Bromine Test

Bromine in tetrachloromethane (carbon tetrachloride) is often used as a color test for unsaturation. The red-brown color of bromine disappears as it is used up in ionic addition to the double bond:



(Q-6)

It also adds to triple bonds, of course; so it is not specific as a test for alkenes. Furthermore, compounds like 3-hexene-2,5-dione (V) which have double or triple bonds in conjugation with electron-withdrawing substituents *might not be reactive enough* to add bromine readily. Also, a few ketones and aldehydes which are considerably enolized like 2,4-pentanedione (VI)



WILL react with bromine. In addition, some highly activated aromatics like benzenol (phenol) and benzenamine (aniline) *are reactive enough* to undergo uncatalyzed electrophilic aromatic brominations, and liberate observable HBr.

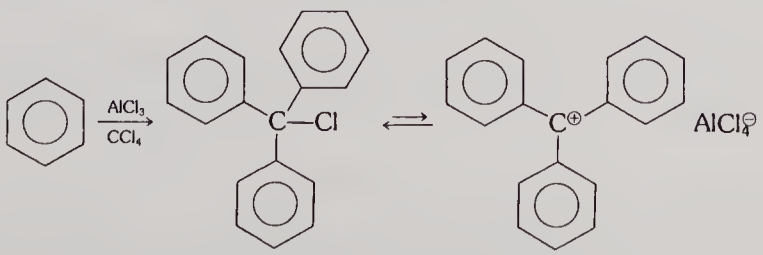
Procedure for the bromine test. Put ½ ml of dioxane or tetrahydrofuran in a test tube. Add two match head sizes of solid or two drops of liquid unknown and stir the mixture to dissolve the substance. Add dropwise with shaking a 2% tetrachloromethane (carbon tetrachloride) solution of bromine. A positive test is indicated by addition of two or more drops of bromine solution before a permanent (more than 1 min) bromine discoloration remains. Hold a piece of damp, blue litmus paper at the mouth of the test tube. If the litmus turns pink, HBr gas is indicated, suggesting aromatic substitution rather than addition to unsaturated carbon-carbon bonds.

Work with bromine solutions in a hood.

It is advisable to wear rubber gloves when working with bromine and potassium permanganate.

The Stable Carbocation Test

Aromatic hydrocarbons that are not deactivated to Friedel-Crafts reactions can be made to react with tetrachloromethane to yield relatively stable carbocations that are highly colored due to their highly conjugated nature. For example, benzene reacts with tetrachloromethane in presence of anhydrous aluminum chloride to yield triphenylmethyl chloride in equilibrium with red-orange triphenylmethyl cation:



(Q-7)

Friedel-Crafts reactions are discussed in detail in Experiment 33.

Procedure for the stable carbocation. Put about 0.1 g of anhydrous aluminum chloride in a Pyrex test tube and clamp the tube to a ringstand in an almost horizontal position with the open end slightly elevated. Heat the bottom of the tube with a flame until the salt has sublimed to a position about 3 cm from the bottom. Permit the tube to cool until it is warm to the touch. Then add to the test tube one drop of liquid or a match head size of solid placing it near the anhydrous aluminum chloride. Next, add three drops of tetrachloromethane. A positive test is observation of bright color where the reactants come in contact with the catalyst.

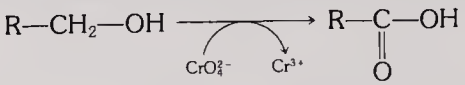
Bottles of $AlCl_3$ which have been closed for a while have a high internal pressure due to release of HCl gas. The lid areas should be wrapped in a dry cloth and opened with care.

Weigh the $AlCl_3$ in a hood.

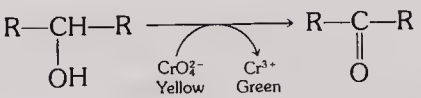
$AlCl_3$ is a strong acid and must not come in contact with skin and eyes. Do not inhale the dust or fumes that arise from the compound.

Q8.2 Characterization of Alcohols

Chromic acid at room temperature oxidizes primary alcohols to carboxylic acids and secondary alcohols to ketones, but tertiary alcohols do not readily react:



(Q-8)



(Q-9)

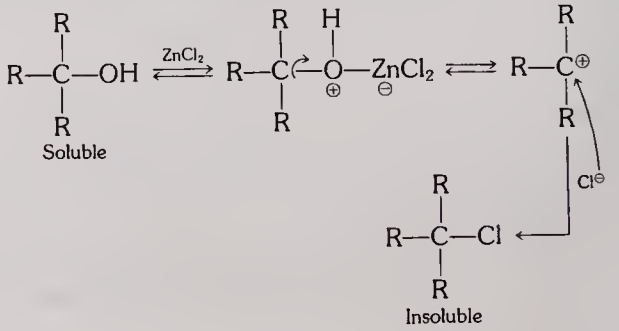
During the reaction the yellow-orange chromate ion is reduced to green chromic ion, and appearance of a green chromic sulfate precipitate constitutes a positive test. The test results must be interpreted with caution, however, because other easily oxidized substances like aldehydes, phenols, and anilines also give a positive test.

Procedure for the chromic acid test. Add a match head size of solid or one drop of liquid unknown to 1 ml of reagent grade propanone (acetone) in a test tube. Then add one drop of chromic acid reagent and shake the mixture. The appearance of an opaque, blue-green color within 2 s is a positive test.

It is advisable to wear rubber gloves when working with chromic acid.

The Lucas Test

The Lucas test is an S_N1 reaction that converts alcohols to alkyl halides. It is a very good complement to the chromic acid test because whereas tertiary alcohols do not give a positive test with chromic acid, they react the fastest in the Lucas test. This test is applicable only to alcohols of no more than six carbons because larger alcohols are not soluble in the reagent solution, which consists of the Lewis acid zinc chloride dissolved in concentrated hydrochloric acid. The function of zinc chloride is to help hydrochloric acid remove the hydroxyl and generate the carbocation:



(Q-10)

The visual indication of a positive test is formation of a second phase, the insoluble haloalkane. The rate of the reaction depends on the ease of carbocation formation in presence of the reagent mixture. Tertiary and benzylic alcohols form a second phase almost immediately, secondary and allylic alcohols react in 3 or 4 min, and primary alcohols do not react at room temperature even after much longer periods.

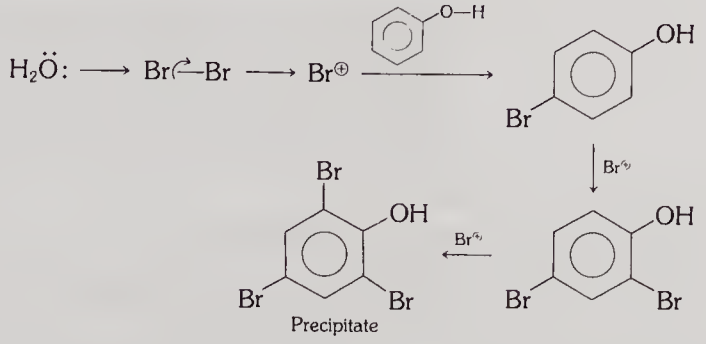
Procedure for the Lucas test. Put 2 ml of Lucas reagent in a test tube, add a few drops of the unknown, and agitate the mixture. Watch for the appearance of the second phase as a turbidity or emulsion.

It is advisable to wear gloves when working with the very corrosive Lucas reagent.

Q8.3 Characterization of phenols

The Bromine-Water Test

Because of the electron donor properties of the phenolic hydroxyl, phenols possess a ring activated to electrophilic aromatic substitution unless a strongly deactivating group like nitro is also present on the ring. Ring activation is sufficient to cause bromination at the *ortho* and *para* positions even without a catalyst:



(Q-11)

Bromination is more rapid in water than in tetrachloromethane because brominium ion, the electrophile, is more readily produced in a polar medium. Visual indication of a positive test is formation of the brominated phenol precipitate. Interpret your results in conjunction with other tests because other ring-activated aromatic compounds like aniline and methoxybenzene also give positive bromine tests.

Procedure for the bromine-water test. Put a match head size of solid or one drop of liquid unknown in a test tube. Add 100 drops of water and agitate the mixture to dissolve the unknown. If necessary to help dissolve the unknown, add dropwise with agitation a few drops of 6*M* aqueous sodium hydroxide. Next, add dropwise with agitation a saturated bromine-water solution until the bromine color no longer disappears. Formation of a precipitate constitutes a positive test.

The Iron(III) Chloride Test

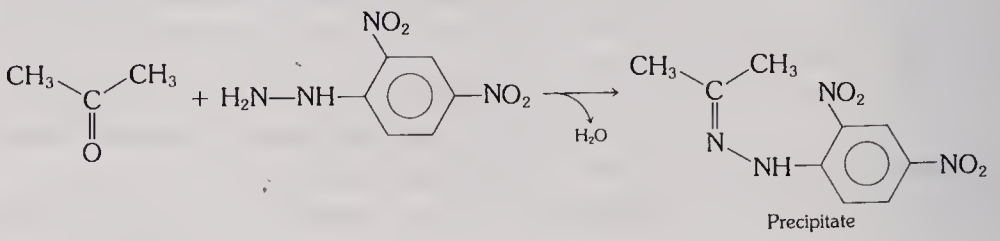
Most, but not all, phenols and enols react with iron(III) to give colored complexes, the structures of which are not well characterized. Because not all phenols and enols react, a negative test is not necessarily proof that a phenol is not present. Most phenols yield purple, red, green, or blue colors; most enols produce red, tan, or violet colors.

Procedure for the iron(III) chloride test. Dissolve a match head size of a solid or one drop of a liquid unknown in 1 ml water. Add four or five drops of 2.5% *aqueous* iron(III) chloride. If the unknown is insoluble in water, dissolve it in 1 ml of trichloromethane (chloroform); then add one drop of pyridine and four or five drops of a 1% trichloromethane solution of iron(III) chloride.

Q8.4 Characterization of Aldehydes and Ketones

The 2,4-Dinitrophenylhydrazine Test

Most aldehydes and ketones will almost immediately react with 2,4-dinitrophenylhydrazine, yielding solid, yellow to red precipitates called 2,4-dinitrophenylhydrazones:



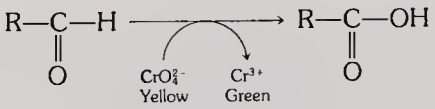
(Q-12)

The color of the precipitate depends on the extent of conjugation, and the more conjugation is extended, the redder the precipitate will be. The color of the reagent, however, is red-orange and to get a true color of the precipitate, you must remove it from the reagent solution and wash it. Because the reagent can oxidize some allylic and benzylic alcohols to aldehydes or ketones, these alcohols also give a positive test. Other alcohols that contain small amounts of oxidation products might also yield a small precipitate. Therefore tiny amounts of precipitates should be ignored.

Procedure for the 2,4-dinitrophenylhydrazine test. Put a match head size of solid or one or two drops of the liquid unknown into a test tube along with 2 ml of 95% reagent grade ethanol. Add 5 ml of 2,4-dinitrophenylhydrazine reagent and shake the test tube vigorously. If no precipitate forms, gently heat the mixture to about 50 °C for 30 s and shake it again. A positive test is one that yields considerable precipitate.

The Chromic Acid Test

Because aldehydes are easily oxidized, chromic acid at room temperature transforms them into carboxylic acids:



(Q-13)

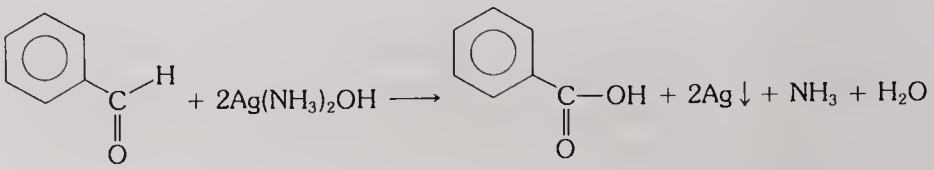
The reagent is the same one used for the characterization of alcohols. Remember that primary, secondary, allyl, and benzyl alcohols also respond to this test. What you observe is the change in color from a yellow-orange solution to a green precipitate. Because ketones do not react in this test, a positive 2,4-dinitrophenylhydrazine test followed by a positive chromic acid test establishes the unknown as an aldehyde.

Procedure for the chromic acid test. Add a match head size of solid or one drop of liquid unknown to 1 ml of reagent grade propanone (acetone) in a test tube. Then add one drop of chromic acid reagent and shake the mixture. The immediate appearance of an opaque, blue-green color is a positive test.

It is advisable to wear rubber gloves when working with chromic acid.

The Tollens Test

You can use the Tollens test to differentiate between aldehydes and ketones. Aldehydes usually reduce ammoniacal silver nitrate to yield a precipitate of silver metal, which appears as a mirror on the test tube wall:



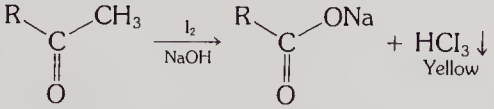
(Q-14)

Procedure for the Tollens test. Thoroughly scrub and rinse a test tube. Add 2 ml of 5% aqueous silver nitrate and one drop of 10% aqueous sodium hydroxide. Add dropwise with shaking 2*M* aqueous ammonium hydroxide until the dark Ag_2O precipitate just dissolves. Add a match head size of the solid or one drop of the liquid unknown and agitate the test tube well to mix the chemicals. Allow the mixture to sit at room temperature for 15 min. If no mirror is deposited, warm the mixture on a 35–40 °C water bath for a few minutes. Be careful not to shake the tube or stir the contents after the initial mixing. A mirror on the wall of the test tube is positive for an aldehyde.

Tollen's reagent on standing has the capability of forming silver fulminate ($AgC_2N_2O_2$), a violently explosive compound. Prepare Tollen's reagent immediately before use and dispose of the test solutions immediately after use down a drain with plenty of water.

The Iodoform Test

This is a characterization test for methyl ketones, ethanal, and methyl carbinols (alkylmethylmethanols). A yellow precipitate of iodoform indicates the presence of one of these kinds of carbonyl compounds:



(Q-15)

The haloform reaction is discussed in detail in Experiment 16.

Procedure for the iodoform test. Dissolve in a test tube 8–10 drops of the unknown in 2–3 ml of water along with the same volume of 5% aqueous sodium hydroxide. If the unknown is quite insoluble in water, add enough dioxane to dissolve it. Then add potassium iodide/iodine stock solution dropwise with shaking until iodine persistently and definitely darkly colors the solution. Shake the solution for 2 or 3 min. If no yellow precipitate forms at room temperature, warm the test tube in a beaker of water at 60 °C. If the iodine color disappears, add more KI/I_2 reagent with shaking until the dark color remains after 2 min at 60 °C. Then add a few drops of 5% sodium hydroxide with shaking until the color just disappears; then continue shaking the solution for a few minutes at 60 °C. Filter the precipitate on a Hirsch funnel and dry it. Obtain a melting point to confirm the identity of the yellow iodoform (IUPAC triiodomethane), which melts at 120 °C.

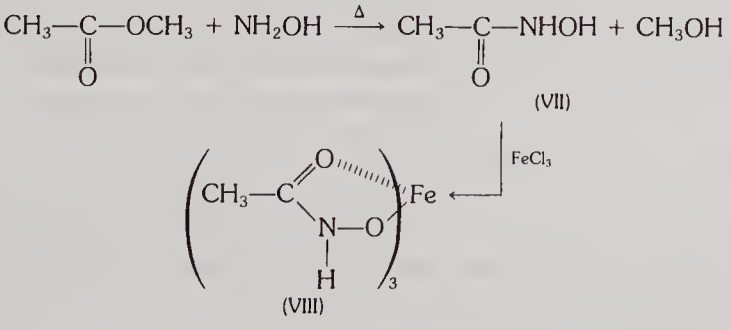
Q8.5 Characterization of Carboxylic Acids

Carboxylic acids are characterized by their solubility behavior and reaction with litmus paper. Follow the instructions in Section Q5.

Q8.6 Characterization of Esters

The Iron(III) Hydroxamate Test

An ester that is heated with hydroxylamine (NH_2OH) in the presence of iron(III) is converted to a hydroxamic acid (VII) that subsequently reacts with iron(III), yielding a highly colored complex (VIII):



(Q-16)

Because highly enolized structures give a positive test with iron(III) in absence of hydroxylamine, you should check a positive test by repeating it without any hydroxylamine.

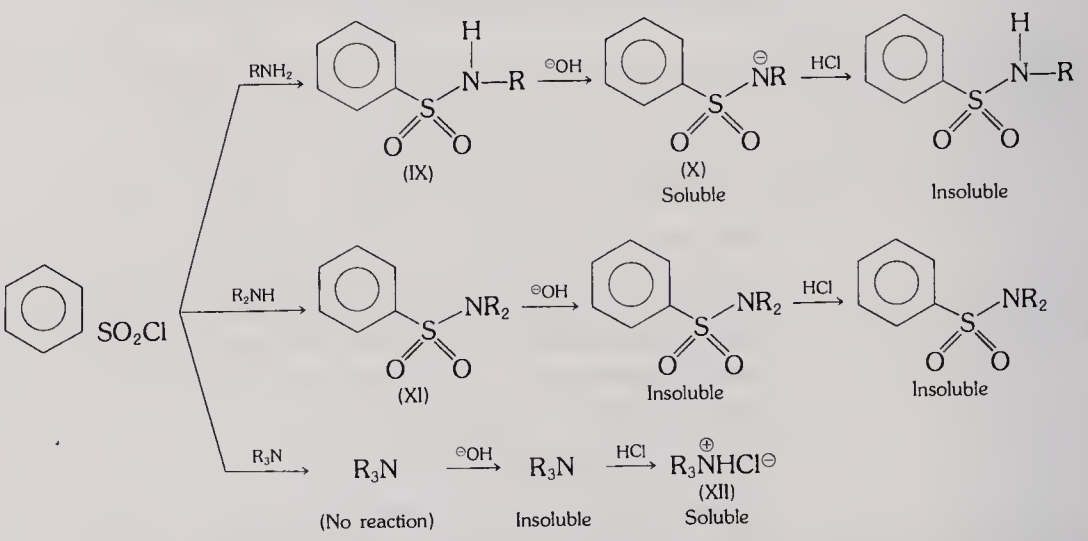
Procedure for the iron(III) hydroxamate test. Put one drop of liquid unknown into a test tube and add 1 ml of 0.5*M* 95% ethanolic solution of hydroxylamine hydrochloride and 0.2 ml of 6*M* aqueous sodium hydroxide. Heat the mixture to boiling for a few minutes; then cool it to room temperature and add 2 ml of 1*M* hydrochloric acid. If the solution appears turbid, add 2 ml more of 95% ethanol. Put in dropwise enough 0.6*M* iron(III) chloride reagent until the color no longer fades. Note the color. A magenta or burgundy color constitutes a positive test.

If the test was positive, dissolve one drop of the liquid unknown in 1 ml of 95% ethanol and add 1 ml of 1*M* hydrochloric acid. Next add one drop of 0.6*M* aqueous iron(III) chloride. Appearance of a color other than yellow indicates enol character.

Q8.7 Characterization of Amines

The Hinsberg Test

Primary and secondary amines react with benzenesulfonyl chloride or 4-methylbenzenesulfonyl chloride in the presence of excess potassium hydroxide to give substituted sulfonamides, whereas tertiary amines do not noticeably react.

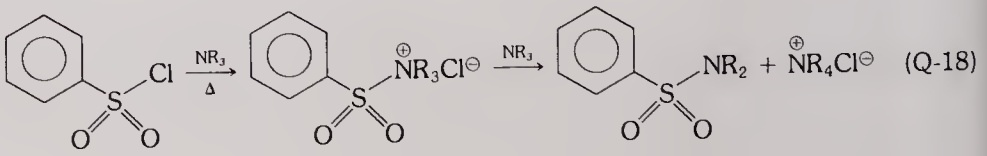


(Q-17)

The primary amine yields a sulfonamide (IX) with an acidic amido hydrogen (K_a = 10^{-11}), and, in presence of excess base, becomes a soluble salt (X). So, a single homogeneous phase is present. Acidification of this mixture restores the proton to the amide and, no longer being ionic, it precipitates. Because benzenesulfonamides are generally more dense than the solution, they tend to settle to the bottom.

A secondary amine yields the insoluble *N,N*-disubstituted sulfonamide (XI) which has no acidic amido hydrogen; hence it does not become a soluble salt in presence of excess base. Addition of acid has no effect on its solubility.

Under the conditions of the Hinsberg test, tertiary amines normally remain unreacted in presence of excess base. Since they are usually insoluble substances, the reaction mixture remains heterogeneous. At this point you could suspect that you are analyzing a secondary amine. However, there are two ways to test this supposition: First, the tertiary amines are generally less dense than the solution and tend to rise to the top, whereas benzenesulfonamides of secondary amines tend to settle to the bottom; second, acidification of the mixture protonates the tertiary amine, yielding the soluble salt (XII). Tertiary amines are likely to react with the benzenesulfonyl chloride if the temperature is too high:



(Q-18)

Notice that using an excess of amine also favors this reaction. At the usual prescribed temperature for the Hinsberg test and within the time normally allowed for observations, the reaction of equation Q-18 is not a serious competitor. However, small amounts of insoluble product must not be interpreted as being positive for secondary amines.

The Hinsberg test must be performed and interpreted carefully. There are side reactions from which you can sometimes draw misleading conclusions. The proportions of reagents must be adhered to, the temperature must not be too high, and the reaction time before observation must not be too long. Furthermore, overacidification with hydrochloric acid can sometimes precipitate byproducts.

In interpreting the results, you should also be aware that with cyclic, branched, and longer chain primary amines like cyclohexylamine, *t*-butylamine, and heptylamine the sulfonamide salt (X) might not be completely soluble. Hence, you might construe the result of the Hinsberg test on such amines as indicative of a secondary amine. Also, you should be aware that tertiary amines sometimes contain secondary amines as impurities. If the determination of basic physical data produced a doubtful boiling point and you did not have sufficient material to carefully purify it by distillation, you might get a positive secondary amine test.

You should normally expect to obtain solid benzenesulfonamides. However, oils are often obtained, especially if the amine is not pure.

Procedure for the Hinsberg test. Put 5 ml of 10% aqueous potassium hydroxide, 0.2 g of a solid or 0.2 ml of a liquid unknown, and 0.7 ml of benzenesulfonyl chloride in a test tube. Stopper the tube tightly and shake it vigorously over a period of 5 min, cooling the mixture if necessary to keep it at about room temperature. Test the solution at the end of 5 min to see if it is basic; if not, add 10% aqueous KOH dropwise with shaking until it is basic.

If a precipitate or second liquid phase has formed, take note of the relative densities; then separate the phases by filtering, decanting, or withdrawing with an eyedropper. Add dropwise with shaking 10% hydrochloric acid to the organic phase. Observe whether the organic phase goes into solution. If not, the unknown is probably a secondary amine; if it does, it is probably a tertiary amine.

If, after the 5-min shaking period of the original reaction mixture there is no second phase, the unknown is probably a primary amine. Acidify the mixture to pH 4 with 10% hydrochloric acid. The presence of a primary amine is confirmed by separation of a precipitate or second liquid layer.

Because of the acylating and lacrymating properties of benzenesulfonyl chloride, work in a hood.

It is advisable to wear rubber gloves because of the corrosive nature of the benzenesulfonyl chloride and the caustic nature of amines.

The Nitroprusside Tests

The nitroprusside tests are useful color tests for characterizing primary and secondary aliphatic amines and primary, secondary, and tertiary aromatic amines. These tests do not work well for tertiary aliphatic amines. The original Simon and Rimini nitroprusside tests for aliphatic amines were developed in 1897 and 1898 using a reagent consisting of sodium nitroprusside ($Na_2[Fe(NO)(CN)_5]$) in 50% aqueous methanol. The modified Simon and Rimini tests for aromatic amines were developed nearly 80 years later using a reagent containing sodium nitroprusside in 80% aqueous dimethylsulfoxide and employing a zinc chloride catalyst, which not only increases the rate but makes the colors of the complexes formed more intense.

The colors of the complexes might change with time; so you should keep careful notes regarding times and colors.

Procedure for the Rimini test. To 1 ml of stock nitroprusside reagent in a test tube add 1 ml of water, 0.2 ml of acetone, and then one drop of liquid amine or a match

head size of solid amine. Shake the test tube to mix its contents. Within a few minutes a deep red color will appear if a 1° or 2° aliphatic amine is present. If after 5 min no color appears, proceed to the modified Rimini test; if the test is positive, proceed to the Simon test.

Procedure for the Simon test. To 1 ml of stock nitroprusside reagent in a test tube, add 1 ml of water, 0.2 ml of 10% aqueous ethanal (acetaldehyde) solution, and then one drop of liquid amine or a match head size of solid amine. Shake the test tube to mix its contents. Within a few minutes a yellow to red-brown color will appear if a 1° amine is present, or a blue color will appear if a 2° amine is present. If after 5 min no color is apparent, proceed to the modified Simon test.

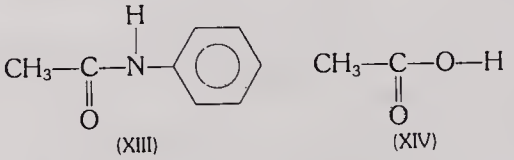
Procedure for the modified Rimini test. To 1 ml of modified nitroprusside reagent in a test tube, add 1 ml of saturated aqueous zinc chloride solution, then 0.2 ml of propanone (acetone), then one drop of liquid amine or a match head size of solid amine. Shake the test tube to mix its contents. Within 5 min a colored solution and/or precipitate will appear: orange to red-brown for 1° and 2° amines, and green for a 3° amine. Return the reagent solution to the refrigerator immediately.

Procedure for the modified Simon test. To 1 ml of modified nitroprusside reagent in a test tube, add 1 ml of saturated aqueous zinc chloride solution, then 0.2 ml of 10% aqueous ethanal (acetaldehyde) solution, then one drop of liquid amine or a match head size of solid amine. Shake the test tube to mix its contents. Within 5 min a colored solution and/or precipitate will appear: orange to red-brown for a 1° and 2° amines, green for a 3° amine. Return the reagent solution to the refrigerator immediately.

Q9. IDENTIFICATION

After characterization has directed you to the correct class of compound, you proceed with the final identification.

The classical method of wet analysis requires preparation of derivatives. A **derivative** is a chemical modification of the unknown substance from which it was prepared. For example, *N*-phenylethanamide (XIII) is a derivative of ethanoic acid (acetic acid), (XIV).



(XIII) (XIV)

It is customary to prepare highly crystalline derivatives with sharp melting points that you can compare to melting points of known derivatives, thereby helping to identify the compound of interest. Your success in identifying compounds by making derivatives depends on finding the derivatives listed in tables of compounds and their derivatives like those found at the end of Part III. You can find much more comprehensive tables in the first two references at the end of Part III, and you can find in the chemical literature many other compounds and their derivatives not listed in standard tables.

Now that modern instrumental methods of analysis are available, you should make use of as many of these as possible; IR (Technique 15, Sections 15.3, 15.4), UV and VIS (Technique 14, Section 14.4), NMR (Technique 16, Sections 16.4, 16.5), GLC (Technique 11, Section 11.3), and refractive index (Technique 13, Section 13.3).

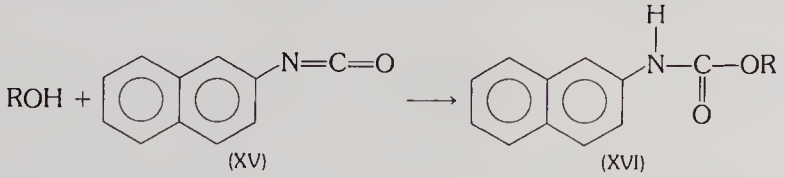
In addition, you will find that it is sometimes helpful to obtain density (Appendix A) and mixture melting points (Technique 3, Section 3.3).

Q9.1 Identification of Alcohols

The two usual kinds of derivatives for alcohols are urethanes (carbamates) and 3,5-dinitrobenzoate esters.

Urethanes

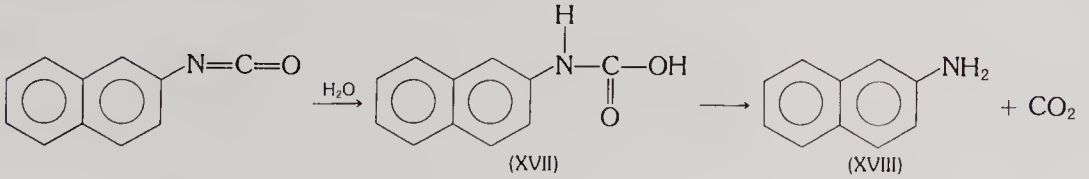
When an alcohol reacts with an aryl isocyanate like 2-naphthyl isocyanate (XV) it combines to make a urethane, or carbamate, called alkyl *N*-2-naphthylcarbamate (XVI):



(XV) (XVI) (Q-19)

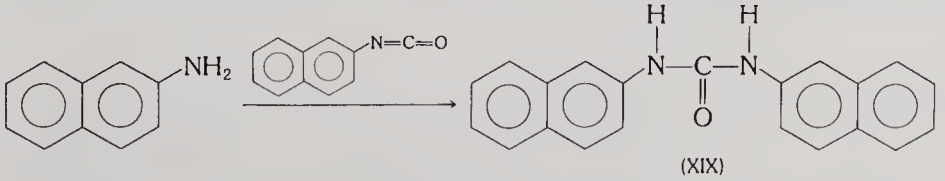
Other isocyanates that are sometimes used are phenyl isocyanate and 4-nitrophenyl isocyanate.

It is important to use anhydrous conditions during this reaction because isocyanates react with water to yield an unstable carbamic acid (XVII) which subsequently decomposes to an amine and carbon dioxide:



(XVII) (XVIII) (Q-20)

The name of this particular carbamic acid is *N*-(2-naphthyl)carbamic acid. The 2-aminonaphthalene (XVIII) can react with more isocyanate to yield a disubstituted urea (XIX):



(XIX) (Q-21)

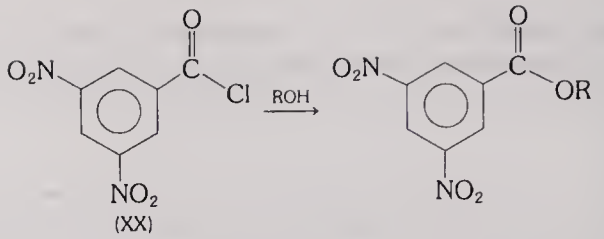
These ureas are high melting solids that when mixed with the product urethane might make it difficult to purify or will give a melting point that is low and over a range of temperatures.

Preparation of urethanes. Put 1 g of anhydrous alcohol and 0.5 ml of 2-naphthyl isocyanate into a test tube. Immediately cap the isocyanate container. Warm the mixture on a steam bath for 5 min; then cool the product mixture in an ice-water bath. Induce crystallization by scratching the sides of the tube with a stirring rod if necessary. Collect the crystals in a Hirsch funnel, recrystallize them from ligroine or tetrachloromethane, dry them, and obtain a melting point. *N,N'*-Di(2-naphthyl)urea has a reported melting point of 293 °C. If your derivative preparation melts in the neighborhood of 293 °C or has a wide, low melting point, prepare the derivative again, taking care to use completely anhydrous conditions. Table Q.1 at the end of Part III lists the 2-naphthylurethane derivatives.

2-Naphthyl isocyanate is toxic and a lachrymator. Work only in a hood and wear rubber gloves.

3,5-Dinitrobenzoates

When an alcohol reacts with 3,5-dinitrobenzoyl chloride (XX) it is converted to an ester:



(XX) (Q-22)

Because the reagent reacts with water to yield the corresponding carboxylic acid, the reaction mixture should be free of all but traces of water.

Preparation of 3,5-dinitrobenzoates. Put 0.5 g of dry unknown in a small round-bottom flask, and add 3 ml of dry pyridine as a solvent if the unknown is a solid. If the unknown is a liquid, omit the pyridine. Add 0.5 ml of 3,5-dinitrobenzoyl chloride (IUPAC 3,5-dinitrobenzenecarbonyl chloride) and a boiling chip. Cap the acyl chloride container immediately. Reflux the mixture 15 min for primary alcohols and 30 min for secondary and tertiary alcohols. Cool the solution to room temperature and cautiously add about 10 ml of 10% aqueous sodium bicarbonate. Swirl and cool the mixture in an ice-water bath. Collect the crystals in a Hirsch funnel using vacuum filtration. Recrystallize the product from ethanol/water, using the mixed solvent technique.

Table Q.1 at the end of Part III lists the 3,5-dinitrobenzoate derivatives.

Acyl chlorides are acylating agents; hence are potential carcinogens. Work only in a hood. It is advisable to wear rubber gloves.

Add bicarbonate solution slowly to avoid excessive foaming.

Q9.2 Identification of Phenols

Two commonly prepared derivatives of phenols are urethanes and multibrominated phenols.

Urethanes

The reactions and preparations are identical to those for alcohols except that you should add as a catalyst a drop or two of pyridine to the reaction mixture.

Bromophenols

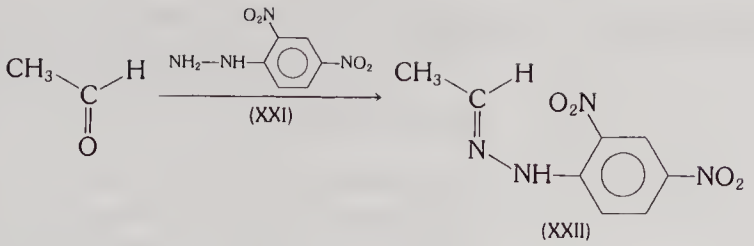
The reaction of phenols with bromine is an electrophilic aromatic substitution reaction as discussed in Section XIII. Table Q.2 at the end of Part III lists 2-naphthylurethane derivatives for phenols.

Preparation of bromophenols. Put 0.2 g of the unknown in a test tube. Add 2 ml of methanol and dissolve the unknown; then add 1 ml of water. Add the stock brominating solution, which consists of KBr, Br_2, and water, dropwise with constant shaking until the bromine color persists for 5 min. Then add 10 ml of water and shake the mixture vigorously. Collect the product in a Hirsch funnel by vacuum filtration and recrystallize it from methanol/water using the mixed solvent technique. Table Q.2 at the end of Part III lists bromo derivatives of phenols.

Remembering that bromine is a very hazardous chemical, you will want to confine your work to a hood and wear rubber gloves.

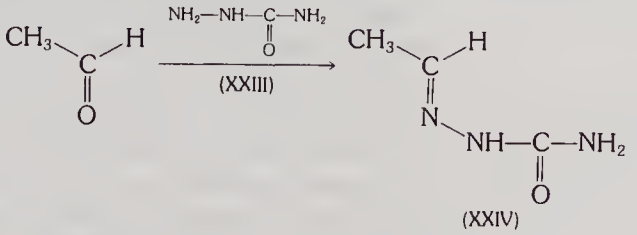
Q9.3 Identification of Aldehydes and Ketones

The most commonly prepared derivatives for these classes are probably the 2,4-dinitrophenylhydrazones and the semicarbazones. For example, ethanal (acetaldehyde) reacts with 2,4-dinitrophenylhydrazine (XXI) to yield ethanal 2,4-dinitrophenylhydrazone (XXII)



(Q-23)

and with semicarbazide (XXIII) to form ethanal semicarbazone (XXIV):



(Q-24)

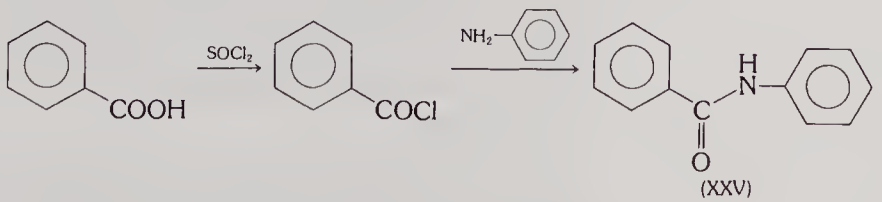
Preparation of 2,4-dinitrophenylhydrazones. Put about 0.2 g of unknown into a small Erlenmeyer flask with enough 95% reagent grade ethanol to dissolve it; then add 6 ml of 2,4-dinitrophenylhydrazine reagent. Agitate the mixture vigorously, then heat it on a water bath for a couple of minutes at 50 °C. Allow it to sit at room temperature for about 15 min while crystallization takes place. Collect the crystals on a Hirsch funnel and wash them with a small amount of cold 95% ethanol. Dry the crystals and obtain a melting point. Very often phenylhydrazones are pure enough that they do not need to be recrystallized. If necessary, they can be recrystallized in a test tube from ethanol or glacial ethanoic acid (acetic acid). Tables Q.3 and Q.4 at the end of Part III list derivatives of aldehydes and ketones.

Due to the toxicity of the reagent, you should work in a hood and preferably wear rubber gloves.

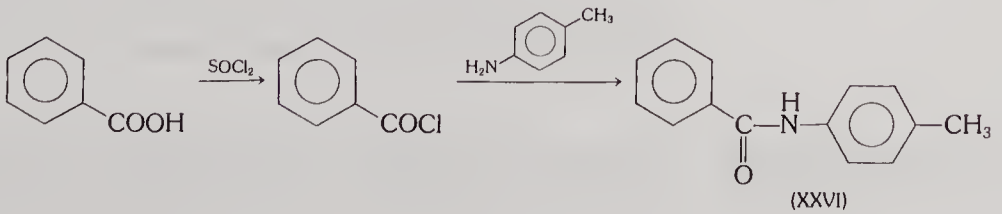
Preparation of semicarbazones. In a test tube, dissolve 0.5 g of semicarbazide hydrochloride and 0.8 g of sodium ethanoate sodium acetate) in 5 ml of water. Add 0.5 ml of the unknown, stopper the test tube, and shake it vigorously. If the unknown is insoluble in water, add enough methanol to dissolve the mixture. Remove the stopper and heat the mixture in a steam or boiling water bath for 5–10 min. Cool the product mixture to room temperature and then in an ice-water bath. If necessary, scratch the inside of the test tube to induce crystallization. Collect the product in a Hirsch funnel and recrystallize it from ethanol or ethanol/water by the mixed solvent technique. Tables Q.3 and Q.4 at the end of Part III list derivatives of aldehydes and ketones.

Q9.4 Identification of Carboxylic Acids

Among the derivatives of carboxylic acids, the *N*-phenyl amides (XXV) and *N*-(4-methylphenyl) amides (XXVI) are most excellent because of their ease of preparation and purification. To prepare these derivatives, you must first convert the acid to its acyl halide; then cause it to react with the amine:



(Q-25)



(Q-26)

Preparation of these derivatives is particularly important when the unknown acid is a liquid.

Another aid to identification of a carboxylic acid is determination of its neutralization equivalent which is discussed in detail in Experiment 43.

Preparation of N-Phenyl Amides or N-(4-Methyl)phenyl Amides. Put 0.5 g of the unknown acid and 2 ml of thionyl chloride in a small round-bottom flask, and attach an acid trap if so directed by your instructor. Reflux the mixture on a steam bath for a half-hour; then allow the mixture to cool to room temperature. Dissolve 1 g of benzenamine (aniline) in 25 ml of toluene and cautiously add it to the round-bottom flask containing the acyl chloride. After the addition is complete, heat the mixture for 5 min on a steam or hot water bath. Cool the mixture to room temperature and pour it into a separatory funnel. Wash it successively with 5 ml of water, 5 ml of 5% hydrochloric acid, 5 ml of 5% aqueous sodium hydroxide, and 5 ml of water. Dry the organic layer over anhydrous magnesium sulfate; then distill off the methylbenzene and put it in a recovery container. Evaporate the remaining solvent from a small Erlenmeyer flask on a steam bath. You can blow air gently into the flask to entrain the vapors and hurry things along. Recrystallize the product from ethanol or ethanol/water using the mixed solvent technique. Table Q.5 at the end of Part III lists *N*-phenylamide derivatives of some carboxylic acids.

When working with thionyl chloride and acyl chlorides, you should do all work, including dish washing, in a hood.

HCl gas is a byproduct of the first step. Trap the gas or work in a hood.

The addition of the amine to the acyl chloride is very exothermic; so proceed with caution and slow addition.

Evaporate methylbenzene in a hood.

Q9.5 Identification of Esters

The preparation of derivatives of esters is a fairly complicated procedure. Complete analysis requires preparation of derivatives for both the carboxylic acid and the alcohol portions of the ester. You will need to hydrolyze the ester, separate the alcohol and acid from each other, then prepare the derivatives.

Other aids particularly useful for identification of esters are determination of density, described in Appendix A, and determination of saponification equivalent, described in detail in Experiment 44. Table Q.6 at the end of Part III lists the boiling point, density, equivalent mass (weight), and refractive index of some esters which might be assigned as unknowns.

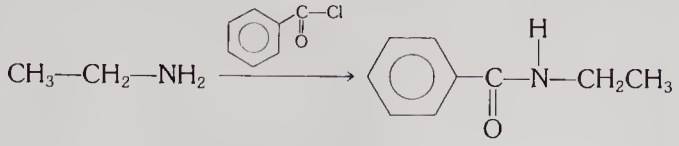
Separation of ester's alcohol and acid. Put 4 KOH pellets, 6 ml of diethylene glycol, and 1 ml of water in a small round-bottom flask and heat the mixture on a steam or hot water bath until dissolution is complete. Cool the mixture to room temperature and mix in 2 ml of ester. Equip the flask with a water-cooled condenser and reflux the mixture for 5 min, using a heating mantle or sand bath on a hot plate if necessary to create reflux. Cool the mixture to near room temperature, equip the flask for small-scale distillation, and distill off the alcohol, taking care to note its distillation temperature. Analyze the alcohol and prepare derivatives. Table Q.1 at the end of Part III lists alcohols and their derivatives.

Add to the pot residue 20 ml of water, then acidify the mixture to pH 1 with 6*M* aqueous HCl. Extract the mixture twice with 10 ml of dichloromethane, dry the solution, and distill off the solvent. Analyze the carboxylic acid residue and prepare derivatives. Table Q.5 at the end of Part III lists carboxylic acids and derivatives.

Q9.6 Identification of Amines

Probably the most common derivatives of primary and secondary amines are the amides of ethanoic (acetic) acid and benzenecarboxylic (benzoic) acid as prepared from the acyl

halides. For example, ethanamine (ethylamine) reacts with benzoyl chloride (IUPAC benzenecarbonyl chloride) as follows:



(Q-27)

Tertiary amines do not form amides, but do react with methyl iodide, yielding crystalline quaternary ammonium salts, for example:

$$Et_3N + CH_3\text{-}I \longrightarrow Et_3N^{\oplus}\text{-}CH_3\ I^{\ominus} \qquad \text{(Q-28)}$$

Preparation of N-phenylamides. Put 0.2 g of the unknown in a 25-ml round-bottom flask and add 2 ml of pyridine. Then add 0.2 ml of benzoyl chloride (IUPAC benzenecarbonyl chloride) dropwise, and heat the mixture to 60 °C on a water bath for 30 min. Pour the mixture into 20 ml of water in a separatory funnel, and shake the funnel for 1 min, periodically releasing pressure. Extract the mixture twice with 10 ml of ether (IUPAC ethoxyethane). Combine the two ether extracts and wash them sequentially with 5 ml of water, 5 ml of 10% hydrochloric acid, and 5 ml of 5% aqueous sodium bicarbonate. Dry the ether layer over anhydrous magnesium sulfate; then distill off the ether on a hot water or steam bath and put it in a recovery container. Recrystallize the solid residue from ethanol or ethanol/water by the mixed solvent technique. Table Q.7 at the end of Part III lists primary and secondary amines and their benzamide derivatives.

Work in a hood. Amines are often toxic, irritating to mucous membranes, and have unsavory odors.

Preparation of quaternary salts. Combine 0.5 g of tertiary amine with 0.5 ml of iodomethane (methyl iodide) in a test tube and warm the mixture on a steam or hot water bath for 5 min. Cool the mixture in an ice-water bath and, if necessary to induce crystallization, scratch the walls of the test tube below the liquid level with a sharp stirring rod. Collect the crystals in a Hirsch funnel and wash them with ice-cold anhydrous methanol. If necessary, recrystallize the product from anhydrous methanol or ethyl acetate (IUPAC ethyl ethanoate). Table Q.8 at the end of Part III lists tertiary amines and their methyl iodide derivatives.

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TABLE Q.1 Alcohols

Alcohol	*bp, °C*	*2-Naphthylurethane mp, °C*	*3,5-Dinitrobenzenecarboxylate mp, °C*
ethanol	78	79	93
2-propanol	83	106	122
2-methyl-2-propanol	83	101	142
1-propanol	97	80	74
2-butanol	99	97	75
1-butanol	116	71	64
3-pentanol	116	71	97
1-hexanol	156	59	58
cyclohexanol	160	128	112
2-heptanol	160	54	49
1-phenylethanol	203	106	95
benzyl alcohol	205	134	112

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XX. Used with permission of John Wiley & Sons, Inc.

TABLE Q.2 Phenols

Phenol	*mp, °C*	*bp, °C*	*2-Naphthylurethane mp, °C*	*Bromo derivative mp, °C*			
				mono	*di*	*tri*	*tetra*
o-chlorophenol	7	175	120		76		
phenol	42	180	133			95	
m-chlorophenol	28	214	158				
p-chlorophenol	37	217	166		90		
p-cresol	36	202	146		49		108
o-iodophenol	43						
o-nitrophenol	45		113		117		
2,4,6-trichlorophenol	67		188				
3,5-dimethylphenol	68					166	
alpha-naphthol	94		152		105		
p-iodophenol	94						
p-nitrophenol	114		151		142		
2,4-dinitrophenol	114			118			

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XLII. Used with permission of John Wiley & Sons, Inc.

TABLE Q.3 Aldehydes and Derivatives

Aldehyde	*bp, °C*	*Semicarbazone mp, °C*	*2,4-Dinitrophenylhydrazone mp, °C*
acetaldehyde	21	162	168
propionaldehyde	48	82	148
acrolein	52	171	165
butyraldehyde	75	95	123
valeraldehyde	102		106
furfural	162	202	212
benzaldehyde	179	222	237
phenylacetaldehyde	195	153	121
salicylaldehyde	197	231	248
p-tolualdehyde	204	234	234

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XXI. Used with permission of John Wiley & Sons, Inc.

TABLE Q.4 Ketones and Derivatives

Ketone	*mp, °C*	*bp, °C*	*Semicarbazone mp, °C*	*2,4-Dinitrophenylhydrazone mp, °C*
acetone		56	187	126
methyl ethyl ketone		80	146	117
diethyl ketone		102	138	156
pinacolone		106	157	125
mesityl oxide		130	164	205
cyclopentanone		131	210	146
methyl amyl ketone		151	123	89
cyclohexanone		156	166	162
acetophenone	20	202	198	238
propiophenone	21	218	182	191
benzophenone	48	305	167	238
4-bromoacetophenone	51	225	208	230

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XXXVII. Used with permission of John Wiley & Sons, Inc.

TABLE Q.5 Carboxylic Acids and Derivatives

Acid	*mp*, °C	*bp*, °C	*N-phenylamide mp*, °C	*Molecular mass, u*
acetic acid	17	118	114	60.05
acrylic acid	13	139	104	72.06
propionic acid		140	103	74.08
methacrylic acid		163		86.09
valeric acid		186	63	102.13
α-chloropropionic acid		186	92	108.53
caproic acid		205	95	116.16
α-bromopropionic acid		205	99	152.99
palmitic acid	62		90	256.42
chloroacetic acid	63		134	94.50
citric acid	100		199	192.12
oxalic acid	101		257	126.07
malonic acid	133d.		224	104.06
acetylsalicylic acid	135		136	180.15
salicylic acid	157		134	138.12
m-chlorobenzoic acid	158		122	156.57

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XIX. Used with permission of John Wiley & Sons, Inc.

TABLE Q.6 Esters and Properties

Ester	*bp*, °C	*Density*, °C, *g/ml*	*Equivalent mass, u*	*Refractive Index*
ethyl acetate	77	0.901, 20	88.10	1.3722
methyl propionate	80	0.915, 20	88.10	1.3777
ethyl propionate	100	0.885, 25	102.13	1.3838
ethyl acrylate	100	0.907, 20	100.11	1.405
methyl methacrylate	100	0.936, 20	100.11	1.413
n-propyl acetate	102	0.877, 20	102.13	1.3844
propyl propionate	123	0.883	116.16	1.3935
n-butyl acetate	126	0.882, 20	116.16	1.3951
dimethyl malonate	181	1.154, 20	66.06	1.4149
ethyl acetoacetate	180	1.025, 20	130.14	1.4209

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XXVII. Used with permission of John Wiley & Sons.

TABLE Q.7 Primary and Secondary Amines and Derivatives

Amine	bp, °C	Benzamide mp, °C
n-propylamine	49	84
diethylamine	55	42
sec-butylamine	63	76
iso-butylamine	69	57
ethylenediamine	116	249
1,2-diaminopropane	120	192
n-hexylamine	128	40
morpholine	130	75
cyclohexylamine	134	149
aniline	183	160
benzylamine	184	105
α-phenylethylamine	185	120
β-phenylethylamine	198	116
o-toluidine	199	143
m-toluidine	203	125
N-ethylaniline	205	60
o-chloroaniline	207	99

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XXIII. Used with permission of John Wiley & Sons, Inc.

TABLE Q.8 Tertiary Amines and Derivatives

Amine	mp, °C	bp, °C	Methiodide mp, °C
p-bromo-*N*-*N*-dimethylaniline	55		185
2,6-dimethylquinoline	60		237
m-nitro-*N*,*N*-dimethylaniline	60		205
8-hydroxyquinoline	75		143d.
p-hydroxy-*N*,*N*-dimethylaniline	76		201
m-hydroxy-*N*,*N*-dimethylaniline	85		182
N,*N*-dimethylbenzylamine		185	179
N,*N*-dimethylaniline		193	228d.
N-ethyl-*N*-methylaniline		201	125
N,*N*-dimethyl-o-toluidine		206	224d.
N,*N*-dimethyl-*p*-toluidine		210	219
tri-*n*-butylamine		211	180
N,*N*-dimethyl-*m*-toluidine		212	177
N,*N*-diethylaniline		218	102

From Shriner, R. L.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1948, Table XXIV. Used with permission of John Wiley & Sons, Inc.

APPENDIXES

APPENDIX A

TECHNIQUES SELDOM USED

A1 Determination of Density

Review Techniques and Principles:

Lab notebook	(1)
Heating and Cooling	(0.5)

INTRODUCTION

Density was at one time one of the important physical constants to be determined for a substance. It is of somewhat lesser importance since spectroscopic methods of identification have become so widespread. Still, it is a property that is often reported and used.

A1.1 DISCUSSION OF DENSITY AND SPECIFIC GRAVITY

Density is defined as the mass of a substance divided by the volume occupied by that mass:

$$d = \frac{\text{mass}}{\text{volume}} \qquad \text{(A1-1)}$$

Density is a measure of how concentrated the mass of a substance or solution is, that is, a measure of how close together the individual particles are. In the metric system, the units of density are g/ml for liquids and solids and g/l for gases. Density is an inverse function of temperature: the higher the temperature, the lower the density. Therefore it is important to report the temperature at which density is determined.

Specific gravity is the density of a substance divided by the density of water:

$$\text{specific gravity} = \frac{d_{\text{substance}}}{d_{\text{water}}} \qquad \text{(A1-2)}$$

In the metric system, density and specific gravity are numerically the same if the density of water was measured at 4 °C, since at this temperature the density of water is 1 (actually, at 3.98 °C the density is 1.000000 g/ml). There are of course no units for specific gravity, and it is customary to report the temperatures at which densities were measured along with the specific gravity. For example, the specific gravity of cyclohexane with density measured at 20 °C and compared to the density of water at 4 °C is 0.7791^{20}.

A1.2 THE TECHNIQUES

There are a number of ways in which density can be measured. We shall discuss three of the more useful methods.

A1.2A Determining Liquid Density with a Volumetric Flask

You can use this method when a reasonably large volume of liquid is available. Tare a volumetric flask along with its stopper on a balance that will supply the desired number of significant figures. Then fill the flask with the liquid in question slightly beyond the mark on the neck of the flask. Adjust the temperature of liquid and flask to the temperature specified on the flask. Now withdraw the excess liquid with a medicine dropper to the point that the lower part of the meniscus rests on the volume line on the neck of the flask. Stopper the flask and weigh it again. Determine the mass of liquid by subtraction and calculate the density, reporting the temperature along with it, as, for example, $0.7791\ g/ml^{20}$.

A1.2B Determining Liquid Density with a Pycnometer

When the volume of liquid is as small as 0.1 ml, density can be determined in a pycnometer, a container designed specifically to measure liquid densities. A **pycnometer** is a modified U tube made of glass tubing. Figure A1.1a illustrates a pycnometer for very small samples. For samples of 1 or 2 ml the pycnometer may have a small bulb at the bottom of the U in order to increase its capacity, as shown in Figure A1.1b.

You can easily make a U tube pycnometer from a 14-cm section of glass tubing with a bore of 2 mm. Two centimeters from one end, bend the tube to a 45° angle, and draw out that bent end to a capillary. Four centimeters from the other end, bend the tube to a 45° angle. Next, bend the tube so that a U is formed with the top of the U at the beginning points of the 45° bends. Put a light scratch on the arm of the tube at the height of the capillary tip of the other arm. This pycnometer will hold about 0.4 ml. Calibrate the pycnometer in the following manner: Using a fine wire, suspend the pycnometer above the pan on a balance and weigh it accurately. Next, fill it with water by suction with a rubber bulb to a point beyond the scratch on the tube arm. Remove the bulb and suspend the tube in a beaker of water at 20 °C for 10 min. Then adjust the amount of liquid in the pycnometer by touching the capillary end with a piece of filter paper until the meniscus in the other arm is at the scratch mark. Remove the pycnometer from the bath, dry it, and accurately weigh it. Calculate the volume of the pycnometer at 20 °C from the density of water at 20 °C (0.9982 g/ml). Record the volume of the pycnometer in your notebook. Immediately blow the pycnometer dry with a gentle stream of air through it. Label the pycnometer and store it so that its capillary tip will not be broken.

To determine the density of any liquid other than water, follow the same procedure as for determining the volume of the pycnometer. The only difference now is that the volume is known and the weight of the liquid is to be determined.

Do not fill a pycnometer by suction with your mouth. Use a rubber bulb.

Before bending glass tubing, check on flame-permit areas and times.

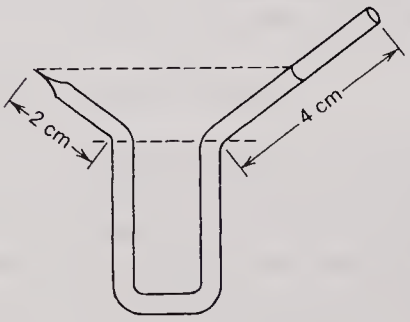
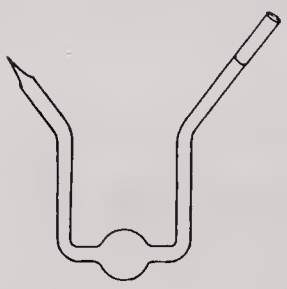


FIGURE A1.1(*a*) U tube pycnometer.



(*b*) U tube pycnometer with bulb.

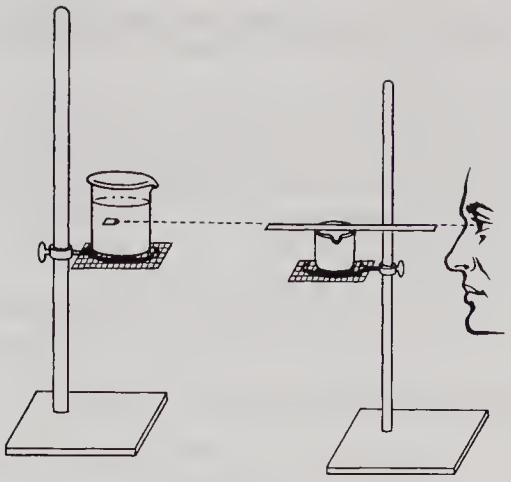


FIGURE A1.2 Checking crystal flotation.

A1.2C Determining Solid Density by Crystal Flotation

In this method, we take the density of a solid to be the same as the density of a nonviscous liquid in which a crystal of the solid will neither sink nor rise. You must use two miscible liquids with a density difference that spans the density of the crystal, and neither of which will appreciably dissolve the crystal.

Put the crystal in a small beaker and add a few milliliters of one of the liquids. The crystal will either sink or float, depending on which liquid was added. Next, add the second liquid slowly with stirring until the crystal remains suspended at the same spot for at least 10 min without sinking or rising. Add the last amounts of liquid dropwise. Make a mark on the beaker at the depth of the crystal and always view it from the same angle. One way to ensure that you do this is to raise or lower the beaker on a ringstand so that the crystal is in line with a straight edge resting across a second beaker or flask, as shown in Figure A1.2. When you are satisfied with the position of the crystal, determine the density of the solution by either method A1.2A or A1.2B.

A2 MOLECULAR MASS

Review Techniques and Principles:

Lab notebook	(1)
Mortar and pestle	(0.10)
Melting points	(3.3)
Sealed tube melting points	(3.3)

INTRODUCTION

Molecular mass (weight), the number of grams per mole, is one of the most important pieces of information for establishing the structure of a compound previously unreported in the literature. It is also sometimes a valuable bit of evidence for identifying an unknown substance.

There are a number of methods for determining molecular mass, but the most accurate and most commonly used method today is mass spectrometry. Of the methods more available within the ordinary laboratory, the most generally used technique is the **Rast method.**

A2.1 DISCUSSION OF THE RAST METHOD

The presence of an impurity in a substance lowers the melting point, and every substance has a molal melting point depression constant. That is, if 1 mole of nonelectrolyte impurity

is dissolved in 1000 g of the substance, the melting point will always be lowered by a fixed number of degrees. The number of degrees is called the *molal melting point depression constant.*

The most precise melting point depression measurements can of course be made when the molal melting point depression constant is large. For this reason, camphor is usually chosen as the solvent substance because its molal melting point depression constant is relatively wide: 39.7 C°/mole. The change in melting point for a known mass of sample dissolved in camphor is

$$\Delta t = \left(\frac{\text{g sample}}{\text{g camphor}}\right)\left(\frac{1000\text{ g camphor}}{\text{m.m. sample}}\right)\left(\frac{39.7\text{ C°}}{\text{mole}}\right) \qquad \text{(A2-1)}$$

Rearrangement to solve for the molecular mass, m.m., of the sample gives

$$\text{m.m.} = \left(\frac{\text{g sample}}{\text{g camphor}}\right)\left(\frac{1000\text{ g camphor}}{\Delta t}\right)\left(\frac{39.7\text{ C°}}{\text{mole}}\right) \qquad \text{(A2-2)}$$

Because camphor sublimes, you must determine the melting points in sealed tubes.

A2.2 THE TECHNIQUES

Tare a small, clean, dry test tube to an appropriate number of significant figures. Put about 0.05 g of sample into the tube and weigh it carefully. Then add about 0.5 g of camphor and again weigh the tube accurately. Next, melt the contents of the test tube to a clear liquid, taking care not to overheat the mixture and not to heat so long that an appreciable amount of camphor sublimes away. Swirl the mixture thoroughly while it is molten, then allow it to solidify. Remove the contents of the tube and grind them in a mortar and pestle to make a fine powder. Put the powdered mixture into a capillary tube, packing it as tightly as possible to a depth of 1–2 cm with a short section of wire. Seal the capillary tube with a flame at a point about 2 cm above the sample. Prepare in the same way a second tube containing pure camphor. Obtain melting points of the two samples in an oil bath, taking the melting point to be the temperature at which the last bit of solid melts (the reported melting point of camphor is 176–177 C°). Obtain several trials on each sample by allowing the sample to refreeze between trials. Take the average of the melting point values as the true melting point. The difference in the melting points of camphor and the mixture is the melting point depression, Δt.

A3 SUBLIMATION

Review Techniques and Principles:

Lab notebook	(1)
Heating	(0.5)
Water aspirator	(4.3)
Suction trap	(7.11)

INTRODUCTION

Sublimation is the process of changing a substance from solid to gas without passing through the liquid state.

Sublimation as a purification technique has some advantages over crystallization: No solvent is necessary, solvated molecules can often be removed from a substance during sublimation, and it is sometimes faster than recrystallization. However, a great disadvantage is that it is a less selective process than recrystallization.

A3.1 DISCUSSION OF PURIFICATION BY SUBLIMATION

Purification by sublimation involves subliming, or vaporizing, a substance in one part of an apparatus and condensing it again in another. It is a sort of distillation from the solid state. To be successful as a method of purification, it requires that either the substance of interest or the impurities sublime, but not both unless their sublimation temperatures are reasonably far apart.

Sublimation is generally a property of relatively nonpolar, symmetrical compounds. Many aromatic compounds, including anthracene, naphthalene (moth balls), *para*-substituted halobenzenes, and many aromatic amines and phenols, sublime quite readily. This is true in general for any solid that has an odor because if it did not have an appreciable vapor pressure you could not smell it.

To sublime many samples readily, you must increase their vapor pressures by gently heating the compound at a very low pressure, preferably at 1 mm Hg or less.

A3.2 THE TECHNIQUES

Assemble a sublimation apparatus like that in Figure A3.1 with the bottom of the cold finger about 1 cm above the impure sample at the bottom of the sidearm test tube. If necessary to get the sample nearer to the cold finger, you can place the apparatus in a horizontal position with the sample laid on the test tube wall beneath the cold finger. With a piece of vacuum hose, connect this sidearm of the test tube to a suction flask trap (Fgure 7.16). Tighten the screw clamp on the trap, and attach the trap to the water aspirator with a section of vacuum hose. Heat the sample carefully with a micro burner at the bottom of the test tube. If the sample starts to melt, remove the burner for a few seconds. When sublimation is complete, remove the heat source, open the screw clamp very slowly so as to not disturb the crystals by a blast of air, and turn off the aspirator. Allow the apparatus to cool; then carefully remove the cold finger so that the sublimed crystals do not fall back into the impure residue. Scrape the crystals with a spatula onto tared weighing paper or directly into a tared vial.

Actually sublimation is most satisfactory if a vacuum pump is used rather than a water aspirator because a much better vacuum is attainable.

Evacuated glassware presents an implosion hazard and should preferably be operated behind a shield.

Check all glassware for stars and cracks; do not use thin-wall glassware for part of the evacuated assembly.

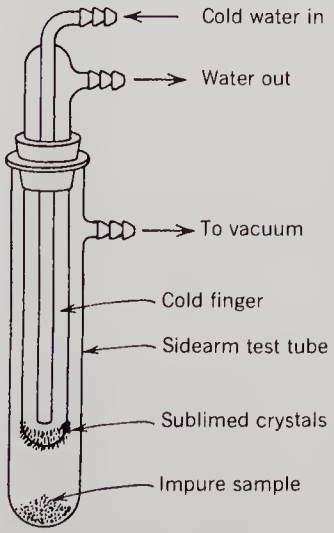


FIGURE A3.1 Sublimation apparatus.

Check with your instructor with regard to flame-permit areas and times for heating the sublimation apparatus.

Evacuated Dewar flasks often used in dry ice-acetone traps should be completely wrapped with friction tape and used behind a safety shield or set inside a protective container.

Be sure you are not touching wet or grounded surfaces when touching or plugging in electrical equipment such as vacuum pumps.

Be certain that moving belts of vacuum pumps are properly guarded. Tie back long hair when working around the pump.

If a manometer is used, the vacuum must be released slowly so that a sudden surge of mercury does not break the manometer and scatter mercury.

APPENDIX B

SIMPLIFIED PRONUNCIATION GUIDE

acacia	uh kay′ shuh
acetanilide	ass et an′ uh lī̄d, ass et an′ uh lid
acetanisole	ass et an′ uh sō̄l
acetic	uh seet′ ik, uh set′ ik
acetone	ass′ e tō̄n
acetophenone	ass ee′ tō̄ fe nō̄n′
acetyl	uh seet′ ul, uh set′ ul, ass′ i tul
acetylate	uh set′ uh lāt
acrolein	uh krō̄′ lee in
acyl	ass ul
acylation	ass uh lay′ shun
acylium	ass il′ ee yum
adherend	ad hir′ und
adsorbent	ad sorb′ unt, ad zorb′ unt
agonist	ag′ uh nist
aldehyde	al′ duh hī̄d
alder	awl′ der
alizarin	uh liz′ uh rin
alkyd	al′ kid
alkyl	al′ kil
alpha	al′ fuh
alumina	uh lōō̄′ min uh
amide	am′ īde, am′id
amido	am′ i duh
amine	uh meen′
amino	uh meen′ ō̄
amyl	am′ il
anhydride	an hī̄′ drī̄d
anil	an′ ul
aniline	an′ uh lin
anisole	an′ i sō̄l
anisotropy	an i sot′ ruh pee
azeotrope	ay′ zee uh trō̄p′
azeotropic	ay′ zee uh trop′ ik
azeotropy	ay′ zee ot′ truh pee
azote	uh zut′
Band	bahnt
Baeyer	bay′ er
Beilstein	bī̄l′ shtīn
benzoyl	ben′ zō̄ ill
Bernoulli	br nōō̄′ lee
beta	bay′ tuh
Büchner	bbok nr
Cannizzaro	kah′ need zah′ rō̄
carbonyl	kar′ buh nil
carboxyl	kar box′ il
casein	kā̄′ seen, kā̄′ see in, kā seen′
cetyl	set′ il, see′ til, set′ eel
Chemisches Zentralblatt	kem′ ish iss Tsen′ trul blaht

chiral	kī′ rul
chlorophyll	klaw′ ruh fill
chromatogram	krō mat′ uh gram
chromatography	krō muh tog′ ruh fee
cirrhosis	si rō′ sis
Claisen	klay′ zun
coniine	kō′ ni een, kō′ni in, kō′ neen
crepe	krāp
cumene	kyōō′ meen
decant	di kant′
delta	del′ tuh
desorb	di zorb′
Dewar	dōō′ er
diazonium	dī uh zō′ nee yum
Diels	deels
diene	dī een′
dienophile	dī een′ uh fīl
drittes	drit′ us
Dupre	dyeh pray′
ebulliator	i bull′ ee ay tr
edema	i dee′ muh
enthalpy	en thal′ pee, en′ thal pee (th as in thick)
entropy	en′ truh pee
epsilon	ep′ si lon
Erganzungswerk	er gen′ tsoongs verk
erstes	ers′ tus
erythema	er i thee′ muh (th as in thick)
esterification	es ter′ if fi kay′ shun
esterify	es ter′ i fī
ethenyl	eth een′ uhl (th as in thick)
ether	ee′ thr (th as in thick)
eutectic	yōō tek′ tik
folic	fō′ lik, fol′ lik
fructose	fruck′ tos
fusel	fyōō′ suhl
gauss	gowss
glycerine	gliss′ r in
glyptal	glip′ tal
Grignard	Green yar′
gypsum	jip′ sum
halide	hā′ līd
haloalkane	hā′ lo al kān′
halogen	hal′ uh jen, hā′ luh jen
Hauptwerk	howpt′ verk
helices	hel′ i seez
Hempel	hem puhl
Hirsch	hirsh
homogeneity	hō′ mō jen ee′ uh tee
hydrolysis	hī drol′ uh sis
imine	i′ meen
Index chemichus	in′ deks kem′ i kus
in situ	in si′ tōō, in sī′ tōō
in vacuo	in vak′ yōō ō
in vivo	in vee′ vō
isoamyl	ī sō am′ il
isoprene	ī′ sō preen

keratin	ker′ uh tin
keto	kee′ tō
ketone	kee′ tōn
kinetics	ki ne′ ticks
Le Chatelier	luh shat el yay′
Leuckart	loy′ kart
lichen	lī′ ken
limonene	lim′ uh neen
luminol	lōō′ min awl
manometer	man o′ muh ter
melanin	mel′ uh nin
mesityl	mes′ i til, mes′ i teel
micelle	mī sell′
mimosa	mi mō′ suh
miscible	miss′ i bl
Neuberg	noy′ berk
nomogram	nom′ uh gram
nucleophile	nōō′ klee uh fīl′
nucleophilic	nōō′ klee uh fil′ ik
olefiant	ō lif′ ee unt, ō luh fī′ unt
omega	ō may′ guh, ō mee′ guh, ō meg′ uh
oxonium	ox ō′ nee yum
pericyclic	per i sik′ lik
pharmacognosy	far muh kog′ nuh see
phene	fen
phenol	fee′ nōl, fee′ nuhl, fuh nawl′
phenolphthalein	fee′ nōl thāl′ een, fee′ nōl fthāl′ een, fee′ nōl thāl′ ee in, (th as in thick)
phenyl	fen′ uhl
phi	fī, fee
pi	pī
pinax	pī′ naks
α-pinene	al′ fuh pī′ neen
Planck	plahnk
polysiloxane	pol′ ee sil ox′ ān
pumice	pu′ miss
pycnometer	pik nom′ i tr
pyrrole	pī rōl′, pir′ ōl
pyruvic	pō rōō′ vik
quinoline	kwin′ uh leen, kwin′ uh lin
racemic	ruh see′ mik
Raoult	rah ōōl′
salicylate	suh liss′ uh lāt
salicylic	sal′ i sil′ ik
saponification	suh pon′ uh fi kay′ shun
säure	zoy′ ruh
sebaceous	si bay′ shus
sebum	see′ bum
silane	sī′ lān
silica	sil′ i kuh
silicone	sil′ i kōn
solute	sol′ yōōt
sublimating	sub′ luh may′ ting
sublimation	sub′ luh may′ shun

subliming	sub lī′ ing
sucrose	sōō′ krōs
Stanislau	stah neez lō′
tau	tow, taw
terpene	tr′ peen
tertiary	tr′ shee er ee
thionyl	thī uh nil
thixotropy	thik sot′ ruh pee
tropeolin	trō pee′ uh lin
vacuum	vak′ yōō um
vehicle	vee′ ik ul
Vigreux	vee′ grō
vinyl	vī′ nil, vī′ nul
Woehler	vay′ lr
xanthophil	zan′ thuh fil
xylene	zī′ leen
zweites	tsvī′ tus

a	= can, at	ī	= ice, mite
ā	= late, cane	o	= on, stop
aw	= awe, raw	ō	= lone, both
ah	= ah ha, on	uh	= mud, under
e	= let, keg	oo	= book, look
ee	= peep, steed	ōō	= soon, loose
i	= dig, pick		

APPENDIX C

CHEMICAL HAZARDS

INTRODUCTION

Your physical well-being depends on use of the information in this appendix. The writer has tried to exercise diligence in listing the compounds that this textbook instructs you to use, as well as the major products of your syntheses. If you should find an omission, use the references listed below or similar literature sources to supply the required information. *Do not begin laboratory work until you have investigated chemical hazards.*

Some references give information that is more detailed than that given herein. They might supply data on acute and chronic effects, on irritants and allergens, and on effects due to inhalation, ingestion, and percutaneous absorption.

DEFINITIONS

Absorption is the uptake of a chemical into the vascular system. It requires passing the substance through skin, mucous membranes, lung tissues, or membranes of the gastrointestinal tract. **Acute** refers to an exposure of relatively short duration with respect to chemicals inhaled, ingested, in contact with tissue, or absorbed through the skin. It refers to a single exposure of seconds to hours. With regard to ingestion, acute refers to a single dose. **Chronic** refers to an exposure of long duration or repeated exposure of days to years. **Local** refers to the toxic effect occurring at the site of exposure. **Systemic** refers to the toxic effect that occurs at a site other than at the point of contact. A systemic effect requires absorption. **Toxicity** is the quality or state of being poisonous. It refers to the ability of a chemical to cause injury once it has reached a susceptible physiological site. **Toxicity hazard** refers to the probability that injury will be caused. **TLV** is the Threshold Limit Value, the time-weighted average concentration for a normal eight hour workday to which nearly all healthy people might be exposed daily without adverse effects. TLV is the maximum recommended concentration permitted in air and is given in parts per million (ppm) for gases and vapors. It is given in milligrams per cubic meter (mg/m^3) for dusts, fumes, and mists. For example, a TLV of 200 ppm would mean that 200 parts of chemical is permitted in 1 million parts of air, for example, 200 molecules per million air molecules. The lower the TLV, the greater is the indication of a hazard. However, each TLV should be evaluated to determine what hazard is being defined (acute, chronic, local, etc.) so that proper precautions can be taken to minimize injury. A **cancer promoter** is a subtance that is involved in the second step of a two-stage process of carcinogenesis. The first step, **initiation,** involves the production of an irreversible cellular change which in itself is not sufficient to produce cancer. The second step, **promotion,** completes the process. Initiation must precede promotion.

USE OF THE TABLE

The compounds are listed in alphabetical order. To find a compound, look for it in the alphabetic section that lists the first letter of the first full word of the compound name. For example, methyl ethanoate would be found in the M section; *N*-(4-chlorophenyl)ethanamide would be listed under C. Numerical prefixes are considered in alphabetizing, that is, tetrachloromethane is listed in the T section.

Toxicity Ratings

Information has been taken from many literature sources, not all of which use the same rating systems. Therefore, given numerical values are *not necessarily those of a toxicologist,* but in some cases only represent the best judgment of the writer. *For greater detail or accuracy, please refer to the literature cited.*

3 Severe toxicity. Body changes will occur which might produce permanent physical impairment and/or disfigurement, or death.

2 Moderate toxicity. Irreversible as well as reversible changes can occur. Moderate toxicity is however not of such magnitude as to immediately threaten life or yield a permanent disorder of serious nature. The quality of future life might be affected, however.

1 Slight toxicity. Changes produced in the body by chemicals of this rating are readily reversible and disappear following termination of exposure.

0 No toxicity known. The chemical causes no toxic effects under any conditions of use or only under very unusual circumstances.

LD50 refers to acute lethal dose to 50% of the test animals.

TLVs are those recommended by the ACGIH (American Conference of Governmental Industrial Hygienists). The TLVs on the following table are listed in ppm except for those enclosed by parentheses, which are mg/m^3. A ceiling, c, designation preceding the TLV denotes the concentration that should not be exceeded during any part of the exposure. The skin, s, notation refers to the potential contribution to the overall exposure by the cutaneous route, including mucous membranes and eyes, either by airborne chemicals or by direct contact with solids and liquids.

If information is not given for a substance, you must be conservative and assume high toxicity. Also you must keep in mind that reaction mixtures often contain many reaction intermediates and products, perhaps unknown to you.

Flammability Ratings

Susceptibility to burning is the basis for assignment of numerical ratings. The method of attacking a fire is influenced by the rating. The fire ratings refer to exposure to flame, spark, or heat (under lamps, in ovens, etc.). These ratings follow the guidelines set up by the National Fire Protection Association.*

4 Very flammable gases or very volatile flammable liquids. Shut off flow and keep cooling water streams on exposed tanks or containers.

3 Materials which can be ignited under almost all normal temperature conditions. Water may be ineffective because of the low flash point.

2 Materials which must be moderately heated before ignition will occur. Water spray may be used to extinguish the fire because the material can be cooled below its flash point.

1 Materials that must be preheated before ignition can occur. Water may cause frothing if it gets below the surface of the liquid and turns to steam. However, water fog gently applied to the surface will cause a frothing which will extinguish the fire.

0 Materials will not burn.

The flash point of the liquid is the minimum temperature at which it gives off sufficient vapor to form an ignitable mixture with the air near the surface of the liquid or within the vessel used. Where available, the flashpoint has been reported in the table in degrees Fahrenheit, as taken from the *Fire Protection Guide on Hazardous Materials* by the NFPA.

*Reprinted with permission from NFPA 704-1985 Standard for the Identification of Fire Hazards of Materials, Copyright © 1985, National Fire Protection Association, Quincy, MA 02269. This reprinted material is not the complete and official position of the NFPA on the referenced subject which is represented only by the standard in its entirety.

Explosivity Ratings

The susceptibility of chemicals to suddenly release energy either by themselves or in combination with water is the basis for assignment of numerical ratings. Conditions of shock, pressure, and fire exposure have been considered in assigning the ratings. These ratings follow the guidelines set up by the National Fire Protection Association, and are reprinted here through the courtesy of this organization.*

4 Materials which (in themselves) are readily capable of detonation or of explosive decomposition or explosive reaction at normal temperatures and pressures. Includes materials which are sensitive to mechanical or localized thermal shock. If a chemical with this hazard rating is in an advanced or massive fire, the area should be evacuated.

3 Materials which (in themselves) are capable of detonation or of explosive decomposition or of explosive reaction but which require a strong initiating source or which must be heated under confinement before initiation. Includes materials which are sensitive to thermal or mechanical shock at elevated temperatures and pressures or which react explosively with water without requiring heat or confinement. Fire fighting should be done from an explosive resistant location.

2 Materials which (in themselves) are normally unstable and readily undergo violent chemical change but do not detonate. Includes materials which can undergo chemical change with rapid release of energy at normal temperatures and pressures or which can undergo violent chemical change at elevated temperatures and pressures. Also includes those materials which may react violently with water or which may form potentially explosive mixtures with water. In advance of massive fires, fire fighting should be done from a safe distance or from a protected location.

1 Materials which (in themselves) are normally stable but which may become unstable at elevated temperatures and pressures or which may react with water with some release of energy but not violently. Caution must be used in approaching the fire and applying water.

0 Materials which (in themselves) are normally stable even under fire exposure conditions and which are not reactive with water. Normal fire fighting procedures may be used.

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Acknowledgments

The writer thanks The Dow Chemical Company for supplying information on chemical hazards not readily available in the literature, and also thanks Deborah Banaszak and Jennifer Stewart for literature searches.

TOXICITY TABLE

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
acetaldehyde							see ethanal
acetanilide							see *N*-phenylethanamide
acetanisole							see 1-(4-methoxyphenyl)ethanone
acetic acid							see ethanoic acid
acetic anhydride							see ethanoic anhydride
acetone							see propanone
acetophenone							see 1-phenylethanone
acetylsalicylic acid							see 2-ethanoyloxybenzenecarboxylic acid
acrolein							see 2-propenal
acrylic acid							see propenoic acid
ammonium tartrate							USED IN TOPICAL EYE MEDICINALS.
t-amyl alcohol							see 2-methyl-2-butanol
t-amyl chloride							see 2-chloro-2-methylbutane
aniline							see benzenamine
anisole							see methoxybenzene
anthracene	1			1	250		MAY BE CARCINOGENIC DUE TO COMMONLY ASSOCIATED IMPURITIES. WASH WITH SOAP AND WATER.
azine	2	2	5	3	68	0	EYE, SKIN, RESPIRATORY TRACT IRRITANT. CAN BE ABSORBED VIA SKIN AND INHALATION. CNS DEPRESSANT. KIDNEY, LIVER DAMAGE. CAN REACT EXPLOSIVELY WITH OXIDIZERS. VAPORS EXPLOSIVE WITH SPARK. EMITS CYANIDES IF HEATED TO DECOMPOSITION.
benzaldehyde							see benzenecarbonal
benzene	2	2	10	3	12	0	CAN BE ABSORBED THROUGH SKIN. SUSPECT HUMAN CARCINOGEN. DESTROYS ABILITY OF BONE MARROW TO MAKE RED CELLS; EFFECT IS CUMULATIVE. CNS DEPRESSANT. WASH WITH SOAP AND WATER; RINSE WITH WATER FOR PROLONGED PERIOD.
benzenamine		3	(S) 2	(2)	158	0	CAN BE ABSORBED VIA SKIN AND INHALATION. SPILLS ON SKIN AND CLOTHING CAN CAUSE SERIOUS METHEMOGLOBINEMIA AND ANOXEMIA. REMOVE VICTIM FROM AREA OF EXPOSURE. WASH WITH WATER; REMOVE CONTAMINATED CLOTHING. CAN REACT VIGOROUSLY WITH OXIDIZERS.

adipoyl chloride						see hexanedioyl chloride
alumina	1	0	(10)	0		0 SOME RECORD OF LUNG DAMAGE BY INHALATION. WASH FROM SKIN WITH SOAP AND WATER.
aluminum chloride	3			0		0 CAN BE VIOLENTLY EXOTHERMIC WITH WATER; PRODUCES HCL GAS. CAN CAUSE SEVERE CHEMICAL BURNS. WASH FROM SKIN WITH SOAP AND WATER, FOLLOWED BY 15 MIN RINSE. ORAL RAT LD50: 3700 MG/KG.
aminobenzene						see benzenamine
4-aminobenzenesulfonamide						ORAL MOUSE LD50: 621 MG/KG. SUSPECT CARCINOGEN. IMPLICATED IN APLASTIC ANEMIA.
ammonium carbonate	1			0		0 SUBCUTANEOUS MOUSE LD50: 96 MG/KG. MILD SKIN IRRITANT; EYE IRRITANT.
ammonium formate						see ammonium methanoate
ammonium hydroxide, concentrated	2		(18)			CAN PRODUCE IRRITATING FUMES AND CHEMICAL BURNS. WASH SKIN AND/OR EYES THOROUGHLY FOR 30 MIN.
ammonium methanoate						ORAL MOUSE LD50: 2250 MG/KG. MODERATE ORAL TOXICITY.
ammonium sulfate	1			0		0 MELTS AND DECOMPOSES AT 235 C, EMITTING AMMONIA AND SULFUR TRIOXIDE. ORAL RAT LD50: 300 MG/KG. CAN REACT VIOLENTLY WITH ACTIVE METALS OR OXIDIZERS.
benzenecarbonal	1	2		2	145	0 CAN CAUSE HEADACHE, NAUSEA, VOMITING, CONTACT DERMATITIS. CNS DEPRESSANT. WASH WITH SOAP AND WATER. ORAL RAT LD50: 1300 MG/KG.
benzenecarbonyl chloride	2			2	162	1 HIGHLY IRRITATING TO EYES AND NOSE. CAN CAUSE CHEMICAL BURNS. POTENTIAL CARCINOGEN. REACTS WITH WATER TO PRODUCE HCL. DANGEROUS WITH HEATED, GENERATING PHOSGENE. REACTS VIGOROUSLY WITH OXIDIZERS. WASH WITH SOAP AND WATER.
benzenecarboxylic acid	1	1		1	250	0 USED AS FOOD PRESERVATIVE. ORAL RAT LD50: 2530 MG/KG. LOWEST PUBLISHED HUMAN TOXIC DOSE: 6 MG/KG.
benzenediazonium chloride		3				4 DANGEROUS IF DRY: EXPLODES WITH HEAT OR SHOCK. POTENTIAL CARCINOGEN. WASH WITH WATER.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
1,2-benzenedicarboxylic anhydride	1		1	1	305	0	DUST AND VAPORS IRRITATE EYES, MOIST SKIN, AND RESPIRATORY TRACT. SUBLIMES AND YIELDS FLAMMABLE VAPORS WHEN HEATED. DUST CAN FORM EXPLOSIVE MIXTURES WITH AIR.
benzenesulfonyl chloride	1	3					MODERATE ACUTE ORAL TOX IN RATS. WASH SKIN WITH SOAP AND WATER FOLLOWED BY 15 MIN RINSE.
benzenol	3	3	S 5	2	175	0	SEVERE CHEMICAL BURNS TO EYES, MUCOUS MEMBRANES, AND SKIN. DEATH CAN COME AS EARLY AS 30 MIN FROM SPILLS ON SKIN OF 64 IN^2 AREA. KIDNEY, LIVER DAMAGE. CANCER PROMOTER IN MICE. REMOVE VICTIM FROM AREA AND IMMEDIATELY REMOVE CONTAMINATED CLOTHING. SOAP AND WATER WASH.
benzoic acid							see benzenecarboxylic acid
benzophenone							see diphenylmethanone
benzoyl chloride							see benzenecarbonyl chloride
benzoyl peroxide	2		(5)	4		4	EYE, SKIN, MUCOUS MEMBRANE IRRITANT. DECREASED HEART RATE; INCREASED TEMPERATURE. SPONTANEOUSLY EXPLOSIVE AT HIGH TEMPERATURES. DRY POWDER VERY SENSITIVE TO SHOCK, HEAT AND FRICTION. SOAP AND WATER WASH.
benzyl alcohol							see phenylmethanol
benzylamine							see phenylmethanamine
benzyl chloride							see chloromethylbenzene
benzyl triethylammonium chloride							
boric acid	2						AFFECTS SKIN AND CENTRAL NERVOUS SYSTEM. HAS PRODUCED EXPERIMENTAL NEOPLASMS (ABNORMAL GROWTHS).
bromine	3		0.1				IRRITATES EYES, RESPIRATORY TRACT. PULMONARY EDEMA FROM SEVERE EXPOSURE. CHEMICAL BURNS. DIZZINESS, HEADACHE, PNEUMONIA. LEAVE AREA OF CONTACT. SOAP AND WATER WASH.
4-bromoacetophenone							see 1-(4-bromophenyl)ethanone

bromobenzene	2	1		2	124	0	EYE, SKIN, MUCOUS MEMBRANE IRRITANT. INHALATION MIGHT CAUSE PARALYSIS. LEAVE AREA OF CONTACT. SOAP AND WATER WASH; aq RINSE.
1-bromobutane	2	2		3	65	0	
2-bromobutane	2	2		3	70	0	
1-bromo-*N*,*N*-dimethylbenzenamine							see 2-bromo-*N*,*N*-dimethylbenzenamine
2-bromo-*N*,*N*-dimethylbenzenamine							CAN EXPLODE WHEN HEATED.
bromoform							see tribromomethane
1-(4-bromophenyl)ethanone						0	WHEN STRONGLY HEATED EMITS TOXIC FUMES.
2-bromo-2-methylbutane	3			3	90	0	
2-bromo-2-methylpropane				3		0	
2-bromopropane	3	3		3		0	
2-bromopropanoic acid	3						HIGH ORAL TOXICITY. WHEN HEATED TO DECOMPOSITION, IT EMITS TOXIC FUMES OF Br.
α-bromopropionic acid							see 2-bromopropanoic acid
bromophenol blue							
bromthymol blue							
butanal	2	2		3	8	0	CHEMICAL BURNS TO EYES, MUCOUS MEMBRANE, RESPIRATORY TRACT. SKIN IRRITANT. CAN REACT WITH OXIDIZERS. VAPORS FORM EXPLOSIVE MIXTURES WITH AIR. EASILY IGNITED, AND FIRES ARE HARD TO CONTROL DUE TO EASE OF REIGNITION. GIVE ARTIFICIAL RESPIRATION IF NECESSARY FROM INHALATION.
2-butanamine	3	3	S C5	3	15		CHEMICAL BURNS TO EYES. SKIN IRRITANT. CAN BE ABSORBED THROUGH SKIN; CAUSES NAUSEA, VOMITING, SHOCK. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME.
butanedioic acid	2						GENERAL PURPOSE FOOD ADDITIVE
1-butanol	1	2	150	3	98	0	EYE, SKIN, NOSE, THROAT IRRITANT; CNS DEPRESSANT. CAUSES HEADACHE. LEAVE AREA OF CONTACT.
2-butanol	2	2	150	3	75	0	EYE, SKIN, NOSE, THROAT IRRITANT; CNS DEPRESSANT—DIZZINESS, HEADACHE. LEAVE AREA OF CONTACT.
2-butanone	1	2	200	3	16	0	SAME EFFECTS AS 2-BUTANOL
n-butyl acetate							see butyl ethanoate
t-butyl alcohol							see 2-methyl-2-propanol
s-butylamine							see 2-butanamine

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
s-butyl bromide							see 2-bromobutane
t-butyl bromide							see 2-bromo-2-methylpropane
t-butyl chloride							see 2-chloro-2-methylpropane
butyl ethanoate	1	2	150	3	72	0	HIGH CONCENTRATION, IRRITATES EYES, RESPIRATORY TRACT. SOAP AND WATER WASH, aq RINSE.
butyraldehyde							see butanal
t-butyl perbenzoate	2			3	>190	4	EYE, SKIN, MUCOUS MEMBRANE IRRITANT. COMPLETE DATA NOT AVAILABLE. REACTIVE, FLAMMABLE, OXIDIZING LIQUID. VAPORS FORM FLAMMABLE MIXTURES WITH AIR. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. CAN REACT VIOLENTLY WITH OXIDIZABLE COMPOUNDS. SOAP AND WATER WASH.
caffeine	0	2					ORAL DOSE > 1 G CAN CAUSE CARDIAC PALPITATION, INSOMNIA, DIZZINESS, HEADACHE.
calcium chloride, anhydrous	2						EYE, MUCOUS MEMBRANE, SKIN IRRITANT.
calcium hydroxide	2		(5)				EYE, MUCOUS MEMBRANE, SKIN IRRITANT. CAN CAUSE DERMATITIS. SOAP AND WATER WASH.
calcium phosphate	2						EYE, RESPIRATORY TRACT IRRITANT; INHALATION OF DUST CAUSES DIFFICULTY IN BREATHING. REMOVE TO CLEAN AIR ENVIRONMENT. INDUCE VOMITING IF INGESTED.
camphor	2	2	2	2	150	0	
caproic acid							see hexanoic acid
carbon, decolorizing	1	0	3.5				DUST CAN IRRITATE EYES AND MUCOUS MEMBRANES. SOAP AND WATER WASH.
carbon dioxide, dry ice	3						CAN QUICKLY FREEZE TISSUE.
carbon disulfide							see dithioxomethane
carbon tetrachloride							see tetrachloromethane
3-carboxy-3-hydroxy-propanedioic acid		0					INHALATION OF DUST IRRITATES NOSE AND THROAT.
catechol							see 1,2-dihydroxybenzene
chloroacetic acid							see chloroethanoic acid
o-chloroaniline							see 2-chlorobenzenamine

chlorobenzene	1	2	75	3	82	0	CNS DEPRESSANT. PROLONGED EXPOSURE BY INHALATION OR PERCUTANEOUSLY CAN DAMAGE LIVER, KIDNEYS. CAN BE ABSORBED THROUGH INTACT SKIN. EYE IRRITANT. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. REMOVE FROM AREA OF INHALATION.
2-chlorobenzenamine	1	3					READILY ABSORBED THROUGH SKIN. INHALATION AND SPILLS ON SKIN AND CLOTHING CAN CAUSE SERIOUS METHEMOGLOBINEMIA AND ANOXEMIA. REMOVE FROM AREA OF EXPOSURE.
3-chlorobenzenecarboxylic acid							MIGHT BE SKIN IRRITANT. EYE IRRITANT. WASH SKIN WITH SOAP AND WATER, 15 MIN RINSE.
2-chlorobenzenol	3	3		2	147	0	POTENTIAL CANCER PROMOTER. ORAL RAT LD50: 670 MG/KG. RAPID ABSORPTION THROUGH SKIN LIKELY. CNS POISON. WASH SKIN IMMEDIATELY AND THROUGHLY WITH SOAP AND WATER. SEE BENZENOL.
3-chlorobenzenol	3	3					POTENTIAL CANCER PROMOTER. ORAL RAT LD50: 570 MG/KG. RAPID ABSORPTION THROUGH SKIN LIKELY. CNS POISON. EMITS HIGHLY TOXIC FUMES WHEN HEATED TO DECOMPOSITION. WASH SKIN IMMEDIATELY AND THROUGHLY WITH SOAP AND WATER. SEE BENZENOL.
4-chlorobenzenol	3	3		1	250	0	POTENTIAL CANCER PROMOTER. ORAL RAT LD50: 500 MG/KG. RAPID ABSORPTION THROUGH SKIN LIKELY. CNS POISON. WASH SKIN IMMEDIATELY AND THROUGHLY WITH SOAP AND WATER. SEE BENZENOL.
m-chlorobenzoic acid							see 3-chlorobenzenecarboxylic acid
chloroethanoic acid	2			1	302	0	STRONG SKIN AND RESPIRATORY TRACT IRRITANT. CAUSES EYE, SKIN, AND MUCOUS MEMBRANE BURNS.
chloroform							see trichloromethane
chloromethylbenzene	3	3	1	2	153	1	EYE, SKIN, AND RESPIRATORY TRACT IRRITANT. IN PRESENCE OF ACTIVE METALS IT UNDERGOES CONDENSATION REACTION WHICH CAN BE VIOLENT.
2-chloro-2-methylbutane	1			3	55	0	MODERATE FIRE HAZARD VIA HEAT, FLAME, SPARKS, OXIDIZERS.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
2-chloro-2-methylpropane				3	<32	0	DANGEROUS FIRE HAZARD VIA HEAT, FLAME, SPARKS, OXIDIZERS.
m-chlorophenol							see 3-chlorobenzenol
o-chlorophenol							see 2-chlorobenzenol
p-chlorophenol							see 4-chlorobenzenol
2-chloropropanoic acid	2	2		1	225	0	MODERATE TOXICITY
a-chloropropionic acid							see 2-chloropropanoic acid
chromic oxide or acid	3			0	—	1	CAUSES DEEP, PENETRATING SKIN ULCERS. INHALATION OF CHROMATE SALTS HAS BEEN ASSOCIATED WITH LUNG CANCER. BLINDNESS EASILY OCCURS. POWERFUL OXIDIZER.
citric acid							see 3-carboxy-3-hydroxypropanedoic acid
copper powder	1	2	(1)				HAS REACTED VIOLENTLY WITH HYDRAZOIC ACID, ACETYLENE, AZIDES, ETHYLENE OXIDE, AND CERTAIN OXIDERS.
copper(I) chloride	1	2					
copper(II) ethanoate	1	2					ORAL RAT LD50: 595 MG/KG. MIGHT BE SKIN IRRITANT.
p-cresol							see 4-methylbenzenol
cupric acetate							see copper(II) ethanoate
cyclohexanamine	2		10	3	88	0	SEVERELY CAUSTIC. INHALATION OR CONTACT WITH LIQUID CAUSES SEVERE SKIN AND EYE BURNS. REACTS WITH OXIDIZERS. EMITS HIGHLY TOXIC FUMES WHEN DECOMPOSED.
cyclohexane	2	2	300	3	−4	0	CNS DEPRESSANT; HEADACHE, DIZZINESS, NAUSEA, UNCONSCIOUSNESS. LEAVE AREA OF CONTACT. ORAL MOUSE LD50: 1297 MG/KG.
cyclohexanol	1	2	50	2	154	0	EYE, RESPIRATORY TRACT, SKIN IRRITANT. CAN CAUSE CORNEAL NECROSIS. SOAP AND WATER WASH; LONG RINSE.
cyclohexanone	2	1	S-25	2	111	0	THROAT AND EYE IRRITANT. CNS DEPRESSANT. SOAP AND WATER WASH; LONG RINSE. ORAL RAT LD50: 1620 MG/KG.

cyclohexene		2	300	3	<20	0	EYE, MUCOUS MEMBRANE, SKIN IRRITANT. CNS DEPRESSANT. DANGEROUS WHEN EXPOSED TO FLAME OR SPARK. SOAP AND WATER WASH FROM SKIN.
cyclohexyl alcohol							see cyclohexanol
cyclohexylamine							see cyclohexanamine
cyclopentanone	2			3	79	0	SKIN IRRITANT. CNS DEPRESSANT. DANGEROUS WHEN EXPOSED TO FLAME. MODERATE TOXICITY PROBABLE VIA ORAL AND INHALATION ROUTES.
1,2-diaminoethane	2	2	10	2	93	0	LIQUID AND HIGH CONC OF VAPOR BURNS EYES; IRRITATES NOSE AND THROAT. SKIN BURNS FROM LIQUID WHEN HEATED TO DECOMPOSITION; IT EMITS TOXIC FUMES OF NITROGEN OXIDES. VAPOR FORMS FLAMMABLE MIXTURES WITH AIR.
1,2-diaminopropane	2	2		3	92	0	
diatomaceous earth	2						CAN CAUSE LUNG FIBROSIS IF INHALED FOR PROLONGED PERIODS. ORAL RAT LD50: 3160 MG/KG.
dibenzoyl peroxide							see benzoyl peroxide
N,N-dibutylbutanamine	2			2	187	0	SEVERE EYE IRRITATION. MUCOUS MEMBRANE AND SKIN IRRITANT. VERY DANGEROUS NEAR FLAME OR HEAT. EMITS TOXIC FUMES WHEN HEATED TO DECOMPOSITION. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. GIVE ARTIFICIAL RESPIRATION IF NECESSARY.
1,4-dichlorobenzene	2	2	75	2	150	0	HAS BEEN REPORTED TO CAUSE LIVER DAMAGE IN HUMANS. AN INSECTICIDE. HIGH TOXICITY BY ORAL ROUTE; MODERATE BY INHALATION. EXPERIMENTAL CARCINOGEN IN ANIMALS. CAN REACT VIGOROUSLY WITH OXIDIZERS. SOAP AND WATER WASH FROM SKIN.
7,7-dichlorobicyclo[4.1.0]heptane							
dichloromethane	2	2	100	1	NONE	0	STRONG EYE, MUCOUS MEMBRANE, SKIN IRRITANT. STRONG CNS DEPRESSANT. PRODUCES CANCER IN SOME TEST ANIMALS SOAP AND WATER WASH; LONG RINSE. LEAVE AREA OF CONTACT.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
7,7-dichloronorcarane							see 7,7-dichlorobicyclo[4.1.0]heptane
diethylamine							see *N*-ethylethanamine
diethyl ether							see ethoxyethane
diethyl ketone							see 3-pentanone
N,N-diethylaniline							see *N,N*-diethylbenzenamine
N,N-diethylbenzenamine				2	185	0	
diethylene glycol							see 1,2-di(2-hydroxyethoxy)ethane
diethyl malonate							see diethyl propanedioate
N,N-diethyl-4-methyl-benzamide							see *N,N*-diethyl-4-methylbenzenecarboxamide
N,N-diethyl-4-methyl-benzenecarboxyamide							
diethyl propanedioate				1	200	0	
1,2-dihydroxybenzene	3	3	5	1	260	0	SEVERE CHEMICAL BURNS TO EYES, MUCOUS MEMBRANES, SKIN. DANGEROUS BY SKIN ABSORPTION. POTENTIAL CANCER PROMOTER. CAN CAUSE CONVULSIONS, BLOOD DAMAGE. IMMEDIATELY REMOVE VICTIM FROM AREA OF CONTACT; REMOVE CONTAMINATED CLOTHING; USE SOAP AND WATER WASH, LONG RINSE.
1,2-di(2-hydroxyethoxy)ethane	1	2		1	255	0	GLYCOL ETHERS ARE GENERALLY QUITE TOXIC BY INGESTION.
N,N-dimethylaniline							see *N,N*-dimethylbenzenamine
N,N-dimethylbenzenamine	3		S 5	2	145	0	CNS DEPRESSANT. CAUSES WEAKNESS, TREMORS, CYANOSIS. SKIN AND EYE IRRITANT. MODERATE FIRE HAZARD. CAN REACT WITH OXIDIZERS. EMITS HIGHLY TOXIC FUMES WHEN HEATED TO DECOMPOSITION. DERMAL RABBIT LD50: 1770 MG/KG.
dimethylbenzenes, mixed isomers	1	1	S 100	3	81–90	0	VAPORS IN HIGH CONCENTRATION ARE CNS DEPRESSANTS. SKIN AND RESPIRATORY TRACT IRRITANT. VAPORS FORM EXPLOSIVE MIXTURES WITH AIR.
dimethyl 1,2-benzenedicarboxylate	2	2	(5)	1	295	0	ORAL RAT LD50: 7 ML/KG. IRRITATING TO MUCOUS MEMBRANES AND EYES. INGESTION LEADS TO CNS DEPRESSION.

N,N-dimethylbenzylamine							see *N*-methyl-*N*-phenylmethylmethanamine
3,5-dimethylbenzenol	3	3		3		0	EYE IRRITANT. POTENTIAL CANCER PROMOTER. WHEN HEATED TO DECOMPOSITION, IT PRODUCES ACRID SMOKE AND FUMES. ORAL RAT LD50: 608 MG/KG. EXPERIMENTAL CARCINOGEN VIA SKIN.
2,3-dimethyl-2,3-butanediol dimethyl malonate							see dimethyl propanedioate
N,N-dimethyl-2-methylbenzenamine	2	3		2		0	MODERATE ORAL TOXICITY. EMITS FUMES OF NITROGEN OXIDES WHEN HEATED TO DECOMPOSITION.
N,N-dimethyl-3-methylbenzenamine	2	3		2		0	
N,N-dimethyl-4-methylbenzenamine	2	3		2		0	
3,5-dimethylphenol							see 3,5-dimethylbenzenol
dimethyl phthalate							see dimethyl 1,2-benzenedicarboxylate
dimethyl propanedioate	2			1		0	SKIN IRRITANT. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION.
2,6-dimethylquinoline		3		1		0	
N,N-dimethyl-*o*-toluidine							see *N,N*-dimethyl-2-methylbenzenamine
N,N-dimethyl-*m*-toluidine							see *N,N*-dimethyl-3-methylbenzenamine
N,N-dimethyl-*p*-toluidine							see *N,N*-dimethyl-4-methylbenzenamine
3,5-dinitrobenzenecarbonyl chloride	3						POWERFUL SKIN, MUCOUS MEMBRANE IRRITANT. DANGEROUS TO EYES. HIGH TOXICITY VIA SKIN, ORAL, OR INHALATION ROUTES. IMMEDIATE SOAP AND WATER WASH.
3,5-dinitrobenzenecarboxylic acid							
2,4-dinitrobenzenol	3	3		1		4	INHALATION OF DUST HAS BEEN FATAL. SKIN IRRITANT; CAN CAUSE DERMATITIS. LOWEST REPORTED HUMAN LETHAL DOSE: 36 MG/KG. MODERATE TOX VIA SKIN.
3,5-dinitrobenzoic acid							see 3,5-dinitrobenzenecarboxylic acid
3,5-dinitrobenzoyl chloride							see 3,5-dinitrobenzenecarbonyl chloride
2,4-dinitrophenol							see 2,4-dinitrobenzenol
2,4-dinitrophenylhydrazine	3	3		1		3	
1,4-dioxane	1	3	S 25	3	54	1	EYE AND MUCOUS MEMBRANE IRRITANT. REPEATED EXPOSURE TO LOW CONCENTRATIONS HAS PROVEN FATAL. CAN BE ABSORBED THROUGH SKIN. VAPORS FORM EXPLOSIVE MIXTURES WITH AIR OVER A WIDE CONCENTRATION RANGE. CAN FORM EXPLOSIVE PEROXIDES.
diphenyl ketone							see diphenylmethanone

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
diphenylmethanone	2			2		1	EYE AND SKIN IRRITANT, WHEN HEATED TO DECOMPOSITION, IT EMITS ACRID AND IRRITATING FUMES. ORAL MOUSE LD50: 2895 MG/KG.
dithioxomethane	1	3	S 10	3	−22	0	POWERFUL CNS DEPRESSANT. PERMANENT CENTRAL AND PERIPHERAL NERVE DAMAGE POSSIBLE. EASILY ABSORBED THROUGH SKIN. VAPORS CAN IGNITE BY CONTACT WITH AN ORDINARY INCANDESCENT BULB. FORMS EXPLOSIVE MIXTURES WITH AIR OVER A WIDE RANGE OF CONCENTRATIONS.
ethanal	3	2	100	4	−38	2	CNS DEPRESSANT; EYE AND SKIN IRRITANT. SEVERE FIRE AND EXPLOSION HAZARD. GIVE ARTIFICIAL RESPIRATION IF NECESSARY FROM INHALATION. WASH SKIN WITH SOAP AND WATER; WATER RINSE.
1,2-ethanediamine							see 1,2-diaminoethane
ethanedioic acid	3	3	(1)	1		0	EYE AND RESPIRATORY TRACT IRRITANT. CAN QUICKLY BE FATAL BY INGESTION. EMITS HIGHLY TOXIC FUMES WHEN BURNED. COMBUSTIBLE BELOW 215 °F. CAN REACT EXPLOSIVELY WITH STRONG OXIDIZERS. LOWEST ORAL HUMAN LETHAL DOSE: 100 MG/KG.
1,2-ethanediol	0	2	C 50	1	232	0	
ethanoic acid, glacial	3		10	2	103	1	CAN CAUSE SEVERE CHEMICAL BURNS. EYE, SKIN, RESPIRATORY TRACT IRRITANT. ANHYDROUS VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. DANGEROUS IN CONTACT WITH OXIDIZERS.
ethanoic anhydride	3		5	2	120	1	POWERFUL EYE, SKIN, RESPIRATORY TRACT IRRITANT. CAN CAUSE SEVERE CHEMICAL BURNS. SKIN QUICKLY WRINKLES, WHITENS, PEELS. IMMEDIATE AQUEOUS WASH. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR.

ethanol	1	2	1000	3	55	0	MUCOUS MEMBRANE IRRITANT. ORAL RAT LD50: 21,000 MG/KG. EXPERIMENTAL CARCINOGEN. EXPOSURE TO OVER 1000 PPM VAPOR CAN LEAD TO HEADACHE, EYE, NOSE, THROAT IRRITATION. DANGEROUS WHEN EXPOSED TO HEAT, SPARK, FLAME.
4-ethanoylamino-benzenesulfonamide 4-ethanoylamino-benzenesulfonyl chloride							MODERATE ORAL ACUTE TOX IN RATS.
2-ethanoyloxybenzenecarboxylic acid	2	1	(5)				10 G INGESTED DOSE CAN BE FATAL. AN ALLERGEN. CONTACT, INGESTION, INHALATION CAN CAUSE ASTHMA. EYE AND NOSE IRRITANT. LOW FIRE HAZARD.
ether							see ethoxyethane
ethoxyethane	2	2	400	4	−49	1	CNS DEPRESSANT. VAPOR-AIR MIXTURES ARE FLAMMABLE OVER A WIDE RANGE OF CONCENTRATIONS; READILY IGNITED BY FLAMES OR SPARK. UNSTABLE PEROXIDES CAN FORM WHEN ETHER IS EXPOSED TO OXYGEN IN AIR, TO SUNLIGHT, OR ON LONG STANDING.
ethyl acrylate							see ethyl propenoate
N-ethylethanamine	3		10	3	−9	0	CORROSIVE TO EYES, SKIN AND RESPIRATORY TRACT. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. WASH FROM SKIN WITH SOAP AND WATER.
ethyl acetate							see ethyl ethanoate
ethyl acetoacetate							see ethyl 3-oxobutanoate
ethyl alcohol							see ethanol
N-ethylaniline							see *N*-ethylbenzenamine
N-ethylbenzenamine	1	3		2	185	0	ORAL RAT LOWEST REPORTED LETHAL DOSE: 300 MG/KG. HIGHLY IRRITATING TO SKIN, MUCOUS MEMBRANES, EYES. ALLERGEN. HIGHLY DANGEROUS WHEN OVERHEATED—DECOMPOSES TO GIVE HIGHLY TOXIC FUMES. SOAP AND WATER RINSE.
ethylenediamine							see 1,2-diaminoethane
ethylene glycol							see 1,2-ethanediol

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
ethyl ethanoate	1	2	400	3	24	0	EYE, RESPIRATORY TRACT IRRITANT. MILD CNS DEPRESSANT. ORAL RAT LD50: 11,00 MG/KG. CAN CAUSE DERMATITIS. SOAP AND WATER WASH.
N-ethyl-*N*-methylaniline							see *N*-ethyl-*N*-methylbenzenamine
N-ethyl-*N*-methylbenzenamine	1	3		2		0	
ethyl 3-oxobutanoate	2	2		2	135	0	ORAL RAT LD50: 3980 MG/KG. CAN REACT WITH OXIDIZERS. MODERATE IRRITANT TO SKIN, MUCOUS MEMBRANES. SOAP AND WATER WASH.
ethyl propanoate	1			3	54	0	SKIN IRRITANT. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. ORAL RAT LD50: 3500 MG/KG. CAN REACT VIGOROUSLY WITH OXIDERS. SOAP AND WATER WASH.
ethyl propenoate	3	3	S 5	3	50	2	CAN CAUSE EDEMA AND VASCULAR DAMAGE IN SKIN. VAPORS BURN EYES AND SKIN AND IRRITATE RESPIRATORY TRACT. CAN REACT VIGOROUSLY WITH OXIDIZERS. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION. GIVE ARTIFICIAL RESPIRATION IF NECESSARY. SOAP AND WATER WASH.
ethyl propionate							see ethyl propanoate
ferric hydroxamate	1						
ferric chloride	1			(1)			ORAL RAT LD50: 900 MG/KG. WHEN HEATED TO DECOMPOSITION EMITS TOXIC FUMES OF HCL. REACTS WITH WATER TO PRODUCE TOXIC AND CORROSIVE FUMES.
ferrous ammonium sulfate	1						
furan							see oxole
furfural							see oxole-2-carbonal
glycerine							see 1,2,3-propanetriol
heptane	2	2	400	3	25	0	
2-heptanol	2			2	160	0	MODERATE EYE AND SKIN IRRITANT. MODERATE FIRE HAZARD. CAN REACT WITH OXIDIZERS. ORAL RAT LD50: 2580 MG/KG.
2-heptanone	2	2	50	2	102	0	CNS DEPRESSANT IN HIGH CONCENTRATION. MUCOUS MEMBRANE IRRITANT. ORAL RAT LD50: 2600 MG/KG. EYE, MUCOUS MEMBRANE IRRITANT. ANESTHETIC IN HIGH CONC.

hexadecanoic acid	1						MILD SKIN IRRITANT. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION.
hexanamine	3			3	85	0	EYE, MUCOUS MEMBRANE, SKIN IRRITANT. HIGH SKIN AND INHALATION TOXICITY. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. REACTS WITH OXIDIZERS.
hexane	1	1	50	3	−7	0	LOWEST INHALATION MOUSE LETHAL DOSE: 120,000 MG/KG.
1,6-hexanediamine	2						MODERATE IRRITANT TO SKIN, EYES, MUCOUS MEMBRANES.
hexanedioic acid				1	385	0	ORAL MOUSE LD50: 1900 MG/KG. FOUND NATURALLY IN FOODS.
hexanedioyl chloride				2	162	0	STRONG EYE, MUCOUS MEMBRANE, SKIN IRRITANT. ACYLATING AGENT—MIGHT BE CARCINOGENIC.
hexanoic acid	3	1		1	215	0	STRONG IRRITANT. DANGEROUS TO EYES. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION.
1-hexanol	2	2		2	145	0	TOXIC BY INGESTION AND INHALATION. AVOID PROLONGED EXPOSURE. EYE BURNS AND SKIN IRRITATIONS. IMMEDIATELY FLUSH EYES AND SKIN WITH WATER.
n-hexyl alcohol							see 1-hexanol
n-hexylamine							see hexanamine
hydrazine	3	3	S 0.1	3	100	2	READILY ABSORBED THROUGH SKIN. CAUSES LIVER DAMAGE AND RED BLOOD CELL DESTRUCTION. VAPORS ARE VERY TOXIC AND ATTACK EYES AND RESPIRATORY TRACT. LIQUID IS CORROSIVE TO EYES AND SKIN. THIS HIGHLY REACTIVE REDUCING AGENT FORMS EXPLOSIVE MIXTURES WITH AIR OVER A WIDE CONCENTRATION RANGE AND CAN SPONTANEOUSLY IGNITE IN AIR WHEN IN CONTACT WITH POROUS MATERIALS LIKE WOOD, CLOTH, OR DIRT; CAN IGNITE IN CONTACT WITH METAL OXIDES, PEROXIDES AND OTHER OXIDIZERS.
hydrobromic acid	3	2	C 3	0	—	0	STRONGLY CORROSIVE TO ALL TISSUES. EXPOSURE TO VAPORS CAN CAUSE PULMONARY EDEMA AND CHEMICAL BURNS.
hydrochloric acid	3		(C) 5	0	—	0	SAME AS FOR HYDROBROMIC ACID
hydrogen bromide	3	2	C 3	0	—	0	see hydrobromic acid

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
hydrogen peroxide	3		1	0	—	3	EYE, SKIN AND RESPIRATORY TRACT IRRITANT. CONCENTRATED SOLUTIONS (>35%) EASILY BLISTER SKIN. DO NOT INHALE THE VAPOR. POWERFUL OXIDIZER. SENSITIVE AND MAKES POWERFULLY EXPLOSIVE MIXTURES WITH MANY ORGANICS SUCH AS ALCOHOLS, ALDEHYDES, AND OTHER OXIDIZABLE COMPOUNDS.
2-hydroxybenzenecarbonal	3	2		2	172	0	POTENTIAL CANCER PROMOTER. MUCOUS MEMBRANES AND EYE IRRITANT. MODERATE SKIN IRRITANT. CAN REACT WITH OXIDIZERS. WHEN HEATED TO DECOMPOSITION, IT EMITS ACRID SMOKE AND FUMES.
2-hydroxybenzenecarboxylic acid	2	1		1	315	0	STRONG GI TRACT IRRITANT. ORAL RAT LD50: 891 MG/KG.
p-hydroxy-*N*,*N*-dimethylaniline							see 4-hydroxy-*N*,*N*-dimethylbenzamine
4-hydroxy-*N*,*N*-dimethylbenzenamine hydroxylamine	2	2		3		3	LOCAL IRRITANT. SYSTEMICALLY CAUSES METHEMOGLOBINEMIA. MODERATE INHALATION HAZARD. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. EXPLODES AT 265 °F (129 °C).
1-hydroxy-4-methylbenzene							see 4-methylbenzenol
1-hydroxynaphthalene	3	3				0	EYE, MUCOUS MEMBRANE, SKIN IRRITANT; MIGHT CAUSE DERMATITIS. POSSIBLE TO ABSORB ENOUGH THROUGH SKIN TO CAUSE LENS AND CORNEAL DAMAGE TO EYES; KIDNEY IRRITATION.
2-hydroxynaphthalene	3	3		1	307	0	AS FOR 1-HYDROXYNAPHTHALENE. ORAL RAT LD50: 2420 MG/KG.
8-hydroxyquinoline	2						A FUNGICIDE. STRONG EYE, MUCOUS MEMBRANE, SKIN IRRITANT. CNS STIMULANT. LOW FIRE HAZARD. DANGEROUS WHEN HEATED TO DECOMPOSITION, EMITTING NITROGEN OXIDES.
iodine	3		C 0.1				SIMILAR TO EFFECTS OF BROMINE, BUT MORE IRRITATING TO LUNGS.
iodobenzene							

2-iodobenzenol	3	2					SEVERE EYE, SKIN, AND MUCOUS MEMBRANE IRRITANT, CAN CAUSE DERMATITIS. CAUSES CYANOSIS. CHRONIC EXPOSURE PRODUCES LIVER DAMAGE. CAN BE ABSORBED THROUGH SKIN. WHEN HEATED TO DECOMPOSITION IT EMITS TOXIC FUMES. POTENTIAL CANCER PROMOTER. REMOVE CONTAMINATED CLOTHING IMMEDIATELY. SOAP AND WATER WASH.
4-iodobenzenol	2						same as for 2-iodophenol
iodoform							see triiodomethane
1-iodo-4-nitrobenzene							
o-iodophenol							see 2-iodobenzenol
p-iodophenol							see 4-iodobenzenol
iron	0	1	(5)				IRON DUST CAN CAUSE EYE IRRITATION.
isoamyl acetate							see 3-methyl-1-butyl ethanoate
isoamyl alcohol							see 3-methyl-1-butanol
isopropyl alcohol							see 2-propanol
lanolin				1	460	0	Relatively nontoxic. Used in skin creams.
lead(II) ethanoate	0	3					AN INSECTICIDE, A CUMULATIVE POISON. READILY BREAKS DOWN RED BLOOD CELLS. EXPERIMENTAL CARCINOGEN. MIGHT REACT VIOLENTLY WITH STRONG OXIDIZERS.
ligroine	2	2	300	2	100–162	0	INHALATION OF CONCENTRATED VAPORS CAN CAUSE HEADACHE, NAUSEA, COMA.
limonene							SYNTHETIC FLAVORING AGENT. SKIN IRRITANT, SENSITIZER. SOAP AND WATER WASH.
linseed oil	1			1	403–432	0	
Lucas reagent							CAN EASILY CAUSE SEVERE CHEMICAL BURNS.
magnesium	0	0		1		2	Mg DUST IS A SLIGHT IRRITANT. INHALATION OF DUST CAN LEAD TO EMPHYSEMA. POWDER CAN FORM EXPLOSIVE MIXTURES WITH AIR WHICH IGNITE WITH FLAME OR SPARK. REACTS WITH ACIDS TO RELEASE HYDROGEN GAS AND REACTS WITH HALOGENS AND OXIDIZERS.
magnesium sulfate, anhydrous	2	2					MIGHT BE A SKIN IRRITANT.
malonic acid							see propanedioic acid
martius yellow							
mesityl oxide							see 4-methyl-3-penten-2-one
methacrylic acid							see 2-methylpropenoic acid

TOXICITY TABLE (*Continued*)

	Toxicity		*TLV*		*Flash*		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
methanol	1	3	200	3	52	0	SLIGHT MUCOUS MEMBRANE IRRITANT. TOXIC EFFECT ON NERVOUS SYSTEM CAN LEAD TO BLURRED VISION OR BLINDNESS AND COMA OR DEATH WITH SEVERE EXPOSURE. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. CAN REACT VIOLENTLY WITH OXIDIZERS.
p-methoxyacetophenone							see 1-(4-methoxyphenyl)ethanone
p-methoxybenzoyl chloride							see 4-methyoxybenzenecarbonyl chloride
methoxybenzene		2		2	125	0	ORAL RAT LD50: 3700 MG/KG. MODERATE FIRE HAZARD WHEN EXPOSED TO HEAT OR FLAME. CAN REACT WITH OXIDIZERS.
4-methoxybenzenecarbonyl chloride				2		1	VAPORS HIGHLY IRRITATING OR CORROSIVE TO EYES, RESPIRATORY TRACT, AND SKIN, MIGHT PRODUCE PHOSGENE WHEN OVERHEATED. POTENTIAL CARCINOGEN BY ACYLATION. REACTS VIGOROUSLY WITH OXIDIZERS AND WATER. ORAL RAT LD50: 1720 MG/KG.
1-(4-methoxyphenyl) ethanone							
1-methoxybutane							
methyl alcohol							see methanol
methyl amyl ketone							see 2-heptanone
o-methylaniline							see 2-methylbenzenamine
m-methylaniline							see 3-methylbenzenamine
p-methylaniline							see 4-methylbenzenamine
p-methylbenzaldehyde							see 4-methylbenzenecarbonal
2-methylbenzenamine	2	3	S 2	2	185	0	ABSORBED THROUGH SKIN. EFFECTS SIMILAR TO THOSE OF BENZENAMINE. CAN CAUSE SEVERE SYSTEMIC DISTURBANCE. COMBUSTIBLE LIQUID; CAN FORM EXPLOSIVE MIXTURES WITH AIR. HIGHLY TOXIC WHEN ABSORBED THROUGH SKIN OR INHALED.
3-methylbenzenamine	2	3	S 2	2		0	CAUSES CYANOSIS, AIR HUNGER, NAUSEA, VOMITING, LOW BLOOD PRESSURE, CONVULSIONS. EYE AND SKIN IRRITANT. MODERATE FIRE HAZARD. CAN REACT VIGOROUSLY WITH OXIDIZERS. WHEN HEATED TO DECOMPOSITION, IT EMITS TOXIC FUMES.

4-methylbenzenamine	2	3	S 2	2	188	0	ABSORBED THROUGH SKIN. EFFECTS SIMILAR TO THOSE OF BENZENAMINE. CAN CAUSE SEVERE SYSTEMIC DISTURBANCES. GIVES OFF FLAMMABLE VAPORS WHEN HEATED; CAN FORM EXPLOSIVE MIXTURES WITH AIR. HIGHLY TOXIC WHEN ABSORBED THROUGH SKIN
methylbenzene	2	2	S 200	3	40	0	OR INHALED. SOME CNS DEPRESSANT EFFECTS. ALMOST ALWAYS CONTAINS SMALL AMOUNTS OF BENZENE. HAS CAUSED ANEMIA AND RARELY AN ENLARGED LIVER. VAPORS FORM EXPLOSIVE MIXTURES WITH AIR. PROLONGED INHALATION CAN CAUSE DEATH BY PARALYSIS OF RESPIRATORY CENTER.
4-methylbenzenecarbonal				2	160	0	HIGHLY IRRITATING TO EYES AND RESPIRATORY TRACT. WHEN HEATED TO DECOMPOSITION, IT EMITS ACRID SMOKE AND FUMES.
methyl benzenecarboxylate	2	3		2	181	0	ORAL RAT LD50: 3430 MG/KG.
4-methylbenzenecarboxylic acid	1	1	1				
2-methylbenzenesulfonic acid	3			1		1	HIGHLY IRRITANT TO TISSUES.
4-methylbenzenesulfonic acid	3			1	363	1	HIGHLY IRRITANT
4-methylbenzenol	2	2	S 5	1	187	0	CORROSIVE TO SKIN AND MUCOUS MEMBRANES. POTENTIAL CANCER PROMOTER. TOXIC BY INHALATION AND SKIN ABSORPTION (SEE BENZENOL). VAPORS FORM EXPLOSIVE MIXTURES WITH AIR.
methyl benzoate							see methyl benzenecarboxylate
2-methyl-2-butanol	2	2	100	3	67	0	ORAL RAT LD50: 100 MG/KG. CAN REACT WITH OXIDIZERS.
3-methyl-1-butanol	2	3	100	2	109	0	EYE AND MUCOUS MEMBRANE IRRITANT. MUCH MORE TOXIC THAN ETHANOL. CAN REACT WITH OXIDIZERS.
3-methyl-1-butyl ethanoate	2	2	100	3	77	0	EXPOSURE TO HIGH VAPOR CONCENTRATION CAN CAUSE HEADACHE, FATIGUE, IRRITATION TO LUNGS, ORAL RAT LD50: 1200 MG/KG.
methylene chloride							see dichloromethane
methyl ethyl ketone							see 2-butanone
methyl 2-hydroxybenzenecarboxylate	2	3		1	205	0	INGESTION BY HUMANS IN "RELATIVELY SMALL AMOUNTS" CAN CAUSE SEVERE POISONING AND DEATH. A CHILD LETHAL DOSE 10 ML/KG. NAUSEA, VOMITING, PNEUMONIA, CONVULSIONS.
methyl formate							see methyl methanoate

TOXICITY TABLE (*Continued*)

	Toxicity		*TLV*		*Flash*		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
methyl iodide							see iodomethane
methyl methacrylate							see methyl 2-methylpropenoate
methyl methanoate	2	2	100	4	−2	0	MODERATE TOXICITY BY INHALATION. EYE IRRITANT. EMITS TOXIC FUMES WHEN STRONGLY HEATED. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR OVER A WIDE COMPOSITION RANGE. CAN REACT VIGOROUSLY WITH OXIDIZERS. ORAL RABBIT LD50: 1620 MG/KG.
methyl 2-methylpropenoate	2	1	100	3	50	2	EYE, NOSE, THROAT IRRITANT. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. CAN REACT WITH OXIDIZERS. MODERATE EXPLOSION HAZARD. GIVE ARTIFICIAL RESPIRATION IF NECESSARY.
1-methyl-2-nitrobenzene		2	S 2	1	223	4	TOXIC BY INHALATION OR ABSORPTION THROUGH SKIN. ORAL RAT LD50: 891 MG/KG. MIGHT EXPLODE IF STRONGLY OVERHEATED. SOAP AND WATER WASH.
1-methyl-3-nitrobenzene		2	S 2	1	223	4	TOXIC BY INHALATION OR ABSORPTION THROUGH SKIN. ORAL RAT LD50: 1072 MG/KG. MIGHT EXPLODE IF STRONGLY OVERHEATED. SOAP AND WATER WASH.
1-methyl-4-nitrobenzene		2	S 2	1	223	4	TOXIC BY INHALATION OR ABSORPTION THROUGH SKIN. ORAL RAT LD50: 2144 MG/KG. MIGHT EXPLODE IF STRONGLY OVERHEATED. SOAP AND WATER WASH.
2-methyl-2-pentenal	3	3					
4-methyl-3-pentene-2-one	3	3	15	3	87	0	EYE AND MUCOUS MEMBRANE IRRITANT. CNS DEPRESSANT IN HIGH CONC. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. GIVE ARTIFICIAL RESPIRATION IF NECESSARY FROM INHALATION. ORAL RAT LD50: 1120 MG/KG. SOAP AND WATER WASH.
methyl phenyl ether							see methoxybenzene
N-methyl-*N*-phenylmethyl methyl propanoate	1			3	28	0	DANGEROUS WHEN EXPOSED TO HEAT OR OXIDIZERS.
2-methyl-2-propanol	1	2	100	3	52	0	EYE AND MUCOUS MEMBRANE IRRITANT.

2-methylpropenoic acid	3		20	2	171	2	SEVERE SKIN, RESPIRATORY TRACT IRRITANT. HIGH INTRAPERITONEAL TOXICITY. MODERATE FIRE HAZARD WITH HEAT, FLAME, OR OXIDIZERS. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION. VAPOR MAKES EXPLOSIVE MIXTURE WITH AIR.
methylpropionate							see methyl propanoate
methyl salicylate							see methyl 2-hydroxybenzenecarboxylate
mineral oil			(10)	1	380	0	relatively nontoxic.
monophenylurea							
morpholine							see perhydro-1,4-oxazine
1-naphthalenol							see 1-hydroxynaphthalene
2-naphthalenol							see 2-hydroxynaphthalene
α-naphthol							see 1-hydroxynaphthalene
β-naphthol							see 2-hydroxynaphthalene
2-naphthyl isocyanate	1						
ninhydrin							ORAL LOWEST REPORTED LETHAL DOSE RATS: 250 MG/KG.
nitric acid	3	3	2	0		0	HIGHLY CORROSIVE TO EYES, MUCOUS MEMBRANES, SKIN AND TEETH. DANGEROUSLY REACTIVE WITH MANY COMPOUNDS. INCREASES FLAMMABILITY OF ORGANIC COMPOUNDS.
o-nitroaniline							see 2-nitrobenzenamine
p-nitroaniline							see 4-nitrobenzenamine
2-nitrobenzenamine		3	S (3)	1		3	HIGHLY TOXIC. CAN BE ABSORBED THROUGH SKIN TO PRODUCE METHEMOGLOBINEMIA, LOW BLOOD PRESSURE, CARDIAC ARYTHMIA. REMOVE CONTAMINATED CLOTHING IMMEDIATELY; SHOWER IMMEDIATELY.
4-nitrobenzenamine		3	S (3)	1	390	3	see 2-nitrobenzenamine
nitrobenzene		3	S 1	2	190	0	CAN BE ABSORBED THROUGH SKIN. CAUSES METHEMOGLOBINEMIA. FATAL AMOUNTS CAN BE ABSORBED THROUGH SKIN OR BY INHALATION. VAPORS FORM EXPLOSIVE MIXTURES WITH AIR.
4-nitrobenzenediazonium sulfate							MIGHT BE EXPLOSIVE IF ALLOWED TO DRY.
2-nitrobenzenol		3					KIDNEY AND LIVER DAMAGE IN ANIMALS. CAN PRODUCE METHEMOGLOBINEMIA. POTENTIAL CANCER PROMOTER. HAS REACTED VIOLENTLY WITH KOH. ORAL RAT LD50: 350 MG/KG. SOAP AND WATER WASH.
4-nitrobenzenol		3					see 2-nitrobenzenol
m-nitro-*N*,*N*-dimethylaniline							see 3-nitro-*N*,*N*-dimethylbenzenamine
3-nitro-*N*,*N*-dimethylbenzenamine		2					CAUSES WEAKNESS, TREMORS, CYANOSIS.
o-nitrophenol							see 2-nitrobenzenol

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
p-nitrophenol							see 4-nitrobenzenol
N-(4-nitrophenyl) ethanamide							
nitroprusside reagent							
octadecanoic acid							INTRAVENOUS RAT LD50: 22 MG/KG. FIRE HAZARD LOW.
octamethylcyclotetrasiloxane							
octane	0	2	300	3	56	0	DANGEROUS WHEN EXPOSED TO FLAME, SPARK, HEAT; SEVERE EXPLOSION HAZARD. CAN ACT AS SIMPLE ASPHYXIANT.
oil of wintergreen							see methyl 2-hydroxybenzenecarboxylate
oxalic acid							see ethanedioic acid
oxolane	3		200	3	6	1	EYE, MUCOUS MEMBRANE IRRITANT. CNS DEPRESSANT IN HIGH CONC. CAUSES LIVER, KIDNEY DAMAGE. CAN FORM EXPLOSIVE PEROXIDES. WHEN HEATED TO DECOMPOSITION EMITS TOXIC FUMES. SOAP AND WATER WASH.
oxole		3	10	4	<32	1	READILY ABSORBED THROUGH SKIN. THOROUGH IMMEDIATE AQUEOUS SOAP AND WATER WASH REQUIRED; PROLONGED aq RINSE. HIGHLY DANGEROUS WHEN EXPOSED TO HEAT OR FLAME. CAN FORM UNSTABLE PEROXIDES. CAN REACT WITH OXIDIZERS.
oxole-2-carbonal	2	2	S 2	2	140	0	DANGEROUS TO EYES. EYE, MUCOUS MEMBRANE, RESPIRATORY TRACT IRRITANT. HIGH VAPOR CONC CAUSES SEVERE LUNG CONGESTION. CNS POISON. CAN REACT WITH OXIDIZERS. MODERATE FIRE AND EXPLOSION HAZARD. INDUCE VOMITING IF INGESTED. GIVE ARTIFICIAL RESPIRATION IF NECESSARY FROM INHALATION. ORAL RAT LD50: 127 MG/KG. SOAP AND WATER WASH.
palmitic acid							see hexadecanoic acid.
para red							
pentanal	1	1	50	3	54	0	MILD IRRITANT AND CNS DEPRESSANT. WHEN HEATED TO DECOMPOSITION, IT EMITS ACRID SMOKE AND FUMES. CAN REACT WITH OXIDIZERS. ORAL RAT LD50: 3200 MG/KG. DANGEROUS IN PRESENCE OF FLAME, SPARK, OXIDIZERS.

pentane		1	600	4	<−40	0	CNS DEPRESSANT IN HIGH CONCENTRATIONS.
pentanoic acid	1	1	50	1	205	0	HIGHLY IRRITATING TO EYES, MUCOUS MEMBRANES. ANIMAL EXPERIMENTS SUGGEST MILD TOXICITY. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION. ORAL MOUSE LD50: 500 MG/KG.
3-pentanol	2	2		2	105	0	METHEMOGLOBINEMIA BY INGESTION. EYE, MUCOUS MEMBRANE IRRITANT. ORAL RAT LD50: 1000 MG/KG.
3-pentanone	2		200	3	55	0	ANIMAL TESTS SUGGEST LOW TOXICITY. SKIN AND EYE IRRITANT. DANGEROUS WHEN EXPOSED TO HEAT OR FLAMES. SOAP AND WATER WASH.
t-pentyl bromide							see 2-bromo-2-methylbutane
t-pentyl chloride							see 2-chloro-2-methylbutane
perhydro-1,4-oxazine	2	2	S 20	3	98	0	BURNS SKIN AND EYES. DANGEROUS WHEN EXPOSED TO HEAT, FLAME OR OXIDIZERS. EMITS DANGEROUS TOXIC FUMES WHEN HEATED TO DECOMPOSITION. GIVE ARTIFICIAL RESPIRATION IF NECESSARY. ORAL RAT LD50: 1050 MG/KG.
petroleum ether	2	2	300	4	<0	0	INHALATION OF CONCENTRATED VAPORS CAN CAUSE HEADACHE, NAUSEA, COMA.
phenylacetaldehyde							see phenylethanal
phenol							see benzenol
phenylacetic acid							see phenylethanoic acid
phenolphthalein		3					
N-phenylbenzenamine		3	(10)				
phenylethanal	2			2	160	0	SIMILAR TO BENZENAMINE HIGHLY IRRITATING TO EYES AND MUCOUS MEMBRANES. MODERATE SKIN IRRITANT. WHEN HEATED TO DECOMPOSITION, IT EMITS ACRID SMOKE AND IRRITATING FUMES. CAN REACT WITH OXIDIZERS. ORAL RAT LD50: 800 MG/KG.
N-phenylethanamide	1	2		1	337		
1-phenylethanamine	2	2		1	239	0	
2-phenylethanamine	2	2		1	241	0	SKIN IRRITANT; POTENTIAL SENSITIZER. ORAL TOXICITY HIGH. WHEN HEATED TO DECOMPOSITION IT EMITS TOXIC FUMES.
1-phenylethanamine hydrochloride	2				1	0	
1-phenylethanammonium tartrate							
phenylacetic acid							see phenylethanoic acid
phenylethanoic acid	1	1		1	>212	0	A FUNGICIDE; PROBABLY HIGHLY TOXIC.
1-phenylethanol	2			1	205	0	MODERATE SKIN IRRITANT. LOW FIRE HAZARD. CAN REACT WITH OXIDIZERS. ORAL RAT LD50: 1790 MG/KG.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
1-phenylethanone	2			2	170	0	CNS DEPRESSANT IN HIGH CONCENTRATIONS. EYE, MUCOUS MEMBRANE, SKIN IRRITANT. MODERATE FIRE HAZARD WHEN EXPOSED TO HEAT OR FLAME. ORAL RAT LD50: 900 MG/KG.
α-phenylethylamine							see 1-phenylethanamine
β-phenylethylamine							see 2-phenylethanamine
α-phenylethylammonium tartrate							see 1-phenylethanammonium tartrate
N-phenylethylformamide							see *N*-phenylethylmethanamide
N-(1-phenylethyl) methanamide	3						
phenylmagnesium bromide							REACTS VIGOROUSLY WITH MOISTURE OF EYES, SKIN, RESPIRATORY TRACT TO PRODUCE BURNS. VERY DANGEROUS TO EYES. USUALLY PREPARED IN ANHYDROUS ETHER (SEE).
phenylmethanamine	3						DIRECT CONTACT CAN CAUSE SEVERE EYE DAMAGE AND SKIN BURNS. MUCOUS MEMBRANE IRRITANT BY INHALATION. REMOVE VICTIM FROM AREA; GIVE ARTIFICIAL RESPIRATION IF NECESSARY. ORAL RAT LD50: 974 MG/KG.
phenylmethanol	1	1		1	200	0	ORAL MOUSE LD50: 1580 MG/KG.
1-phenyl-1-propanone	1			1	210	0	ORAL RAT LD50: 4490 MG/KG.
phosphoric acid	2		(1)	0		0	IRRITATING TO EYES, SKIN AND MUCOUS MEMBRANE. CONTACT WITH ACTIVE METALS PRODUCES HYDROGEN GAS WHICH CAN FORM FLAMMABLE MIXTURES WITH AIR. WHEN HEATED TO DECOMPOSITION, IT FORMS DANGEROUS FUMES.
phthalic anhydride							see 1,2-benzenedicarboxylic anhydride
picric acid							see 2,4,6-trinitrobenzenol
plumbous acetate							see lead(II) ethanoate
polydimethylsiloxane							
potassium	3			1		2	FUMES FROM BURNING POTASSIUM HIGHLY IRRITATING TO EYES, SKIN, RESPIRATORY TRACT. EXTREMELY DANGEROUS IN CONTACT WITH MOISTURE, RELEASING HYDROGEN GAS WITH EXOTHERM SUFFICIENT TO CAUSE IGNITION OR EXPLOSION. SOLID CAN IGNITE IN CONTACT WITH AIR. REACTS EXOTHERMICALLY WITH BODY MOISTURE

potassium carbonate	3	3					TO PRODUCE SEVERE CHEMICAL BURNS WHICH MIGHT HEAL SLOWLY. REACTS VIOLENTLY WITH HALOGENATED COMPOUNDS. SOAP AND WATER WASH. STRONGLY CAUSTIC. ORAL RAT LD50: 1860 MG/KG.
potassium dichromate	3		(0.05)	0		1	CORROSIVE ACTION ON SKIN AND MUCOUS MEMBRANES. CHROMATE DUST IS ASSOCIATED WITH LUNG CANCER. IN CONTACT WITH REDUCERS CAN REACT RAPIDLY ENOUGH TO CAUSE IGNITION, PERHAPS VIOLENTLY.
potassium ferric ferrocyanide	1	1					
potassium ferricyanide	1	1					
potassium hydrogen sulfate	3	3					
potassium hydroxide	3	3	C (2)	0		1	SEVERE EYE HAZARD. EXTREMELY CAUSTIC. SOLID IN CONTACT WITH MOISTURE MIGHT GENERATE ENOUGH HEAT TO START FIRE ON COMBUSTIBLE MATERIALS. REACTS WITH SOME METALS TO GENERATE HYDROGEN GAS.
potassium monohydrogen phosphate							food additive
potassium iodide		2					
potassium permanganate	3	3					STRONG IRRITANT. ORAL RAT LD50: 1090 MG/KG. POWERFUL OXIDIZER. SPONTANEOUS FLAME ON CONTACT WITH GLYCERINE, ETHYLENE GLYCOL, ETC.
propanal	2	2		3	−22	1	QUITE TOXIC BY INHALATION; MODERATELY TOXIC BY SKIN ABSORPTION. AVOID ALL EXPOSURE TO VAPORS. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. RAT SUBCUTANEOUS LD50: 820 MG/KG.
propanamine	3	3		3	−35	0	SOAP AND WATER WASH. STRONG IRRITANT AND SKIN SENSITIZER. CAUSES SKIN AND EYE BURNS, LUNG EDEMA. VERY DANGEROUS WHEN EXPOSED TO HEAT, FLAME, OR OXIDIZERS. EMITS NITROGEN OXIDES WHEN HEATED TO DECOMPOSITION. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR.
propanedioic acid	3						SEVERE SKIN AND EYE IRRITATION. INGESTION LEADS TO GASTRIC PAIN, HEADACHE, VOMITING. EMITS ACRID FUMES WHEN HEATED TO DECOMPOSITION. ORAL RAT LD50: 1310 MG/KG.
1,2,3-propanetriol	1	1	(10)	1	390	0	ORAL MOUSE LD50: 470 MG/KG. CAN REACT VIOLENTLY WITH OXIDIZERS.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
propanoic acid	2	1	10	2	126	0	HIGHLY IRRITATING TO EYES, MUCOUS MEMBRANES, SKIN. DO NOT INHALE VAPORS. ORAL RAT LD50: 1510 MG/KG.
1-propanol	1	1	S 200	3	74	0	SKIN AND EYE IRRITANT. HIGH VAPOR CONC CAN PRODUCE DIZZINESS, VOMITING, UNCONSCIOUSNESS. REACTS VIGOROUSLY WITH OXIDIZERS. DANGEROUS WITH HEAT OR FLAME. MODERATELY EXPLOSIVE IN PRESENCE OF FLAME. ORAL RAT LD50: 1870 MG/KG.
2-propanol	1	2	400	3	53	0	SKIN AND EYE IRRITANT. HIGH VAPOR CONC CAN LEAD TO DIZZINESS, VOMITING. DANGEROUS WHEN EXPOSED TO HEAT OR FLAME CAN REACT VIGOROUSLY WITH OXIDIZERS. GIVE ARTIFICIAL RESPIRATION IF NECESSARY FROM INHALATION.
2-propanone	2	2	750	3	−4	0	EYE AND MUCOUS MEMBRANE IRRITANT. PROLONGED SKIN CONTACT CAUSES DERMATITIS, CRACKED SKIN. DANGEROUS WHEN EXPOSED TO FLAME, HEAT OR OXIDIZERS. ORAL RAT LD50: 9750 MG/KG.
propenal	3	3	0.1	3	−15	2	SMALL AMOUNT IS HIGHLY TOXIC. REMOVE CONTAMINATED CLOTHING IMMEDIATELY. STRONG LACHRYMATOR. ASTHMATIC RECTION UPON INHALATION. STRONG EYE, MUCOUS MEMBRANE, SKIN IRRITANT. INCOMPATIBLE WITH ACID, BASE, AMINES, OXIDANTS. DANGEROUS WITH HEAT, FLAME, OXIDIZERS. INDUCE VOMITING IF TAKEN INTERNALLY. ORAL RAT LD50: 46 MG/KG.
propenoic acid	3	3	10	2	122	2	SHORT CONTACT CAN SERIOUSLY BURN EYES OR SKIN. EYE AND NASAL IRRITANT BY INHALATION. LACHRYMATOR. INGESTION CAN LEAD TO SEVERE GASTROINTESTINAL DAMAGE. GET PROMPT MEDICAL ATTENTION FOR ALL EXPOSURES. VAPOR FORMS EXPLOSIVE MIXTURES WITH AIR. ORAL RAT LD50: 340 MG/KG.
propionaldehyde							see propanal
propionic acid							see propanoic acid
propiophenone							see 1-phenyl-1-propanone
n-propyl acetate							see propyl ethanoate

sec-propyl alcohol							see 2-propanol
n-propylamine							see propanamine
propyl ethanoate	1	2	200	3	55	0	CNS DEPRESSANT. PROLONGED INHALATION HAS BEEN FATAL. ORAL RAT LD50: 9800 MG/KG. CAN REACT VIGOROUSLY WITH OXIDIZERS.
propyl propanoate	1	2		3	175	0	CAN REACT WITH OXIDIZERS. ORAL RABBIT LD50: 3950 MG/KG.
n-propyl propionate							see propyl propanoate
Prussian blue	1	1					
pyridine							see azine
quinoline		3		1		0	MUCOUS MEMBRANE, SKIN IRRITANT. HIGHLY TOXIC BY INHALATION. CAN CAUSE INFLAMMATION OF RETINA. SOAP AND WATER WASH; PROLONGED RINSE. ORAL RAT LD50: 60 MG/KG.
salicylaldehyde							see 2-hydroxybenzenecarbonal
salicylic acid							see 2-hydroxybenzenecarboxylic acid
semicarbazide hydrochloride	1	1					ORAL MOUSE LD50: 123–176 MG/KG. EXPERIMENTAL CARCINOGEN IN ANIMALS. HIGH TOXICITY BY ALL ROUTES.
silica	2	0	(10)				DISABLING SILICOSIS CAN RESULT FROM INHALATION.
silver nitrate	3		(0.01)				SKIN, EYE, RESPIRATORY TRACT IRRITANT. POWERFUL CAUSTIC. CAN CAUSE CORNEAL OPAQUENESS ON CONTACT BY CONCENTRATED SOLUTION. INCREASES FLAMMABILITY OF COMBUSTIBLE MATERIALS.
silver fulminate	3		(0.01)	3			EXPLOSIVE. MUST BE KEPT IN SOLUTION AND DISPOSED OF PROMPTLY.
sodium	3	2					DANGEROUS IN CONTACT WITH MOISTURE, RELEASING HYDROGEN GAS WITH ENOUGH EXOTHERM TO CAUSE IGNITION OR EXPLOSION. SOLID CAN IGNITE IN CONTACT WITH AIR. FUMES FROM BURNING SODIUM HIGHLY IRRITATING TO EYES, SKIN AND RESPIRATORY TRACT. REACTS EXOTHERMICALLY WITH BODY MOISTURE TO PRODUCE CHEMICAL BURNS WHICH MAY HEAL SLOWLY. REACTS VIOLENTLY WITH HALOGENATED COMPOUNDS. SOAP AND WATER WASH.
sodium acetate							see sodium ethanoate
sodium bicarbonate							ORAL RAT LD50: 4220 MG/KG.
sodium bisulfite	3		(5)				TOXIC SULFUROUS ACID LIBERATED ON CONTACT WITH MOISTURE.

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
sodium borohydride	2						HIGHLY CAUSTIC TO EYES, MUCOUS MEMBRANES, SKIN. ORAL RAT LD50: 160 MG/KG. SOAP AND WATER WASH.
sodium bromide	2	2					
sodium carbonate	2	1					EYE, RESPIRATORY TRACT IRRITANT. SOAP AND WATER WASH; LONG RINSE.
sodium chloride	1	0					
sodium dichromate	3						as for potassium dichromate
sodium ethanoate	1	0					MILDLY TOXIC. ORAL RAT LD50: 3530 MG/KG.
sodium hydrogen sulfite	2	2	(5)				EYE, MUCOUS MEMBRANE, SKIN IRRITANT. INTRAVENOUS RAT LD50: 115 MG/KG. AN IRRITANT.
sodium hydroxide	3	2	C (2)				HIGHLY CAUSTIC TO TISSUES. CORROSIVE AND IRRITATING. HIGHLY DANGEROUS TO EYES.
sodium hypochlorite	2		(3)				
sodium-lead alloy	3		(3)				CORROSIVE TO TOUCH. REACTS LIKE SODIUM METAL, BUT LESS VIOLENTLY.
sodium methoxide							STRONGLY CAUSTIC TO ALL TISSUES. PRODUCES CHEMICAL BURNS AND DEEP ULCERATIONS. SOAP AND WATER WASH; PROLONGED RINSE.
sodium nitrite		3					PRODUCES METHEMOGLOBINEMIA.
sodium sulfate, anhydrous							ORAL MOUSE LD50: 5989 MG/KG. MIGHT IRRITATE SKIN, EYES.
sodium sulfite							INTRAVENOUS RAT LD50: 115 MG/KG.
stearic acid							see octadecanoic acid
sulfuric acid, conc.	3	3	(1)	0		2	CAUSES SEVERE, DEEP BURNS; HAS VERY CORROSIVE EFFECT. HIGHLY REACTIVE AND CAN IGNITE FINELY DIVIDED COMBUSTIBLE MATERIALS ON CONTACT. REACTS VIOLENTLY WITH WATER AND ORGANICS.
(+)-tartaric acid	1	0		1	410	0	
tetrachloromethane	0	3	S 5	0		0	CNS DEPRESSANT. CAN CAUSE DEATH, DAMAGE KIDNEYS, LUNGS, LIVER. CARCINOGENIC IN ANIMAL TESTS. HIGHLY TOXIC BY INHALATION.
tetrahydrofuran							see oxolane
tetramethylsilane	3			4		2	

thionyl chloride	3		C 1	0		2	DECOMPOSES IN PRESENCE OF H_2O TO HCL AND SO_2, BOTH OF WHICH ARE CORROSIVE. SEVERELY BURNS EYES, MUCOUS MEMBRANES, SKIN. DECOMPOSES WHEN HEATED ABOVE 140 °C. SOAP AND WATER WASH; PROLONGED RINSE.
tin	2		S (0.1)				
tms							see tetramethylsilane
Tollen's reagent							see silver nitrate and silver fulminate
p-tolualdehyde							see 4-methylbenzenecarbaldehyde
toluene							see methylbenzene
o-toluidine							see 2-methylbenzenamine
m-toluidine							see 3-methylbenzenamine
p-toluidine							see 4-methylbenzenamine
tribromomethane	2	2	0.5	0	NONE	0	LACHRYMATOR. SERIOUS LIVER DAMAGE. CNS DEPRESSANT. REMOVE VICTIM FROM AREA OF EXPOSURE. SUBCUTANEOUS MOUSE LD50: 1820 MG/KG. VIOLENT REACTION WITH ACTIVE METALS.
tri-*n*-butylamine							see *N,N*-dibutylbutanamine
2,4,6-trichlorobenzenol	3	3					POTENTIAL CANCER PROMOTER. CAN PRODUCE SEVERE EYE AND SKIN BURNS.
trichloromethane	1	3	10	0		0	EYE IRRITANT. SERIOUS EFFECTS ON KIDNEYS, LIVER, HEART. CNS DEPRESSANT. KNOWN CARCINOGEN. REMOVE VICTIM FROM AREA OF EXPOSURE.
triethanolamine	0	1		1	380	1	MODERATE EYE AND SKIN IRRITANT. CAN BECOME UNSTABLE AT ELEVATED TEMPERATURES. ORAL RAT LD50: 8680 MG/KG.
2,4,6-trichlorophenol							see 2,4,6-trichlorobenzenol
1,2,3-trihydroxypropane	1	1			390	0	
triiodomethane	2	2	0.6				ORAL MOUSE LD50: 629 MG/KG. WHEN HEATED TO DECOMPOSITION CREATES DANGEROUS FUMES.
2,4,6-trinitrobenzenol	2	3	S (0.1)	4		4	EYE SKIN, RESPIRATORY TRACT IRRITANT. HIGHLY EXPLOSIVE AND DANGEROUS. IT SHOULD BE KEPT WET WITH AT LEAST 10% WATER. POTENTIAL CANCER PROMOTER.
2,4,6-trinitrophenol							see 2,4,6-trinitrobenzenol
trisodium phosphate	2						STRONGLY CAUSTIC; CAN CAUSE CHEMICAL BURNS. ORAL RAT LD50: 430 MG/KG.
urea							LOWEST REPORTED LETHAL INTRAVENOUS DOSE TO DOGS: 300 MG/KG.
valeraldehyde							see pentanal

TOXICITY TABLE (*Continued*)

	Toxicity		TLV		Flash		
	Local	*Systemic*	*ppm (mg/m³)*	*Flammability*	*Point, °F*	*Explosivity*	
valeric acid							see pentanoic acid
xylenes							see dimethylbenzenes
3,5-xylenol							see 3,5-dimethylbenzenol
zinc chloride, anhydrous	2		(1)				STRONG DESICCANT AND IRRITANT ACTION REPORTED. CAN CAUSE CHEMICAL BURNS. LOWEST LETHAL INTRAVENOUS DOSE TO RATS: 30 MG/KG.

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