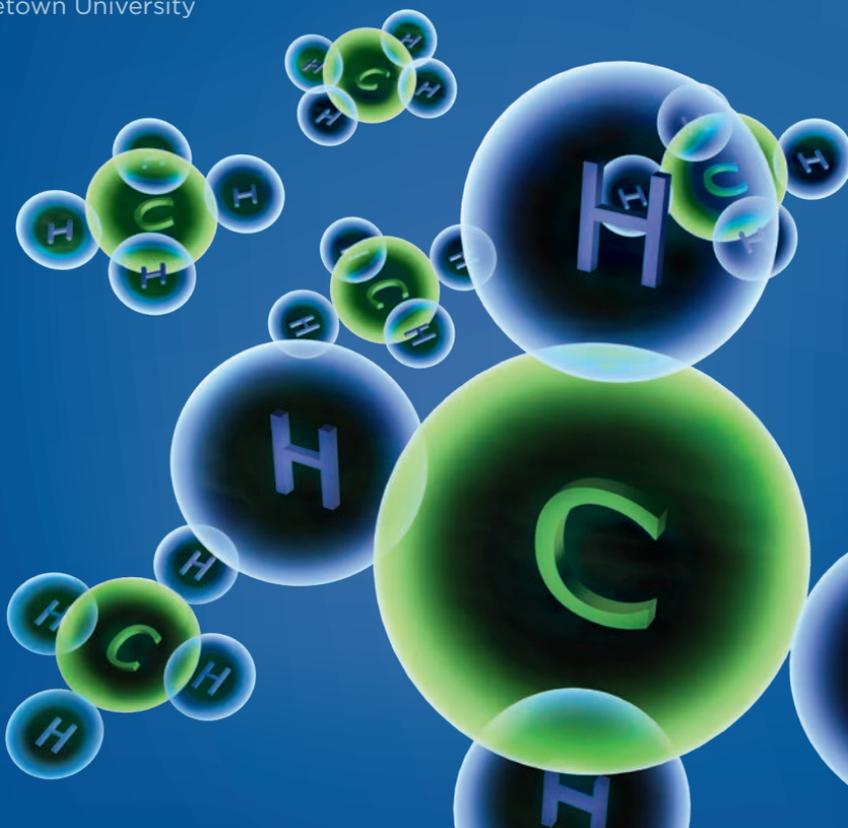


Foundations of Organic Chemistry

Course Guidebook

Professor Ron B. Davis Jr.
Georgetown University



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Professor Davis's research has been published in such scholarly journals as *Proteins* and *Biochemistry* and has been presented at the Annual Symposium of The Protein Society. He also maintains an educational YouTube channel and provides interviews and content to various media outlets, including the Discovery Channel.

At Penn State, Professor Davis was the recipient of a Dalalian Fellowship and the Dan Waugh Teaching Award. He is also a member of the Division of Chemical Education of the American Chemical Society. ■

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Foundations of Organic Chemistry

Scope:

Chemistry is defined as the study of matter and its properties. With regard to this definition, the roots of the study of chemistry can be traced back to more than one ancient civilization. Most notably, the Greeks and Chinese each independently postulated thousands of years ago that there must be a small number of elemental substances from which all other things were created as admixtures. Remarkably, both civilizations theorized that air, earth, water, and fire were among those elements. It was much more recently, however—just about 300 years ago—that famed French nobleman and chemist Antoine Lavoisier correctly identified one of the elements experimentally. Lavoisier’s discovery is often cited as the event that heralded the birth of chemistry as a proper science. Theorizing based on observation of natural systems began to give way to controlled testing of the properties of matter, leading to an explosion of understanding, the echoes of which are still ringing in modern-day laboratories.

Organic chemistry is the subject dedicated to the study of a deceptively simple set of molecules—those based on carbon. Even today, centuries after the most basic governing principles of this subject were discovered, many students struggle to make sense of this science. At the university level, professors are often in a race against time to dispense the vast body of knowledge on organic chemistry to their students before semester’s end, leaving little time for discussion of exactly how this information came to be known or of just how new experimentation might change the world we live in. This course endeavors to fill that gap.

As humanity’s understanding of chemistry grew, so did the library of elements that had been isolated and identified, yet even as this library of elements grew, one of the simplest of them—carbon—seemed to play a very special and indispensable role in many small molecules. This was particularly true of the molecules harvested from living organisms. So obvious was the importance of this role that chemists dubbed the study of the fundamental molecules of life “organic chemistry,” a science that today has

been expanded to include any molecule relying principally on carbon atoms as its backbone.

In this course, you will investigate the role of carbon in organic molecules—sometimes acting as a reactive site on molecules, sometimes influencing reactive sites on molecules, but always providing structural support for an ever-growing library of both naturally occurring and man-made compounds.

Other elements will join the story, bonding with carbon scaffolds to create compounds with a stunningly broad array of properties. Most notable are the elements hydrogen, nitrogen, oxygen, chlorine, and bromine. The presence of these elements and others in organic chemistry spices up the party, but none of them can replace carbon in its central role.

The goal of this course is to take the uninitiated student on a tour of the development and application of the discipline of organic chemistry, noting some of the most famous minds to dedicate themselves to this science in the past few centuries, such as Dmitry Mendeleev (of periodic table fame), Friedrich Wöhler (the father of modern organic chemistry), and Alfred Nobel (the inventor of dynamite and founder of the most influential scientific prize in the history of humanity). You will also meet some very famous scientists from other fields whose forays into organic chemistry helped shape the science, such as Louis Pasteur of microbiology fame and Michael Faraday, the father of electromagnetism.

Approximately the first half of the course is dedicated to building the foundations of understanding modern organic chemistry. In this portion of the course, you will investigate the structure of the atom, the energetic rationale for chemical bonding between atoms to create compounds, how specific collections of atoms bonded in specific ways create motifs called functional groups, and ultimately the ways in which the bonds in these functional groups form and break in chemical reactions that can be used to convert one compound into another.

Next, you will apply that understanding of organic fundamentals to more complex, but often misunderstood, molecular systems, such as starches, proteins, DNA, and more. In the final portion of the course, you will turn

your attention to how organic chemists purify and characterize their new creations in the laboratory, investigating techniques as ancient as distillation and as modern as nuclear magnetic studies.

After completing this course, the successful student will have all of the tools needed to have a meaningful dialogue with a practicing organic chemist about the theory behind his or her work, the interpretation of the results that he or she obtains in the lab, and—most of all—the impact that modern experimentation in organic chemistry might have on the future of humanity. ■

Why Carbon?

Lecture 1

In this lecture, you will explore what organic chemistry is, how it got started, and how our understanding of it has changed over the years. This lecture will scratch the surface of explaining how carbon's abundance, bonding complexity, and bonding strength all combine to make it such a unique and versatile element for building complex small molecules. You will also learn how the decoration of these scaffolds with groups of other atoms can lead to a diverse library of useful compounds.

What Is Organic Chemistry?

- Scientists define chemistry as the study of matter and its properties—particularly those of atomic and molecular systems. One of the defining tenets of chemistry is the idea that that all substances can be broken down into their basic elements, which can no longer be subdivided while still retaining their identity.
- Because carbon is central to the chemistry of life—and serves as the structural basis for materials of incredible strength, fuels with tremendous amounts of stored chemical energy, and life-saving medicines—we have honored it with something no other element has: its own branch of chemistry, called organic chemistry.
- Given that all objects in the universe can be classified as matter, and that nearly all matter is made of atoms and molecules, chemistry is an extremely broad field of study. With such a tremendous field to cover, those practicing this science divide their interests into subdisciplines, such as biological chemistry, physical chemistry, organic chemistry, and many more.
- Organic chemistry is most simply defined as the study of carbon-based molecules. Compounds such as the hydrocarbons in gasoline, the sugars in the foods we eat, and many modern materials ranging

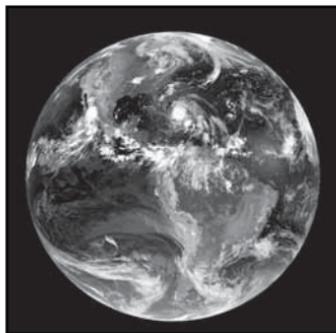
from explosives to plastics are all built on carbon-based backbones and, therefore, fall into this category.

Why Carbon?

- With over 100 elements in the modern periodic table, why does carbon get its own branch of chemistry? The answer to this question lies in a balance of three key factors: abundance, complexity, and stability. When we compare carbon to other elements in the first three rows of the periodic table, we find that only carbon is able to blend these three factors in a unique way.
- If we were to make a table of the estimated relative abundance of elements in our solar system by mass, we would discover that many elements are so vanishingly rare that they do not even register on our chart. Hydrogen is the clear winner at about 73%, followed by helium at 24%, and then oxygen at about 1%.
- Out of more than 100 known elements, just this trio makes up 98% of all the matter in the solar system. But coming in at number four is carbon, making up about one-half of 1% of the matter in the solar system. Based on this information alone, you might expect to find subdisciplines of chemistry focusing on the chemistry of hydrogen, helium, or oxygen as well. However, these subdisciplines do not exist.
- These numbers are a bit different when we consider just the Earth, or even portions of it. The truth is that we aren't quite sure just how much of each element makes up the overall mass of our planet. We do know, however, that as the planet cooled 4 billion years ago, denser elements like iron and nickel found their way to the core of the planet, and intermediate-sized elements like silicon and aluminum were sorted into the crust, leaving behind lighter elements like carbon in higher concentrations at the surface.
- So, carbon is ever present near the surface of the Earth in the environments that might support life as we know it, but our best estimates of the amount of carbon in those environments—the

world's atmosphere, oceans, and crust—is never more than about 1% of the total mass. This means that there is enough carbon there to work with, but if abundance were the only concern, then there would clearly be better choices.

- However, when we turn our attention to our own bodies, we see that we are actually made up of about 20% carbon by mass. This is far more than the relative abundance of carbon in our environment—far more than the oceans, the atmosphere, or dry land. So, carbon is available, but so are many other candidates. There is something about carbon that makes it a better choice for the structural basis of organic molecules.



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Carbon is ever present near the surface of the Earth.

Contenders for the Role of Backbone Molecule

- All atoms consist of a positively charged nucleus surrounded by a cloud of negatively charged electrons. The electron clouds of two or more atoms can interact with one another in ways that confine those atoms to a fixed distance in space. We call this interaction between atoms a covalent chemical bond.
- Remarkably, 19th-century Russian chemist Dmitry Mendeleev's brainchild, known as the periodic table of the elements, accurately predicts the maximum number of these covalent bonding interactions that a particular atom can form with others.
- If we start from the left of the table, elements of the first column can form one bond at most. Those of the second row can form two, and the trend continues until we reach the fourth row. After this, the maximum number of possible bonds begins to decrease again, to three, two, one, and then zero. This makes hydrogen a relatively uninteresting nucleus from the bonding perspective, because it can only form a single bond with another atom.

- So, hydrogen atoms are the end link in chains of bonded atoms. They can't bond with any more atoms to continue creating a complex structure, because doing so would require that they make a second bond. That makes hydrogen the placeholder of organic chemistry, occupying locations on a molecule in which differing groups of atoms might be placed to alter that molecule's identity and reactivity.
- Helium (nature's second most abundant element overall, but vanishingly rare on Earth) appears in group eight of the table, making it unlikely to form any bonds at all. Helium usually only exists naturally as isolated atoms that don't commonly react with other elements. It's not essential to life on Earth.
- The final contender with carbon for the role of a backbone molecule is oxygen. Oxygen typically makes two bonds to other atoms. In doing so, oxygen can act either as a bridge, bonding to two different atoms perpetuating a chain, or as a terminal atom, making what is known as a double bond.
- But once oxygen's two bonds are established, it is satisfied, and there are no additional locations available to decorate or modify an oxygen chain. Using oxygen as a backbone atom would lead to a rather dull set of molecules—a set of ever-lengthening chains of oxygen atoms with no additional complexity.
- But carbon interests organic chemists because it is found in group four of the table, meaning that it can, and often does, form four bonds to complete its octet—more bonds than any other element in the second row of the periodic table. This allows carbon to bond to itself to form chains, branches, loops, and more.
- Furthermore, these complex carbon scaffolds often have remaining unsatisfied bonds that can be terminated by hydrogen atoms or decorated by bonding them to any number of other candidates. Clearly, those extra bonds that carbon can form will make all the difference.

Lecture 1: Why Carbon?

The Periodic Table of the Elements

Hydrogen *** H 1.008	Helium *** He 4.003																									
Lithium * Li 6.941	Beryllium * Be 9.012	Boron * B 10.81	Carbon * C 12.01	Nitrogen *** N 14.01	Oxygen *** O 16.00	Fluorine *** F 19.00	Neon *** Ne 20.18									Argon *** Ar 39.95										
Sodium * Na 22.99	Magnesium * Mg 24.31	Aluminum * Al 26.98	Silicon * Si 28.09	Phosphorus * P 30.97	Sulfur * S 32.07	Chlorine *** Cl 35.45	Argon *** Ar 39.95									Krypton *** Kr 83.80										
Potassium * K 39.10	Calcium * Ca 40.08	Scandium * Sc 44.96	Titanium * Ti 47.87	Vanadium * V 50.94	Chromium * Cr 52.00	Manganese * Mn 54.94	Iron * Fe 55.84	Cobalt * Co 58.93	Nickel * Ni 58.69	Copper * Cu 63.55	Zinc * Zn 65.39	Gallium * Ga 69.72	Germanium * Ge 72.63	Arsenic * As 74.92	Selenium * Se 78.96	Bromine * Br 79.90	Krypton *** Kr 83.80									
Rubidium * Rb 85.47	Strontium * Sr 87.62	Yttrium * Y 88.91	Zirconium * Zr 91.22	Niobium * Nb 92.91	Molybdenum * Mo 95.94	Technetium * Tc [98]	Ruthenium * Ru 101.07	Rhodium * Rh 102.91	Palladium * Pd 106.42	Silver * Ag 107.87	Cadmium * Cd 112.41	Indium * In 114.82	Tin * Sn 118.71	Antimony * Sb 121.76	Tellurium * Te 127.60	Iodine * I 126.90	Xenon *** Xe 131.29									
Cesium * Cs 132.91	Barium * Ba 137.33	Lanthanides * La [138.91]	Hafnium * Hf 178.49	Tantalum * Ta 180.95	Tungsten * W 183.84	Rhenium * Re 186.21	Osmium * Os 190.23	Iridium * Ir 192.22	Platinum * Pt 195.08	Mercury * Hg 200.59	Thallium * Tl 204.38	Lead * Pb 207.2	Bi * Bi 208.98	Po * Po [209]	Astatine * At [210]	Rn * Rn [222]										
Francium * Fr [223]	Radium * Ra [226]	Actinides * Ac [227]	Rutherfordium * Rf [261]	Dubnium * Db [262]	Seaborgium * Sg [266]	Berkelium * Bk [267]	Californium * Cf [285]	Einsteinium * Es [287]	Fermium * Fm [289]	Mendelevium * Md [291]	Nobelium * No [293]	Lutetium * Lu [175]	Ytterbium * Yb [173]	Thulium * Tm [169]	Erbium * Er [167]	Holmium * Ho [165]	Dysprosium * Dy [163]	Terbium * Tb [159]	Gadolinium * Gd [157]	Europtium * Eu [152]	Samarium * Sm [150]	Promethium * Pm [145]	Neodymium * Nd [144]	Praseodymium * Pr [141]	Cerium * Ce [140]	Lanthanum * La [139]

- Nitrogen and silicon are still on the list of possible backbone elements for larger, complex scaffolds. Nitrogen and silicon have withstood the test of both abundance and complexity, with nitrogen abundant in the atmosphere and able to form three bonds, while silicon makes up a large part of the Earth's crust and is able to make four bonds.
- What separates carbon from nitrogen and silicon is the last factor to consider: strength. Just like a building, organic molecules need a support structure tough enough to hold the functional parts of the compound in place. Any candidate for this role will have to be tough enough to withstand the conditions that cause other parts of the compound to react. So, the final factor leading to nature's choice of carbon for small-molecule scaffolds is the stability of the carbon-carbon bond.
- Bonding is an energetically beneficial arrangement, and a bond's strength is usually measured by the amount of energy required to separate the bonded atoms. Scientists call this the bond enthalpy. The larger the bond enthalpy, the harder it is to pull two bonded atoms apart, and the stronger the chemical bond should be.
- If we compare the bond enthalpies of all first-, second-, and third-row elements to other atoms of the same kind, we can see that only hydrogen and boron form single bonds to other atoms of the same kind with the same strength as carbon.
- So, hydrogen does bond to itself strongly and is very abundant, but its one-bond limit rules it out. Boron can form stable bonds with itself in networks with up to three bonds, but it's so vanishingly rare in the environment that it can't play an important structural role in the chemistry of life.
- The last two viable candidates, nitrogen and silicon, are finally ruled out when we consider bond strength. With bonds only half as strong as carbon, nitrogen can't compete, and even silicon, a favorite candidate as carbon's alternate because of its abundance and ability to form four bonds, fails to meet the final standard

because a covalent network of silicon atoms would simply not be stable enough to survive chemical reactions meant to modify other bonds within the molecules it would comprise.

- So, if we consider the first three rows of the periodic table, removing elements of prohibitively low abundance, elements incapable of forming more than two bonds, and those that do not form strong single bonds to themselves, it now becomes obvious how these three factors make carbon uniquely suited to the formation of molecular scaffolds.

The Complexity of Carbon Scaffolds and Organic Molecules

- Carbon atoms can combine to form distinct structures, and decorating these structures with other atoms can lead to a rich and diverse library of compounds. Part of what makes carbon scaffolds so prolific and diverse is the multiple ways in which the four bonds to carbon atoms can be arranged in space.
- Chemical bonds are formed when electron clouds overlap, and this produces a region of dense negative charge between the atoms' nuclei. These bonds, made up of negatively charged electrons, can be thought of as being negatively charged themselves. Because they are made up of like-charged particles, they repel one another, positioning themselves as far apart as possible around the central atom.
- So, when a carbon atom is connected to two other atoms, either by two double bonds or a single and triple bond, the connected atoms are 180 degrees apart from one another, forming a linear geometry. When a carbon atom is connected to three other atoms—two atoms by single bonds and another atom by a double bond—the atoms form a planar geometry in the shape of an equilateral triangle, with bond angles of 120 degrees. We call this type of geometry trigonal planar.
- But the real magic happens when we use all four bonds to connect four distinct bonding partners. In this case, a planar geometry would require 90-degree angles. But giving these bonds access to the third

dimension allows them to separate even more, forming bond angles of 109.5 degrees. We call this arrangement tetrahedral, because tracing lines among all bonded atoms produces a tetrahedron.

- So, by bonding carbon atoms together using some or all of these geometries—linear, trigonal planar, and, in particular, tetrahedral—we can form almost any three-dimensional arrangement imaginable. Furthermore, there are remaining bonds terminated by hydrogen atoms that could be replaced by other sets of atoms, which means that each carbon scaffold can act as a backbone supporting hundreds, thousands, or even millions of distinct atom combinations.
- By designing molecules in this way, chemists are able to create compounds with very specific and rationally designed shapes, physical properties, and reactivities. This quickly leads to a virtually limitless library of possible compounds, all of which rely on the stability and geometry of their carbon scaffold to function.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chap. 1 preface.

Morris, *The Last Sorcerers*.

Smeaton, “The Legacy of Lavoisier,” *Bulletin for the History of Chemistry* 5 (1989): 4–10.

Wade, *Organic Chemistry*, Chap. 1.1.

Questions to Consider

1. What are the three crucial properties that carbon combines to make it the best choice for small-molecule scaffolds?
2. How did Mendeleev’s revelation about periodicity accelerate our discovery of new elements and their properties?

Structure of the Atom and Chemical Bonding

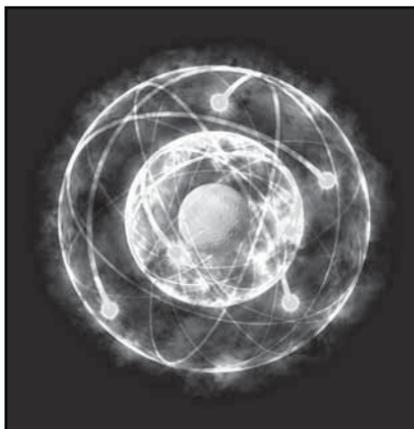
Lecture 2

Chemical bonds form the basis for not only organic chemistry, but also all of chemistry. Bonding is, in fact, much more than just a way to connect atoms to form larger molecules. Bonding has a way of changing atoms in ways that alter their physical properties and reactivity so profoundly that many materials of identical atomic composition have drastically different properties. In this lecture, you will learn about the structure of the atom and how atoms form bonds.

The Structure of the Atom

- Atoms are comprised of three types of subatomic particles: positively charged protons, uncharged neutrons, and negatively charged electrons. Niels Bohr is famous for many scientific accomplishments but most notably for his model of the atom, in which a dense, positively charged core of protons and neutrons called the nucleus is orbited by a cloud of small, fast-moving, negatively charged electrons. Each of these three particles plays a role in the properties of any given atom.
- Protons provide the atom with its identity. For example, a nucleus with six protons means carbon. Regardless of the number of other subatomic particles in the structure, a nucleus containing six protons is always carbon.
- Neutrons add mass to an atom but do not alter its identity. For example, a carbon atom may have six neutrons, as in carbon 12; seven neutrons, as in carbon 13; or eight neutrons, as in carbon 14. When atoms have the same number of protons—meaning that they are the same element—but have differing numbers of neutrons, thus giving them a different atomic mass, we refer to them as isotopes of one another.

- Electrons most directly affect the charge of an atom. In order for an atom to be neutral, it must have the same number of electrons and protons. When the number of electrons in the electron cloud is not equal to the number of protons in the nucleus, a charged species results. We call these charged species ions.



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Niels Bohr's most notable scientific contribution was his model of the atom.

- If electrons outnumber protons, the atom takes on a net negative charge and becomes what we call an anion. If, instead, protons outnumber electrons, a cation is formed. As the discrepancy in the population of electrons and protons grows, so does the charge on the ion. For example, a carbon atom with seven electrons in its cloud would have a net charge of -1 .
- Bohr's model was the first of its kind to suggest that electrons are not spread evenly throughout the volume of an atom but, rather, that they only make up the outer portion of the atom. Furthermore, he suggested that there are distinct energy levels around the nucleus, each of which can only hold a finite number of electrons and which fill sequentially from smallest to largest. He also postulated that each energy level was divided into specific volumes that could only hold two electrons each. We call these volumes orbitals.

Principal Energy Levels

- If we limit ourselves to neutral atoms, meaning that the addition of electrons must match the rate at which we add protons, each of the first three rows of the periodic table represents the filling of different energy levels by electrons. Because energy levels

Hydrogen *** H 1.008 1									Helium *** He 4.003 2
Lithium * Li 6.941 3	Beryllium * Be 9.012 4								
Sodium * Na 22.99 11	Magnesium * Mg 24.31 12	Boron * B 10.81 5	Carbon * C 12.01 6	Nitrogen *** N 14.01 7	Oxygen *** O 16.00 8	Fluorine *** F 19.00 9	Neon *** Ne 20.18 10		
		Aluminium * Al 26.98 13	Silicon * Si 28.09 14	Phosphorus * P 30.97 15	Sulfur * S 32.07 16	Chlorine *** Cl 35.45 17	Argon *** Ar 39.95 18		

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fill from lower energy to higher, only the highest energy level in any atom can be unfilled. We call this outermost energy level the valence shell.

- Let's begin by adding protons and neutrons to a hypothetical atom, one pair at a time, tracking our progress through the periodic table. Our first pair gives us a hydrogen atom. The first energy level will be the valence shell for this atom. Currently, it has one electron in its first energy level. Addition of a second pair takes us to helium, which has two electrons in its first energy level. So, the first level is still the valence shell.
- As we prepare to continue, however, we notice that the first energy level is completely full. Our third electron must be placed in the second energy level, so we begin a new row on the table—a row of elements with their valence shell in the second energy level.
- The second energy level is much larger than the first and can hold as many as eight electrons, so as we progress through beryllium, carbon, nitrogen, oxygen, fluorine, and neon, we see that the same energy level is being populated.
- As we round out our trip through the first three rows, we begin populating the third energy level, which can also hold only eight electrons. The filling of this energy level is comprised of sodium, magnesium, aluminum, silicon, phosphorus, sulfur, chloride, and argon.

The Octet Rule

- The free energy of a substance is simply a measure of its stability. It tells us something about how much potential the system has to do work. Just as physical processes trend toward lower energy states—such as a ball rolling down a hill or heat transferring from a hot radiator into a cold room—it is the more stable states of matter that tend to form in chemical processes as well.
- This concept was developed by American chemist Willard Gibbs in the late 1800s. Gibbs modeled the free energy of a system as a function of two important factors. The first of these is enthalpy, which is simply energy contained within a system (H). The second term of the Gibbs free energy calculation is the temperature in kelvins multiplied by the entropy of the system (S). Entropy is often simply defined as randomness or disorder.
- The total Gibbs free energy of a system at a given temperature is equal to the enthalpy of the system minus the absolute temperature at which the process takes place multiplied by the entropy of the system. At a given temperature, the change in free energy (ΔG) is equal to the change in enthalpy (ΔH) minus the unchanging temperature multiplied by the change in entropy (ΔS):
$$\Delta G = \Delta H - T\Delta S.$$
- When the Gibbs free energy change for a process is negative, we call the process spontaneous. Spontaneous processes are favored because the energy of the products is lower. A spontaneous reaction will eventually happen on its own, but it may not happen.
- Entropy (or disorder) is not on the side of chemical bonding, because bonds attach freely moving atoms into higher-order structures. So, the entropic penalty of bonding must be overcome somehow if we expect a bond to form at all.

- The key to chemical bonding is its effect on the enthalpy of a system, or the energy released when a bond forms. If this process of fixing atoms in space relative to one another is to be spontaneous, then there must be something about the linkage that lowers their chemical potential energy, but what is that driving force?
- The answer to this question is the octet rule, an observation first made in 1919 by Irving Langmuir, who noted that atoms of smaller elements seemed to have an unusual stability when the outermost energy level of their electron cloud was filled with electrons. The octet rule is that having a full outer energy level lowers the energy of an atom.
- Only helium, neon, and argon naturally have these completely filled outer energy levels when they are isolated neutral atoms. This makes helium, neon, and argon particularly stable and unreactive, earning this column of the table the moniker “noble gasses.”

Covalent and Ionic Bonding

- Chemical bonding, simply defined, is an energetically beneficial interaction between atoms that requires them to maintain a specific distance from one another in space. Atoms are so small, and when bonded the distances between them are so short, that a special unit of distance, called an angstrom, is used to measure bond lengths. One angstrom is one ten-billionth of a meter.
- Introductory chemistry courses often teach that there are two kinds of bonds: ionic and covalent. But the truth is that there is a continuum of bonds, with ionic at one extreme and covalent at the other. These two modes of bonding are distinct, but both are driven by the same drive for atoms to obtain a full valence shell.
- Ionic bonding occurs when atoms of significantly different electronegativity come together. Simply put, electronegativity is a measure of how hungry an atom is for electrons. In general, if we neglect the noble gasses, electronegativity increases as we move from left to right on the periodic table because the nuclei of atoms

are becoming increasingly positively charged. Electronegativity also increases from bottom to top because the electron clouds are becoming smaller, screening the nucleus from the outer electrons the least.

- The alternative end of the bonding spectrum is the covalent bond. When we pair two atoms of very similar electronegativity, neither is particularly willing to exchange electrons with the other. But there is another solution to this problem: the sharing of electrons rather than the transfer of them, in which each atom is fooled into thinking that it has its own octet. This is the driving force behind covalent bonding.
- But the complexity of electron sharing doesn't stop there. There are also double bonds, in which two pairs of electrons are shared, and polar covalent bonds, which give water its high polarity among common solvents.

Atomic Orbitals

- All valence electrons are not equal. There is more to defining the orbits of electrons than just the principal energy level in which they reside. In order to show the specific volume of space in which each electron resides within an energy level, we have to introduce a second level of organization: atomic orbitals.
- All energy levels contain a single *s* orbital. *S* orbitals are spherical in shape and increase in size with increasing principal energy level. The 1*s* orbital is smaller than the 2*s*, which is again smaller than the 3*s*.
- Because each *s* orbital can only hold two electrons, the remaining six electrons from the second and third principal level must find another home. They do so in an array of three distinct *p* orbitals per level. Like *s* orbitals, *p* orbitals increase in size with increasing principal energy level. Unlike *s* orbitals, however, *p* orbitals are shaped like a dumbbell, with a node at the nucleus of the atom. All three *p* orbitals of any level are slightly higher in energy than the corresponding *s* orbital but are equal in energy to one another.

Sigma and Pi Bonding

- Two major classes of covalent bonds pervade the science of organic chemistry: sigma bonds and pi bonds. Sigma bonds form whenever orbitals overlap along the internuclear axis, such as two *s* atomic orbitals overlapping. Atoms with available *p* orbitals can also accomplish this type of bonding by overlapping one lobe of a *p* orbital.
- Placing electron density directly between the two positively charged nuclei screens them from repelling one another, creating a very strong bond. In fact, sigma bonds are so stable that they are always the first type of bond to form between two atoms. It does, however, create a bond around which the attached atoms can spin, like the axle of a vehicle, giving these bonds free rotation.
- Pi bonds, on the other hand, form when *p* atomic orbitals overlap in a side-to-side fashion. There is no electron density along the internuclear axis, but rather above and below the bonded atoms. This makes pi bonds somewhat weaker than sigma bonds but also gives them some very interesting properties, such as restricted rotation—and, in many cases, greater reactivity, because their electrons are easier to remove.

Orbital Hybridization

- The elegant, simple symmetry of methane (CH_4) was a puzzle to chemists until renowned physical chemist Linus Pauling published his theory on orbital hybridization in 1931. Pauling postulated that atomic orbitals could combine with one another, creating new sets of orbitals with some *s* character and some *p* character—which he referred to as hybrid orbitals.
- Remarkably, Pauling's theory was spot on, and methane—the simplest of all organic molecules—was all the evidence he needed. Its four identical carbon-hydrogen bonds can only be explained by Pauling's proposed orbital hybridization theory.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 1.1–1.8.

Wade, *Organic Chemistry*, Chaps. 1.2–1.8.

Questions to Consider

1. Why is it that the first bond between two atoms is always a sigma bond, while the second and third bonds are always pi bonds?
2. If chemical bonding lowers the enthalpy of a system, what induces chemical bonds to break when reactions are taking place?

Drawing Chemical Structures

Lecture 3

How do scientists communicate to one another the structures of molecules and the changes they undergo? In many cases, effective communication requires that scientists help others understand the geometric relationships of bonds and atoms. In this lecture, you will investigate the challenge of providing a reader with the right structural information about molecules. You will learn about the techniques that are widely used to help researchers communicate effectively, predicting and explaining the properties of new compounds.

Communicating the Identity of the Atoms

- We often model molecules as connected spheres, in which atoms are represented by the spheres and the sticks tell us where bonds connect these atoms. These models are called ball-and-stick models. By far the most popular color choices for these cartoonlike representations of atoms are those pioneered by Robert Corey, Linus Pauling, and Walter Koltun—called the CPK color scheme.
- The problem, of course, is that building models isn't always practical. We often need to quickly depict the structure of a molecule using little more than a pen and paper or a two-dimensional computer screen. When chemists endeavor to draw molecules for one another, they must convey three critical types of information: the identity of the atoms, the connectivity of those atoms, and the geometry of the molecule.
- The empirical formula of a compound gives us the identity and ratio of each element in the compound. For example, a molecule containing two carbon atoms and four hydrogen atoms called ethene has an empirical formula of CH_2 , because the ratio of its two constituent elements is one to two. Of course, many different compounds may have the empirical formula CH_2 , including a molecule known as butylethylene.

- But the empirical formula is limited in its ability to distinguish among compounds of similar composition. Unlike the empirical formula, a molecular formula gives us the exact number of each type of atom in the compound (rather than its simplest whole-number ratio). Using its molecular formula, we would describe ethene as C_2H_4 and butylethylene as C_6H_{12} .

Communicating the Connectivity of the Atoms

- Imagine a situation in which molecular formulas might be the same for two different compounds. Although the molecular formula solves the ambiguity between ethene and butylethylene, consider comparing butylethylene to a similar yet distinct chemical cousin: tetramethylethylene. Both will have the molecular formula C_6H_{12} , but the atoms are connected differently.
- This is where the second parameter—connectivity—becomes important. Each compound consists of 6 carbon atoms and 12 hydrogen atoms, but the double bond is in a different location between the two.
- Hydrogen is the placeholder of organic chemistry, meaning that it can be substituted with other atoms or groups. So, when we have a different or more complex group in a place that would otherwise be bonded to a hydrogen, we call these groups substituents.
- In order to convey this difference in connectivity, we move on to a condensed structural formula, in which each carbon, its hydrogens, and its substituents are written as an individual formula in a series. For example, butylethylene would be represented as $CH_2CHCH_2CH_2CH_2CH_3$, while tetramethylethylene would be represented as $(CH_3)_2CC(CH_3)_2$.
- In some cases, chemists use the expanded structural formula for a compound, which explicitly shows each bond. Although there is no additional information in this representation, it requires less effort on the part of the viewer to thoroughly understand it.

- You can probably imagine how use of structural formulas can quickly create a page overly crowded with letters, numbers, and lines. When this is the case, we sometimes turn to what are known as line-angle formulas. In this shorthand method of drawing, the terminus or angle in any line is understood to be a carbon atom. All other atoms are expressly written in, with the exception of hydrogen atoms that are bonded to those carbons. It is, therefore, understood that when a carbon atom appears to be missing bonds to complete its octet, there must be hydrogen atoms connected to those carbon atoms.

Communicating the Arrangement of Atoms

- It is the complex three-dimensional frameworks provided by carbon that make organic compounds so diverse and useful. But this three-dimensional complexity comes with a cost. How do we effectively convey three-dimensional structures onto a two-dimensional screen or page?
- It takes time to create such complex constructs, even with the benefit of software like ChemDraw. Chemists often quickly construct images to convey three-dimensional arrangements, relying on a trick inspired by cartographers.
- Most early maps were straightforward and simple to construct due to the misconception that the Earth was flat. But about 500 years ago, it started to become obvious that the Earth is not flat but round, meaning that it has a third dimension that must be considered. Mapping a globe proved to be much more complicated because the three-dimensional curvature of the object affects the appearance of the two-dimensional projection. In cartography, this problem is solved by the projection of some or all of the globe onto a two-dimensional surface in various ways.
- While it may seem a stretch to relate the field of cartography to that of chemistry, chemists in fact have devised similar schemes to project three-dimensional objects of interest onto two-dimensional surfaces. The only difference is that we are not concerned with globes but molecules.

- The most commonly employed ways in which we try to show the relative positions of atoms, particularly at the introductory level, are by perspective formulas, Newman projections, Fischer projections, and stereoisomers. In all cases, we do this by projecting the three-dimensional molecule onto a two-dimensional surface.
- Just as there are many schemes for the projection of global maps onto a flat surface, there are many techniques used to project a molecule. Each of these preserves certain relationships that might be of interest to us, so they tend to be used in varying situations and on different types of molecules.

Perspective Formulas

- Suppose that you want to draw a butane molecule in a specific orientation with all carbon atoms sharing the plane of the page. When you do this, you are forced to place all but two of the hydrogen atoms out of the plane—either in front of it or behind it. So, if you needed to show specific hydrogen atoms, how might you do this?
- The method that is used to convey the location of the remaining atoms is to draw their bonds differently depending on whether they are within the plane of the page, coming forward out of the page, or falling behind the plane of the page.
- In the perspective formula, we only draw the bonds in the plane of the page as lines. A solid wedge is used in place of a line to connect atoms closer to the viewer, and a dashed wedge is used for those that would be farther away.

Fischer Projections

- Although perspective formulas are very useful for conveying the arrangements of atoms in small molecules, they can become unwieldy when larger chains of atoms are involved. In 1891, Emil Fischer was dealing with just such a problem when he was researching carbohydrates, which commonly consist of carbon chains numbering anywhere from three to six atoms in length and can be even longer.

- With so many atoms in the chain, perspective drawings can sometimes become difficult to interpret. So, Fischer devised an alternate method for showing these arrangements in the longer chains he was dealing with. In Fischer's scheme, each atom in the molecule is projected with the chain oriented up and down on the page in such a way that the chain itself is falling behind the page.
- When this is done, the two groups not in the chain have bonds that appear horizontal but are located above the page. So, projecting this arrangement onto a two-dimensional surface casts a "shadow" of the molecule, in which all vertical bonds are pointing behind the page and all horizontal bonds are pointing above the page.

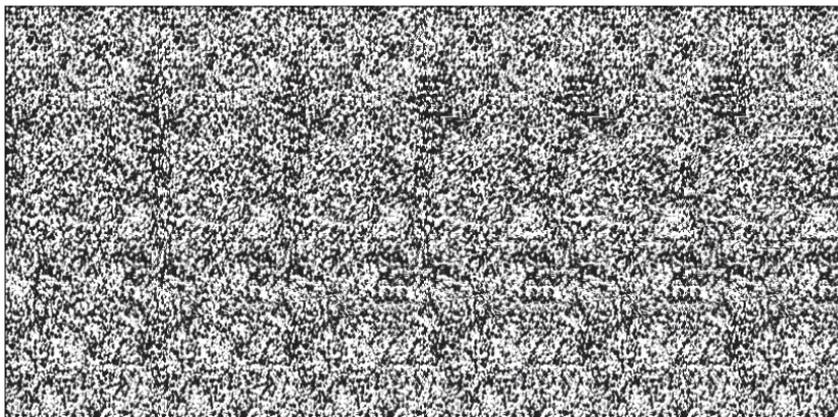
Newman Projections

- The third method of projection we owe to Melvin Spencer Newman, who was an American organic chemist working at Ohio State University in the middle of the 20th century. Newman is famous for his prolific career synthesizing and characterizing hydrocarbons, but arguably his most useful contribution to the science is the tool he created that bears his name: the Newman projection.
- In some cases, not only is the connectivity of atoms crucial, but also the rotational state of the bonds in a molecule can affect its reactivity. Certain reactions require that substituents on adjacent atoms be aligned in certain ways. We define this sort of angle between substituent bonds on adjacent carbons as dihedral angles. As the carbon-carbon bond rotates, these dihedral angles change. Chemists call these different states of the same molecule differing only by the dihedral angles of their substituents "rotamers."
- Newman's problem was that while perspective formulas and Fischer projections are both effective methods of communicating the arrangement of atoms about tetrahedral centers, neither is particularly useful for clearly and concisely depicting a specific dihedral bond angle.

- To view dihedral angles better, in Newman projections, the closer (or proximal) atom is drawn as a circle, and its bonded substituents are depicted with lines going all the way to the center. The farther (or distal) atom is obscured by the closer (or proximal) atom, and the other three bonded substituents are depicted with lines that end at the perimeter of the proximal atom, as though they are behind it. The other three groups bonded to the proximal atom are connected by lines that run all the way to the center of the projection. In this way, any rotational state for the chosen bond can be easily and accurately shown on paper.

Stereoimages

- One of the great fads of the 1990s was what we popularly refer to as “magic eye” posters, which have a hidden three-dimensional image buried within a seemingly simple pattern. The trick to seeing the three-dimensional image is to focus your eyes on a point far beyond the picture in the distance. When this is done with the viewer standing at the requisite distance, a three-dimensional image appears to leap off of the page.



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Stereoimages are helpful in visualizing three-dimensional models on two-dimensional surfaces.

- This neat trick used to create novelties to hang on your wall can also be used to place any three-dimensional drawing on a two-dimensional page. Magic eye posters work because what appears to be only one complex pattern in fact contains two adjacent patterns: one intended for your left eye and the other for your right. Focusing on a distant point causes your eyes to see separate images that convey slightly different perspectives, simulating a phenomenon called parallax. When your left eye and your right eye see slightly different images, your brain combines these images and interprets the differences to create depth.
- If you want to use this method to show a molecule in three dimensions, you can use software to generate an image of the molecule and then a second image just slightly rotated, producing the two images your brain would use to help you perceive depth. Placing these images side by side at just the right distance creates an image akin to the magic eye posters.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 1.1–1.8, 2.5.

Wade, *Organic Chemistry*, Chaps. 1.4, 1.8–1.11.

Questions to Consider

1. When using a Newman projection to depict dihedral bond angles, does it matter which atom is depicted as proximal and which is depicted as distal?
2. When viewing a stereoimage intended for wall-eyed viewing, how would the image appear to a viewer who is crossing his or her eyes instead (reversing the images for the left eye and right eye)?

Drawing Chemical Reactions

Lecture 4

As useful as it is to have representations showing compounds in their most stable, ideal states, chemists are ultimately concerned with a material's physical and chemical properties in the real world, where bonds vibrate and electrons move through clouds around those bonds. These physical and chemical changes are best communicated not by a single ideal representation but by how the molecule truly behaves as time passes. In this lecture, you will learn how to create drawings that depict the transfer of electrons from one location to another, resulting in the formation, alteration, or breaking of connections between atoms.

Depicting Resonance

- Electrons within a molecule's electron cloud are always in motion, and pi bonds have a unique ability to form and break without altering the connectivity of atoms, because their stronger sigma bonds can remain intact while the weaker pi bonds are broken.
- So, electron pairs that are not involved in bonding at all—sometimes called lone-pair electrons—and pi-bonding electrons can be more mobile within a molecule's overall electron cloud and can sometimes occupy a region much larger than just that defined by a hybrid orbital or an isolated pi bond. They can traverse great distances across molecules using *p* orbitals without disrupting the connectivity of the atoms.
- These long, interconnected systems of *p* orbitals are sometimes called pi systems. So, as electrons move through these pi systems, no reaction is taking place, but our method of drawing an individual structure begins to fail.
- The phenomenon of electrons moving about a molecule is called resonance, and each drawing of the molecule is called a resonance contributor. In general, the more resonance contributors you

can draw, the more free electrons are to move around within a molecule's electron cloud. This freedom of electron motion tends to stabilize compounds.

- To show resonance, we place brackets around all contributing structures, and we use straight, double-headed arrows to separate each contributor. These are your cues to create the best possible approximation of the molecule's structure by mentally combining all of the resonance contributors into a weighted-average structure called the resonance hybrid, which will give you the best approximation of the structure if you want to predict the reactivity or properties of it. Contributors with less charge separation tend to be a closer representation of the hybrid than their charge-containing counterparts.

Depicting Change with Time

- Creating a static depiction of a system that is changing through time can be a challenging undertaking, but it is one that humanity has deemed worthy since prehistory. For example, the cave painters of Paleolithic Europe and Africa tried to document their hunts with just a few simple markings.
- Similarly, modern-day comic strip artists tell a story using a storyboard of static images depicting different moments in the narrative. It is up to the readers to combine these images in their minds to create a seamless, running story.
- Organic chemistry is no different. Someone might show you the chemical structures of ammonium cyanate and urea, but unless that person gives greater detail, it is up to you to decide how you think the transition took place using your understanding of how organic chemistry works.
- Of course, technology has progressed to the point at which we often do not have to perform this exercise anymore. Computer animation fills in all of the gaps and can give us maximum detail about how a process takes place.

- But even with the advantages of modern technology, fully animating a story is not always the best choice. It certainly leaves out most ambiguities, but it requires a great deal of effort to create and also special devices to view. For the purposes of day-to-day communication, chemists prefer to use a faster, shorthand style of depicting reactions that has developed over the centuries.

Reaction Schemes

- The simplest possible illustration of a chemical change is a reaction scheme. Chemists often do not know or feel the need to convey minute mechanistic details of a chemical reaction as it takes place. Sometimes their argument simply depends on what was present at the beginning of the reaction and what is present at the end.
- When this rudimentary level of detail is sufficient, we often use reaction schemes to show the four most crucial details of any chemical reaction: starting materials, products, conditions, and reversibility. We always write reactions from left to right when possible, indicating reagents on the left and products on the right.
- We separate these two groups of materials with an arrow or arrows that tell us something about the reversibility of the reaction, and above these arrows is a notation of special conditions, catalysts, or other crucial information about the reaction.

Reaction Mechanisms

- So far, the drawing examples we have learned about have been limited in the sense that they convey a great deal about what we start and end with but relatively little about what goes on in the interim. Because reaction schemes only show a list of starting materials and products, we are left to wonder exactly how those starting materials go about becoming products. One might make the analogy that it is like having a pile of boards, screws, and other pieces and a picture of the table they make when assembled, but the step-by-step manual is missing.

- When organic chemists want to convey the process of conversion in more detail, they turn to a style of drawing known as a mechanism. A mechanism, just like that manual for assembling our table, is a series of elementary steps, each not only showing the starting material, reversibility conditions, and products, but also explicitly showing how electrons from each species are exchanged to make and break bonds.
- By drawing a mechanism, we increase the amount of information in our illustration by including the intermediates in our drawing. “Intermediate” is a term used by chemists to describe those species that form transiently during a reaction but quickly go on to react again to complete the process.
- But far from simply showing these punctuated states throughout the reaction, we want to demonstrate how each interconverts. This means depicting the flow of electrons that makes and breaks bonds during each step. We accomplish this using curved arrows. When two electrons are involved, we use a full head on the arrow, and when just one electron is moving, we use a half-headed arrow.

Energy Diagrams

- So, we are now acquainted with the techniques used not only to draw molecular structures, but also in the elements of drawing used to convey elementary steps and the electron transitions that take place in each one. But there is one more piece of information that is crucial to understanding how these transitions occur: the chemical energetics of the process.
- Just like in classical physics, chemists think in terms of potential energy. Just as a physical object, like a ball, is expected to roll down a hill, thereby decreasing its potential physical energy and reaching a more stable state, so will a molecular system react in a way that decreases its overall potential chemical energy, also making it more stable. The difference is that chemical energy is a bit less intuitive to determine.



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Just as a ball has an associated physical potential energy that it would like to release, a collection of molecules will have an associated chemical free energy in their initial state.

- Still, to fully understand the process of a chemical reaction, we need a quick and convenient method for demonstrating whether a particular transition increases or decreases the overall chemical free energy of the system and by how much.
- To better understand this concept, consider the simple example of a ball perched just behind a hilltop. Classical physics tells us that the potential energy of that ball in its current position is higher than that of the same ball at the bottom of the hill. When given a small push to overcome the barrier, the ball will spontaneously roll downward, presumably coming to rest at the bottom in the lowest energy state available.
- Chemical systems are a perfect analogy for the physical system that was just described. Just as the ball has an associated physical potential energy that it would like to release, a collection of molecules will have an associated chemical free energy in their initial state. When a small energetic barrier is overcome by the addition of heat, catalysts, or other perturbations, the system can then convert spontaneously to its lower energy state.

- Chemists often convey this energetic landscape of a chemical reaction mechanism using this hill analogy in what is known as a reaction coordinate diagram—the only difference being that the “hill” is one of chemical potential energy rather than one of physical potential energy. So, these diagrams are essentially plots of system free energy as a function of reaction progress.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 3.6–3.9.

Wade, *Organic Chemistry*, Chap. 4.

Questions to Consider

1. Reversible processes are taking place all around us on every scale—from cosmological to atomic. What are some equilibria that you encounter on a daily basis that could be written as a scheme and manipulated using Le Chatelier’s principle?
2. Molecules are constantly bending, twisting, and vibrating objects that we often draw in rigid form using average bond angles and distances. What are some of the potential pitfalls of using these rigid models to predict the behavior of dynamic molecules?

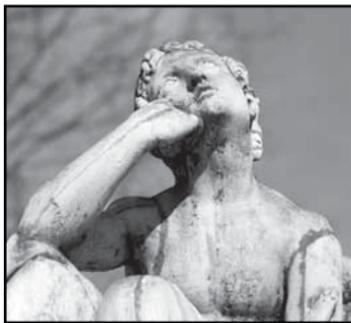
Acid–Base Chemistry

Lecture 5

It may seem daunting to consider the sheer number of possible molecular structures and how they might all interact with one another. But many reactions follow similar pathways and generally obey similar rules, so chemists group reactions into just a few fundamental classes. Probably the simplest of all of these reactions is the proton-transfer reaction, in which an acid and a base exchange just one simple hydrogen nucleus. In this lecture, you will learn about the three classifications of acids and bases, the reaction between acids and bases, and what makes one acid stronger than another.

Classifying Acids and Bases

- Acids tend to dissolve metals and cause color changes in certain substances, and many have very acrid odors and sour tastes. Acidity is a property granted by the presence of hydrogen—specifically, hydrogens that can be removed as H^+ ions. Of course, hydrogen ions are essentially protons, so we use these terms interchangeably.
- In chemistry, bases are the alter ego of acids. The presence of bases lowers the concentration of hydrogen ions. Acids transfer their acidic protons to bases. Sometimes the transfer of protons from one molecule to another happens with desirable results, and sometimes with undesirable results—but always with powerful results. The transfer of protons from acids to bases is by far the most common and arguably the most influential reaction in all of organic chemistry.



Acidity is responsible for the weathered look of some statues.

© Milous Chabri/Stock/Thinkstock

- There are three ways in which chemists categorize acids and bases: Arrhenius, Brønsted–Lowry, and Lewis systems. Each of these is named for the chemists who first proposed the system, and each was devised to be most useful in certain situations.
- Arrhenius acids increase the concentration of protons when added to water. Arrhenius bases increase the concentration of hydroxide ions when added to water. In the Brønsted–Lowry system, acids are still defined as proton donors, but bases are instead defined as proton acceptors. Lewis acids are those species that can easily accept an electron pair to form a new bond, while Lewis bases donate electron pairs to bonds.

Proton Transfer

- Proton-transfer reactions are usually very fast, reaching equilibrium long before other reactions can occur. There are, of course, exceptions to this rule, but in general, we can expect that a system will reach its most stable protonation state long before any other reactions can occur.
- The proton-transfer reaction is an equilibrium—a state of dynamic interconversion between or among products and reactants. In some cases, just a small amount of products coexists with reagents at equilibrium. In others, the roles may be reversed, with a sample consisting of nearly all products and just a small amount of reactants. The extent to which this equilibrium lies in favor of products or reactants is dependent on the strengths of the acids appearing in the equation.
- The strength of an acid—for example, a hypothetical compound HA—can be thought of simply as how easily that acid loses its acidic proton. Upon loss of a proton, an acidic molecule becomes a base. We call such a pair of species (differing by only one hydrogen and one unit of charge) conjugate acids and bases, and we call this reaction an acid dissociation. So, in our simple acid dissociation, the conjugate acid–base pair is HA and A^- , respectively.

- The strength of acid HA can be modeled mathematically as an equilibrium process, which produces an equilibrium constant expression of conjugate base concentration multiplied by proton concentration divided by conjugate acid concentration. For any given acid, this expression will always produce the same number at equilibrium. We label this value K_a for the acid in question.
- Because K_a values can be extremely large or small, spanning dozens of orders of magnitude, we often report these values as $\text{p}K_a$, or the negative log of the K_a value. Using this system, a K_a of 0.1 becomes a $\text{p}K_a$ of 1, a K_a of 0.01 becomes a $\text{p}K_a$ of 2, a K_a of 0.001 becomes a $\text{p}K_a$ of 3, and so on. In general, $\text{p}K_a$ values are a valuable means of quickly comparing acid strengths.
- But if proton transfer occurs between an acid and a base, we have to consider the properties of the base partner, too, right? If we are interested in determining the extent to which a proton transfer can take place, we need simply to compare the strengths of the acids present on each side of the equation.
- If we take two hypothetical compounds, HA and HA', we can write a proton-transfer reaction between the two in which a hydrogen and a unit of positive charge are transferred from one to the other. When we do this, we get a product of A⁻ and HA'.
- But we can break this down into two separate reactions, one being the acid dissociation of HA in the forward direction and the other being the acid dissociation of HA' in the reverse direction. Because we can sum the two reactions to learn the overall process, we can multiply their equilibrium constants to determine the equilibrium constant for the overall process.
- The new equilibrium constant now tells us not only which side of the proton-transfer reaction is favored, but by how much. Increasingly larger constants increasingly favor products, while smaller constants increasingly favor reactants.

Factors Affecting Strengths of Acids and Bases

- Careful consideration of a compound's structure allows us to estimate its acidity or make an assertion about the relative acidities of two compounds, though not necessarily to predict their exact pK_a values. Because the loss of a proton by an acid always produces its conjugate base, one way to predict acidity is to simply assess the stability of the conjugate base that forms. A more stable conjugate base means a stronger acid with a higher K_a and a lower pK_a .
- In general, two factors combine to affect the stability of such conjugate bases. First is the electronegativity of nearby atoms causing electrons to be pulled away from the site at which the proton would be held.
- Second is nearby pi systems providing the stabilizing effect of resonance. Both of these factors affect stability essentially the same way—by spreading and delocalizing the charges that can form when proton removal occurs.
- These trends offer chemists a quick way to estimate relative acidities of compounds—a property that can be critical in synthesis, purification, and identification.

Polyprotic Acids

- Monoprotic acids have just one acidic hydrogen because their other hydrogens are bonded strongly and directly to the carbon scaffold, so their acid–base chemistry is limited to a simple two-state system in which the molecule is either protonated or deprotonated. We call these types of acids “monoprotic” because they have just one acidic hydrogen that can be removed under all but the most extreme conditions.
- This makes acid–base equilibria involving monoprotic acids very easy to model, because there are only two potential states: protonated or deprotonated.

- When an acid can—and sometimes actually does—lose two or even three protons in an acid–base reaction, we refer to it as a “polyprotic” acid, because it has multiple acidic hydrogens. The conjugate bases that still contain acidic hydrogens have the very interesting property of being able to act either as an acid, losing a proton, or as a base, accepting a proton. We call these species that can act as acids or bases “amphoteric.”

Tautomers

- There is a special type of proton transfer called tautomerization. During this process, a proton is transferred within the molecule itself. This can take place as a completely intramolecular process, or with a bit of assistance from a base to transport it.
- For a proton transfer to be considered tautomerization, a proton must be relocated without disturbing the connectivity of the other atoms in the molecule.
- One example of this is called a keto–enol tautomerization, in which a double-bonded oxygen accepts a proton while a nearby carbon loses a proton. In this case, the resulting charge separation is rectified by relocating a double bond. Because the atom connectivity is not disturbed, this is a true tautomerization.

Zwitterions

- A second type of intramolecular proton transfer takes place in amino acids like glycine, which contains an acidic site and a basic site on the same molecule. Just as in the case of tautomers, the acidic site loses a proton while the basic site accepts it.
- The distinction is that a zwitterion cannot neutralize the resulting charges by resonance. Glycine, just like all other amino acids, has an sp^3 carbon between the two sites, which prohibits us from drawing any resonance structures that redistribute charges.

- Instead, the proton transfer creates a species with two isolated regions of charge. We call species with distinct regions of opposing charge zwitterions. The name comes from the German word *zwitter*, meaning “hybrid.”

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 1.10–1.12.

Wade, *Organic Chemistry*, Chap. 1.12.

Questions to Consider

1. Weak acids and bases are often used to initiate reactions by protonating or deprotonating just a small fraction of a starting material at equilibrium. Often, this can lead to a complete conversion to products. How is this possible?
2. The pH scale is theoretically infinite. Why is it that we often see a scale of 0 to 14 used when discussing aqueous solutions?
3. Does any given acid or base have only one associated pK_a value, or can conditions like temperature and solvent have an effect on the acidity or basicity of a compound?

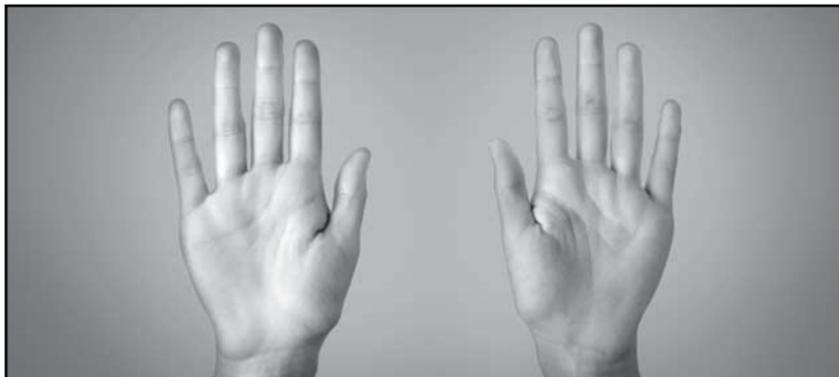
Stereochemistry—Molecular Handedness

Lecture 6

In this lecture, you will investigate the phenomenon of stereoisomerism. Specifically, you will explore the idea of handedness and how chemists have given this phenomenon a different name: chirality. In addition, you will learn how tetrahedral centers in molecules can be chiral and how handedness can be inverted. You will also be introduced to some examples of stereoisomers, including enantiomers and diastereomers. You will explore how it is possible for compounds to have stereoisomers even when they do not have chiral centers. Finally, you will learn about a system for ranking substituents around stereocenters and about how chiral centers are categorized.

Handedness

- Carbon atoms can have up to four sigma bonds, meaning four different bonded substituents arranged tetrahedrally about the central atom. When these four substituents are all distinct from one another, there are two different possible arrangements that have the same connectivity.



Like stereoisomers, human hands are non-superimposable mirror images of one another.

- Consider a tetrahedral center with four distinct substituents. If you make an exact copy of the structure and then interchange the location of two substituents, the resulting structure has all of the same connectivity but cannot be superimposed with the original by translation or rotation.
- These two hypothetical molecules have handedness. For example, the direction of the thumb, palm, and fingers are all unique to a person's right hand. If you try to superimpose your left and right hands, you cannot make all of those objects superimpose simultaneously.
- When interchanging two substituents on a central atom produces a new molecule, that central atom is called a stereocenter. A tetrahedral carbon is this tetrahedral center with four distinct substituents, which chemists call chiral centers. The result is nonsuperimposable objects with identical connectivity, which chemists call stereoisomers.

Enantiomers, Diastereomers, and Meso Compounds

- Pairs of stereoisomers fall into several distinct categories, and understanding each of them is critical to understanding the physical and chemical properties of some organic compounds. The first class of stereoisomers is enantiomers. These can be thought of as nonsuperimposable mirror images or as a pair of compounds in which all of the stereocenters are inverted.
- In the simplest example of a tetrahedral center with just one stereocenter, this is the only possible relationship that we can develop (because you can't invert a fraction of a stereocenter).
- When more than one chiral (or "handedness") center is present in a molecule, the picture becomes a bit more complicated. Take the example of a compound with two nonidentical stereocenters. Inversion of both stereocenters produces a mirror image that cannot be superimposed with the original. A set of enantiomers can be

made. Recall that enantiomers are compounds in which all chiral centers have been inverted.

- But now that we have multiple centers, it is possible to invert only one chiral center while leaving the other in its original state. When we do this, the result is a compound with identical connectivity that is neither superimposable nor a mirror image. Such pairs of compounds are called diastereomers.
- Sets of diastereomers are distinct from sets of enantiomers in that they can, and often do, have different physical properties, such as boiling and melting points.
- A third and somewhat unusual situation arises when a compound contains two stereocenters with the same four substituents attached to each. In this instance, it is possible to have a situation in which a complete inversion of stereochemistry leads to a mirror image that is still superimposable with the original. We call compounds like this meso compounds.

Achiral Stereoisomers

- Not all stereoisomers contain chiral centers. Recall that the definition of “stereocenter” is that interchanging two groups on the center changes the identity of a molecule. Recall also that pi bonds have restricted rotation, owing to the side-to-side overlap of *p* atomic orbitals that cannot be interrupted unless we break the pi bond. Because we cannot rotate pi bonds, it is possible to have a compound that has multiple stereocenters, even though there are no tetrahedral atoms in the stereocenter.
- A simple example of this is the molecule commonly called beta-butylene. At a glance, beta-butylene seems simple enough, but each carbon in the pi bond has two other distinct substituents bonded to it. Combined with the fact that the pi bond restricts rotation, there are actually two different isomers: one with the larger CH_3 groups at opposition and the other with the larger CH_3 groups on the same side of the molecule.

- The presence of the pi bond makes these two isomers distinct from one another, because breaking the pi bond between the intervening carbons would be necessary in order to achieve the kind of rotation necessary to make them superimposable. This sort of thing doesn't tend to happen on its own; it takes a very special set of circumstances to encourage such a change.

The Cahn-Ingold-Prelog Convention

- Because multiple isomers of compounds with stereocenters are possible, naturally we need to come up with a labeling system to distinguish them from one another. Several systems exist, but the most commonly used is the Cahn-Ingold-Prelog convention, which is named after the three chemists who proposed it: Robert Cahn, Christopher Ingold, and Vladimir Prelog.
- The Cahn-Ingold-Prelog convention gives us a way to assign a rank to all of the substituents around a stereocenter. We can then use these ranks to describe the geometric arrangement of a compound quickly and easily.
- The system that Cahn, Ingold, and Prelog suggested was one of a sequential comparison of atoms within competing substituents. In short, as one moves out from the stereocenter one bond at a time, comparing all atoms encountered, the substituent with the first instance of a heavier atom wins a higher priority. Any time a double or triple bond is encountered, the doubly or triply bonded atom is counted twice or thrice, respectively.
- A very common “gotcha” associated with the Cahn-Ingold-Prelog convention is that we only consider one bond at a time when determining priorities. This means that groups that overall appear very large can sometimes be of lower priority than groups that appear smaller but have a heavier atom close to the stereocenter.

The *R/S* System

- The ranking system proposed by Cahn, Ingold, and Prelog gives us the basis for assigning a universal stereochemistry designation to particular chiral centers, but we have yet to define exactly how we use these rankings to define the geometry of stereocenters. The most common use of these rankings is in what is called the *R/S* system of nomenclature.
- In this system, each chiral center is given a designation of (*R*) or (*S*), depending on the arrangement of the ranked substituents about the center in the following way. We rank all four substituents, placing the fourth ranked substituent at the back of the molecule. Next, we draw a curved arrow passing the first, second, and third ranked substituents. If the arrow traces out a clockwise rotation, we call this the (*R*) enantiomer (from the Latin *rectus*, or “right”). If, instead, it traces out a counterclockwise path, we call it the (*S*) enantiomer (from the Latin *sinister*, or “left”).
- One very useful aspect of the *R/S* system is how simple it is to tell if you are dealing with enantiomers or a meso compound in cases with two similar chiral centers.

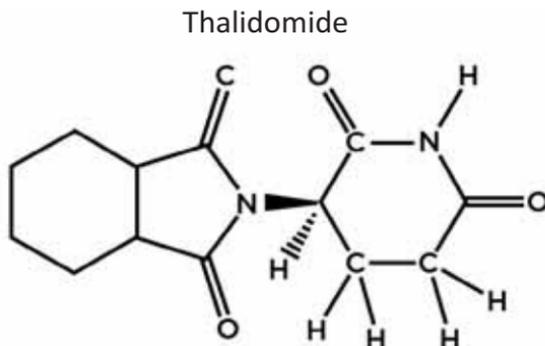
The *E/Z* System

- The Cahn-Ingold-Prelog convention is also used in designating stereoisomers that contain double bonds but are not chiral. Let's return to the example of beta-butylene. Remember that the pi bond in the molecule restricts rotation about the central carbon-carbon bond, meaning that one version of the molecule exists in which both CH₃ groups are on the same side of the molecule and another in which they are at opposition.
- We sometimes call these isomers “cis” and “trans,” respectively. But in the *E/Z* system, we use a parenthetical (*Z*) for the isomer with higher-priority groups on the same side and (*E*) for the isomer with higher-ranking substituents on opposing sides. The *E* and *Z* designations are derived from German words for “opposite” and “together.”

- The real utility of the *E/Z* system comes when you have a double-bonded carbon with two non-hydrogen substituents, such as 2,3-dibromo-2-butene. In this case, *cis* and *trans* can be a bit ambiguous, because it isn't abundantly clear which groups we are comparing. But applying the Cahn-Ingold-Prelog convention makes it obvious which is *E* and which is *Z*.

Thalidomide

- Once touted as a miracle cure for a variety of ailments, thalidomide is now infamous for its ability to cause birth defects in growing fetuses. Like many drugs, thalidomide contains a chiral center. One isomer of thalidomide has desirable pharmacological properties, but the other isomer, which was thought to be completely innocuous, was in fact a powerful angiogenesis inhibitor, meaning that it inhibits the development of blood vessels critical to proper fetal growth.
- Interchanging two of the four substituents of thalidomide produces a mirror image of the original that cannot be superimposed. We could call these two compounds enantiomers of one another. It is the (*R*) enantiomer of thalidomide that has desirable sedative properties, but its (*S*) enantiomer causes defects in developing fetuses. Knowing this, can we simply remove the (*S*) enantiomer from the product?



- In the case of thalidomide, this is unfortunately not possible, and the reason why goes back to acid–base chemistry. Because the hydrogen on the chiral center is weakly acidic, it can be removed by weak bases in the bloodstream, and then replaced from the other side. This means that any attempt to get pure (*R*) thalidomide into the bloodstream would only result in its conversion to a racemic mixture within minutes.
- But many pharmaceutical products in use today—from simple anti-inflammatories like ibuprofen to opiates like methadone—contain chiral centers creating sets of stereoisomers, only one of which has the desired pharmacological properties.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chap. 6.

Stephens, *Dark Remedy*.

Wade, *Organic Chemistry*, Chap. 5.

Questions to Consider

1. In general, a tetrahedral (sp^3) center is necessary for a compound to have a stereocenter. Cumulenes (compounds with two adjacent double bonds) violate this trend, exhibiting the potential for chirality about a carbon that is sp hybridized. Why do cumulenes sometimes exhibit chirality?
2. What are some examples of achiral and chiral objects that you encounter on a daily basis, and how does their symmetry or asymmetry affect their design and use?

Alkanes—The Simplest Hydrocarbons

Lecture 7

In this lecture, you will learn about alkanes, including their basic molecular formula and the way in which they are named. You will discover that millions of realistic possible alkane structures exist with just a few carbon atoms. In addition, you will learn how structure affects physical properties of alkanes. You also will be introduced to a few chemical reactions involving alkanes, including combustion in oxygen and free-radical halogenation, and to the phenomenon of hyperconjugation, which helps explain why radical halogenations tend to occur best at more-substituted carbons.

Introduction to Alkanes

- Hydrocarbons are historically and commercially important compounds. Alkanes are the simplest class of hydrocarbons. The term “alkane” refers to any hydrocarbon in which all of the carbon atoms are sp^3 hybridized, meaning that there are no pi bonds present.



Hydrocarbons are historically and commercially important compounds, providing power, heat, and light.

- Because all of the carbons in an alkane must have four bonds, the empirical formula of alkanes is always $C_n H_{2n+2}$. The smallest three alkanes possible are methane, ethane, and propane. We can continue adding carbons to our chains to create the familiar stove and lighter fuel, butane.

Branched Alkanes and Structural Isomerism

- One can imagine how dull the science of hydrocarbons might be if only one type of hydrocarbon existed for each number of carbons. Limiting ourselves to an ever-lengthening straight chain of carbon only provides one distinct hydrocarbon for each molecular formula.
- Fortunately, this is only the case for three of them: methane, ethane, and propane. When we reach four carbons, new connectivities become possible, and the number of possibilities quickly grows as we add more.
- The addition of the fourth carbon atom leads to a situation in which more than one structural arrangement of atoms is possible—what chemists call structural isomerism. For example, the carbons of butane can form a straight chain, but a second possible arrangement is possible in which the fourth carbon atom is branched off from a chain of three. Each of these molecules is a hydrocarbon of the formula C_4H_{10} , yet they are different chemical entities because of the difference in bond connectivity.
- But these two isomers of butane only scratch the surface of a vast library of alkanes, because each additional carbon atom exponentially increases the number of possibilities. There are 2 structural isomers of butane, 3 isomers of pentane, 5 isomers of hexane, 9 isomers of heptane, and 18 isomers of octane. If we double that carbon count to just 16, a staggering 10,359 structural isomers exist for the same alkane.

Nomenclature of Alkanes

- Because the structures of alkanes can be exceedingly complex, a system of nomenclature is in order so that we can unambiguously define which structure or structures we are talking about. Much like the base names of linear alkanes, some of the simpler branched alkanes have common names. “Isobutane,” for example, is used to convey a branched four-carbon molecule, while “isopentane” and “neopentane” are often used to describe the two-branched forms of pentane.
- Using common names for isomers of butane and pentane seems like a fine idea. There are, after all, just a few extra structural isomers to consider for each. But the sheer number of possibilities as alkanes grow larger shows us how unwieldy such a system would be.
- The International Union of Pure and Applied Chemistry (IUPAC) is a professional standards agency that makes recommendations on standardization of all things chemistry, including nomenclature. IUPAC has come up with a method of nomenclature that is highly systematized. The IUPAC rules for nomenclature of alkanes are as follows.
 1. Find the longest continuous carbon chain in the molecule.
 2. Name all of the branched substituents using its prefix, ending in “-yl.”
 3. Number the parent chain carbon atoms sequentially, giving the lowest possible substituent number.
 4. Construct the compound name, indicating the location and names of all substituents alphabetically, followed by the parent hydrocarbon.

Physical Properties of Alkanes

- Alkanes do not have polar bonds that can affect the attractive forces between them. They have only their electron clouds, which are soft and polarizable. This means that as electrons move about the molecule's electron cloud, an intermittent charge buildup, or dipole, can form in one molecule and induce a second intermittent dipole in a neighboring molecule, provided that they are close enough.
- These two dipoles cause compounds to attract one another slightly, resulting in higher boiling points and increased viscosities. We call this type of attractive force London dispersion forces.
- One can imagine that longer alkanes with larger electron clouds can produce stronger London dispersion forces than their shorter counterparts. This is clearly manifested in the phase behavior of hydrocarbons. Smaller chains making up methane, ethane, propane, and butane are easily recognized as gasses at typical pressures and temperatures, at which pentane, hexane, heptane, and octane are liquids.
- Chemists use the term "volatility" to describe the tendency of a compound to vaporize. So, we would say that methane is more volatile than pentane or that octane is less volatile than propane. This term should not be confused with the more colloquial meaning of volatility, which is taken to mean unstable, unpredictable, or explosive.
- But the trend in volatility does not stop there. The boiling points of each hydrocarbon just mentioned systematically increase as chains lengthen and dispersion forces increase attraction among similar molecules.
- Branching also has a predictable effect on physical properties. As hydrocarbons of the same mass become increasingly branched, they boil at lower and lower temperatures. This is a reflection of the reduced surface area contact possible between branched molecules.

Chemical Properties of Alkanes

- Alkanes are not terribly reactive from the organic chemistry standpoint. Their lack of polarity leads to structures that do not tend to participate in most reactions, but it does give them the ability to dissolve a wide array of more reactive compounds. For this reason, liquid-phase alkanes are commonly used in organic chemistry labs as solvents.
- Among the reactions that can be undertaken with alkanes is combustion with oxygen, which leads to a mixture of carbon dioxide and hydrogen in an irreversible process. This is one of the processes that we rely on to power engines, provide heat, and give us light.
- But chemists rely on combustion for yet another purpose. We can use it as a means for comparing the stability of similar compounds. This type of experiment is called calorimetry.
- A calorimeter is a sealed system that is charged with a known amount of a given compound and enough oxygen to completely combust it. If the combusted materials produce the same products (in the case of hydrocarbons, this would be carbon dioxide and water), then any difference in the heat released must be a result of differences in the stability of the starting material. More heat released means that a less stable compound was combusted.



Combustion of hydrocarbons is a process we rely on to power our engines.

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Radical Halogenation

- With such a large supply of varied hydrocarbons available, they make an attractive entry point to organic synthesis for many different carbon scaffolds. Despite their relatively low reactivity, alkanes are frequently used for this purpose in labs and chemical plants around the world.
- One of the most important uses from a synthetic organic chemistry standpoint is as a starting material used in the synthesis of a set of compounds called alkyl halides. Because carbon-carbon and carbon-hydrogen bonds are so stable, we have to use an unusual trick to get them to react. We have to present them with a highly reactive atom of a halogen, such as fluorine, chlorine, iodine, or bromine.
- The mechanism for this reaction begins with activation of a halogen molecule by a photon of a very specific wavelength, usually in the ultraviolet part of the spectrum. We usually represent light activation with the characters $h\nu$, which are actually variables representing Planck's constant and frequency. When multiplied together, these terms yield the amount of energy carried by a photon of a given type of light.
- When a halogen molecule like chlorine absorbs this photon, the bond between the two halogen atoms breaks, sending one bonding electron to each atom. We call this sort of bond breaking "homolytic" because the bond breaks symmetrically. This is called the initiation step of the reaction.
- The result of this process is two halogen atoms, each of which contains an unpaired electron. We call species with unpaired electrons "radicals." In our example, these two chlorine radicals only have seven valence electrons and want desperately to fill their octet.

- One chlorine radical accomplishes this by removing a hydrogen from the alkyl halide, generating an alkyl radical. So, now our alkyl radical has a carbon with an incomplete octet, and it finds a second halogen molecule to react with. This process satisfies the alkyl radical but generates a new chlorine radical that can react similarly with another alkane.
- This phase of the reaction is known as propagation. During propagation, new product is forming, but new chlorine radicals are also forming, carrying on in a chain reaction.
- Finally, the chain reaction terminates when two alkyl radicals react in a homogenic bond formation. Just as homolytic bond breaking sends two bonding electrons in separate ways, homogenic bond formation takes place when a new bond forms from two electrons, one from each bonding partner.
- At the end of this reaction, we have reacted an alkane and chlorine by a photoactivated reaction to form hydrochloric acid, an alkyl halide, and a small amount of the termination product. This is a very distinctive reaction—not only because it is a photoactivated radical reaction, but also because it is a chain reaction. We turn to this technique to modify alkanes because their remarkable stability requires such extreme measures.

Hyperconjugation

- What happens when there are multiple carbons in the hydrocarbon starting material? The answer is that the halogenation will occur preferentially at the most substituted carbon possible. The exception to this is quaternary carbons, because they do not have a bonded hydrogen, which is required for the reaction to take place.
- For example, propane has primary and secondary carbons, and even though it is outnumbered two to one, it is the secondary carbon that will get the chlorine atom in greatest abundance and, therefore, will be the major product.

- To understand why this happens, we need to invoke a phenomenon called hyperconjugation. Any time a p atomic orbital makes an appearance adjacent to an sp^3 bonding orbital, there can be an alignment that allows electrons to be intermittently shared between the two. In the case of a radical, there is only one electron in the nonbonding p orbital, but placing a methyl group next to it means that there will be a bonding orbital that can align with it, sharing just a small amount of its electron density with its electron-deficient neighbor.
- Distribution of electrons tends to lead to stability, so when we compare the two possible radicals that can form from propane in this process, we see that a primary radical can form in which one stabilizing hyperconjugation is present, but in the secondary radical, there are two of these interactions.
- Because it is more stable, the secondary radical is expected to form in greater abundance during this process, leading to modification of the secondary carbon as the major product.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 2.1–2.4.

Wade, *Organic Chemistry*, Chaps. 3.1–3.9.

Questions to Consider

1. Some of the earliest recorded waterproofing used by boat builders was a hydrocarbon-based material called bitumen. What is it about the structure of hydrocarbons that makes them so effective at repelling water?
2. The radical chlorination of isobutane can potentially form two different products. Which is expected to form in excess, and why?

Cyclic Alkanes

Lecture 8

This lecture will focus on the structural and chemical implications of wrapping our carbon chains into loops, forming what are sometimes called cycloalkanes. You will start by learning the general formula of cyclic alkanes, and then you will learn the nomenclature of this new class of hydrocarbons and how cyclization creates new geometric relationships among hydrogens and substituents. In addition, you will be introduced to the phenomenon of ring strain. Finally, you will be introduced to a few bicyclic hydrocarbons.

Cyclic Alkanes

- The connectivity of carbon atoms in hydrocarbons leads to millions of possible geometric isomers, including cyclic chains. Because carbon can bond so well to itself, a chain of atoms frequently turns back on itself and creates a cyclic chain. We see such cyclic chains in a variety of organic compounds, from medicines to explosives.
- The simplest possible cyclic hydrocarbon, one with three carbon atoms, has found uses as a starting material for many organic syntheses, as well as medical applications as an anesthetic, so this deceptively simple molecular structure belongs to a powerful and versatile organic compound.
- Starting with its linear cousin, propane, and then cyclizing the compound, notice that bonding the two terminal atoms has several consequences. First, the terminal carbon atoms must each give up a hydrogen to make space available for the cyclizing bond. This means that the generic formula for a cyclic alkane is C_nH_{2n} , compared to C_nH_{2n+2} , as in its analogous linear hydrocarbon.

- Next, notice that even though all of the carbons are sp^3 hybridized and, therefore, should have free rotation, they in fact do not. The ring structure prohibits the carbon-carbon bond axis from rotating. This leads to a new type of isomerism—one in which the side of the ring to which substituents are attached makes a difference. When substituents are placed on the same side of the ring, we use the term “cis” to describe their relationship. When substituents are on opposite sides of the ring, we use the term “trans.”

Nomenclature of Cycloalkanes

- The IUPAC system of nomenclature for cycloalkanes is similar to that for linear alkanes (Lecture 7), with a few basic modifications. First, the root name is given the prefix “cyclo-” to indicate that the parent chain is in fact cyclic. So, the three-membered ring that is the cousin of propane would be named cyclopropane. Similarly, rings of increasing size would be named cyclobutane, cyclopentane, and cyclohexane.
- Our next consideration is that those cyclic alkanes with a single substituent do not require a number to give that substituent its location on the ring. This, of course, stems from the fact that all carbons on any unsubstituted ring are equivalent. So, we would name this molecule methylcyclobutane.
- When two identical substituents are bonded to the ring, we designate their locations using 1 as the first, and then proceed around the ring in a manner that gives the lowest second number to the other substituent. For example, we would begin naming this compound 1,3-dimethylcyclobutane.
- When two or more different substituents are present, we number the ring atoms starting with the substituent that comes first alphabetically, and then proceed around the ring in a direction that leads to the lowest substituent numbers. For example, we would name this compound 1-ethyl-3-methylcyclobutane.

- But there is more to this structure. Because the carbon-carbon bonds can no longer freely rotate, placing two substituents on the same side of the ring produces an isomer that is distinct from the one that has substituents on opposite sides of the ring. To distinguish these isomers, we name them “cis” for the same side and “trans” for the opposite sides: cis-1-ethyl-3-methylcyclobutane and trans-1-ethyl-3-methylcyclobutane.
- Such molecules can have chiral centers that must be ranked by the Cahn-Ingold-Prelog convention and given (*R*) and (*S*) designations.

Ring Strain

- In addition to new nomenclature and isomerism, small cyclic alkanes (those containing 3 to 10 atoms) come with yet another consideration that affects their reactivity. In cyclopropane, the carbon-carbon bonds must be 60 degrees, because the 3 atoms are necessarily coplanar.
- Yet we already know that sp^3 carbons ideally form bond angles of 109.5 degrees. The fact that the ring structure forces bond angles into suboptimal geometries is known as angle strain, sometimes also referred to as Baeyer strain, which is named for notable chemist and Nobel Prize winner Adolf von Baeyer, who first proposed this concept.
- Also, if we turn the cyclopropane molecule on its side and produce a Newman projection, it becomes clear that all of the substituents of this compound are locked in an eclipsed conformation. This inability to achieve a staggered conformation is referred to as torsional strain.
- When we combine these two forms of strain—angle and torsional—we get an overall measure of instability known as ring strain. It is the total energetic cost of having CH_2 groups forced into the geometry dictated by the ring, as opposed to freely rotating CH_2 groups in a hypothetical linear alkane.

How Penicillin Works

- Penicillin works by inhibiting an essential enzyme called transpepsidase, which is used by certain types of bacteria to build their cell walls. When a molecule of penicillin interacts with this enzyme, the four-membered lactam ring (which is under considerable ring strain) opens as the molecule reacts with the enzyme's active site—the region of the enzyme where the cell wall reinforcing bonds are normally made.
- By bonding to the enzyme, penicillin chemically modifies its active site, causing the enzyme to malfunction. It can do this with remarkable efficiency because the formation of the new bond to the enzyme is energetically driven by the opening of a four-membered ring, guaranteeing that the process proceeds with a reduction in overall free energy.

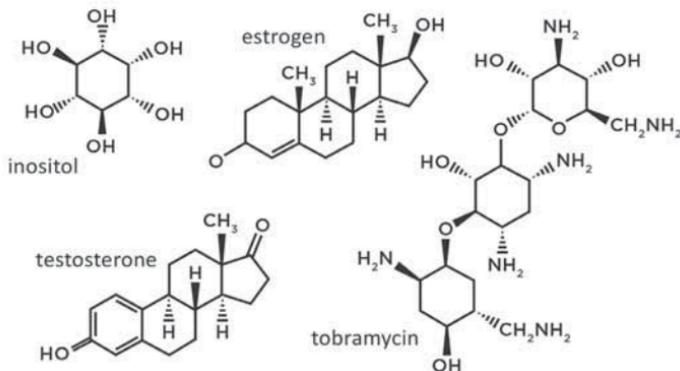


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The age of modern antibiotic revelation began with Alexander Fleming and his discovery of penicillin.

Conformational Analysis of Cyclohexane

- A strained ring of sp^3 atoms can give a molecule powerful chemistry. But lack of strain can be every bit as important of a feature in a biologically relevant molecule. For example, it is its lack of strain that makes cyclohexane a pervasive motif in the chemistry of life. We see this structure in powerful hormones like human sex hormones testosterone and estrogen, the antibiotic drug tobramycin, and the metabolite inositol. It is this ubiquity and versatility that make cyclohexane the gold standard of cyclic alkanes in any organic chemistry course.



- When a cyclohexane molecule is drawn in the chair conformation, we can approximate the ring of carbon atoms with a circle. If we do this, we can see that there are two distinct substituent positions: one above and below the ring and another around the ring's perimeter. Because these positions are distinct from one another, we give them the names axial and equatorial, respectively.
- But molecules are not static entities. Their bonds vibrate and twist under the influence of thermal energy, and because of this, cyclohexane is capable of a remarkable transformation known as a ring flip. When a ring flip takes place, the headrest and footrest of the imaginary chair interchange, and in doing so, they create a second chair conformer in which all of the axial substituents are now equatorial—and all of the equatorial substituents are now axial. Far from simply rotating the molecule, a ring flip is in fact a conformational change, which progresses through several other higher-energy conformations.
- In this case, all of the substituents are the same (hydrogen). But if we are dealing with a substituted cyclohexane molecule with various groups attached to the ring, the ring flip becomes a very, very important conformational change.

Bicyclic Compounds

- When two hydrocarbon rings share one or more atoms, we call them bicyclic systems. By extension, we might call a molecule like testosterone a tetracyclic molecule, because it actually has four rings, each of which shares atoms with others.
- The combination of cyclic structures in alkanes can be accomplished in three different ways. When two rings share only a single carbon atom, we call this a spiro bicyclic compound. When the rings are conjoined by two adjacent carbons, we call them fused, and when their linkage is at two nonadjacent carbons, we call them bridged.
- In the case of spiro compounds, two rings are linked through a single central sp^3 -hybridized carbon atom. We can mentally construct one simply from two five-membered rings by linking them through a single atom. Obviously, this is not how they are made, but it is this concept of joining two rings that gives bicyclics their name.
- We name these compounds using “spiro-” as a prefix. Next, we catalog the lengths of the two bridges joined by the spiro atom. In this case, there are five atoms in one bridge and five atoms in the other bridge. So, we place these two numbers into brackets, separated by a decimal. Finally, we count the total number of atoms in the compound, including the spiro atom, and name our alkane: spiro[5.5]nonane. If these numbers were not equal, we would arrange them in increasing order within the brackets.
- The tetrahedral geometry of this atom leads spiro compounds to have a twist to them, sort of like an airplane propeller. This twist does not make them inherently chiral, but it does mean that some substituted spiro compounds can have a chiral spiro atom.
- When two rings are joined by two adjacent shared carbon atoms, we refer to it as a “fused” bicyclic compound. The IUPAC name for fused bicyclics are constructed using the prefix “bicyclo-”

followed by a bracketed list of the number of atoms in each bridge. Finally, just as before, we inventory all of the atoms in the system and name this compound.

- What makes fused bicyclics so interesting from a structural perspective is their ability to form two different isomers: one in which the hydrogens on the shared carbons are anti to one another and a second in which they are gauche. We call these isomers *trans*-decaline and *cis*-decaline. And it should be clear from the two structures that the *trans* isomer is a bit more stable than its *cis* isomer, because it has only two gauche interactions, compared to three in the *cis* isomer.
- Because it is more stable, it is not surprising that the *trans*-decaline geometry is the one we see in most biomolecules, such as testosterone and estrogen. If either of these molecules were made in the *cis* conformation, their biological activity would be completely different than their *trans* isomer.
- Finally, when two rings are joined by sharing two nonadjacent carbons, we refer to these as “bridged” bicyclic compounds. We start by writing “bicyclo” to show that we are talking about a bicyclic compound, and then we identify the size of each bridge created by the geometries. This is done in brackets, longest bridge to shortest bridge. Finally, we name the compound based on the total number of atoms in the entire fused bicyclic structure.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 2.7–2.11.

Wade, *Organic Chemistry*, Chaps. 3.10–3.16.

Questions to Consider

1. Explain why *trans*-1-ethyl-2-methylcyclohexane tends to exist as only one conformer while *trans*-1-ethyl-3-methylcyclohexane interconverts readily between two different conformers.
2. Is it possible for decaline molecules to undergo ring flips like their non-fused cyclohexane counterparts?

Alkenes and Alkynes

Lecture 9

In this lecture, you will investigate how pi bonds change the chemistry of hydrocarbons. You will be introduced to alkenes, which are hydrocarbons containing double bonds, and alkynes, which are hydrocarbons containing triple bonds. In addition, you will discover how the work of two chemists on trends in the stability of alkenes led to our understanding of trends in stability among various stereoisomers of the same molecular formula. You will also learn about the unusual acidity of terminal alkynes. Finally, you will learn about the effect of pi bonds on cyclic structures.

The Structure of Pi Bonds

- The first bond between any two atoms in organic chemistry is almost always a sigma bond. The electrons in these bonds occupy the area along the internuclear axis, so they can rotate like the axle of a car without any meaningful energetic input.
- But pi bonds are quite different. During the formation of double and triple bonds, the second and third bonds must find a different region of space to inhabit—one that still screens the two nuclei from one another but does not occupy the space directly between them, because the original sigma bond electrons already have claim to that space.
- Pi bonds form as a consequence of side-on overlap of u -hybridized atomic p orbitals. The shape of the p orbitals allows them to overlap in a region above or below the internuclear axis. This leads to two distinct differences between pi bonds and sigma bonds.
- The first is that double and triple bonds cannot rotate freely the way single bonds can. Rotation of the bond would require that the pi bond be broken completely, leaving only the remaining sigma bond intact.

- The second is that pi bonds are weaker than sigma bonds. Being located in a less centralized molecular orbital means that pi electrons tend to be held less tightly in the resulting bonding orbital. This means that less energy is required to break a pi bond.
- It is possible to break just a pi bond of a double bond while leaving the sigma bond intact, if the proper energy is provided. So, the atoms can be kept connected even while free rotation is temporarily restored.
- Pi bonds make up the second and third pair of electrons in double and triple bonds, respectively. However, there is no such thing as a quadruple bond in introductory organic chemistry. It is physically, geometrically impossible to obtain the orbital alignments required to form a carbon-carbon quadruple bond.

Alkenes and Alkynes

- Hydrocarbons like alkanes, consisting of only sigma-bonded hydrogen and carbon atoms, are called saturated hydrocarbons. Conversely, hydrocarbons that contain pi bonds are sometimes collectively referred to as unsaturated hydrocarbons.
- At the most basic level of organization, there are saturated hydrocarbons, which are also called alkanes, and two classes of unsaturated hydrocarbons—those with a double bond, called alkenes, and those with a triple bond, called alkynes.
- The simplest possible hydrocarbon containing a double bond is ethene, which is also known by the more common name ethylene. Ethylene is a naturally occurring alkene and a plant hormone that is critical to the ripening process in a number of fruits and vegetables.



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Ethylene is a naturally occurring alkene and plant hormone critical to ripening.

- Ethylene has a molecular formula of C_2H_4 , and its generic molecular formula is C_nH_{2n} . This is the generic molecular formula for all simple alkene hydrocarbons (“simple” means having just one double bond in the hydrocarbon) like propylene, butylene, and beyond.
- The simplest possible alkyne is a compound called acetylene. This compound is most well known for its use as a torch fuel, but just like ethylene, its reactive pi bonds also make it a very useful synthetic precursor to many important compounds.
- Ethylene has a molecular formula of C_2H_2 , and its generic molecular formula turns out to be C_nH_{2n-2} . All simple alkyne hydrocarbons, such as methylacetylene and ethylacetylene, will have this generic formula.
- When the localized pi system of an alkene or alkyne is in the middle of a longer carbon chain, we call this an internal alkene or an internal alkyne. When the pi system is instead at the end of a chain, we call them terminal alkenes and terminal alkynes.

Naming Alkenes and Alkynes

- The presence of weaker—and, therefore, more reactive—pi bonds gives alkenes and alkynes a special place among motifs in nomenclature. We call them functional groups rather than substituents. As functional groups, they receive special attention in IUPAC nomenclature. These and all other functional groups are indicated not at the beginning of a molecule’s name like substituents, but rather at the end.
- For example, a three-carbon alkane would be called propane. Insertion of a double bond leads to propene, and conversion of this to a triple bond gives us propyne. Note that it is the *suffix* that indicates the presence of the functional group: “-ane” for simple alkanes, “-ene” for alkenes, and “-yne” for alkynes.

- In situations requiring that we give the functional group an address, we use the lowest numbered carbon participating in the multiple bond. For example, dimethylethylene becomes 2-butene, and ethylethylene becomes 1-butene.
- You may also see the number for the functional group appearing between the root and suffix, such as but-2-ene, but-1-ene, but-2-yne, and but-1-yne. This change was made by the IUPAC in the 1990s, so it hasn't yet had the time to reach full acceptance. Most modern texts teach naming both ways.
- But the special treatment of functional groups doesn't stop with their position in the name. It also gets special priority in the numbering scheme for the parent chain.

Stereoisomers of Alkenes

- Vladimir Markovnikov and Aleksandr Zaitsev were two of the most influential chemists in the development of the understanding of alkenes. They were contemporaries studying under another great chemist, Aleksandr Butlerov, in the Russian system in the 1870s.
- With respect to the stability of alkenes, Markovnikov believed that less-substituted alkenes, such as 1-butene, were more stable, while Zaitsev held the opposing view—that more-substituted alkenes, such as 2-butene, were more stable. In this crucial debate, Zaitsev proved victorious with a paper published in 1875.
- Just as with hydrocarbon radicals, alkenes have *p* orbitals. In this case, they are participating in bonding with an adjacent *p* orbital, but they can still align with other hybrid orbitals on adjacent carbon atoms. So, more adjacent carbon atoms means more places for electrons to move, which leads to extra stability.
- Zaitsev used an alcohol dehydration reaction to demonstrate that alkenes of higher substitution are indeed more stable. Zaitsev needed to use this system because, frankly, it was one of very few understood reactions in his day. Modern chemists can much

more easily verify Zaitsev's conclusions. Today, we often compare the stability of unsaturated hydrocarbons using the technique of calorimetry.

- In a calorimetry experiment, a reaction is allowed to run to completion in a closed, well-insulated vessel, and the temperature of the contents is monitored. On completion of the reaction, the amount of chemical potential energy gained or lost by the reacting molecules is proportional to the temperature change of the surroundings within the calorimeter.
- Conducting a simple calorimetry experiment gives us great insight into the factors affecting alkene stability. An equal quantity of 1-butene releases more heat when hydrogenated, which validates Zaitsev's rule. We also see that not only is Zaitsev's rule validated, but the geometric arrangement of larger substituents also appears to affect stabilities, with (*E*)-2-butene being more stable than (*Z*)-2-butene.
- The difference in stability between the (*E*) and (*Z*) isomers is usually attributed to sterics—that is, the physical proximity of substituent electron clouds in the molecule. Placing two larger alkyl substituents close to one another, as in the (*Z*) isomer, causes a natural repulsion that is not present when those substituents are at opposition in the (*E*) isomer.
- Not surprisingly, internal alkynes also prove more stable than their external counterparts. So, we see the same trend that Zaitsev would predict for internal and terminal alkynes, though the linear geometry of these compounds precludes any geometric isomerism.

Alkynes and Acidity

- We know from the geometry of a carbon-carbon triple bond that alkynes are not capable of the kind of stereoisomerism that makes alkenes so fascinating. But that doesn't make them uninteresting. Alkynes have their own properties that make them interesting to organic chemists.

- One very interesting property of alkynes is their acidity. Internal alkynes do not have a very acidic proton, because all of their hydrogens are on sp^3 carbons, just like an alkane. The pK_a of a terminal alkyne, however, is about 26, which may seem like a very weak acid, and in fact it is.
- But compared to the acidity of alkenes, with a pK_a of about 44, and of alkanes, whose pK_a is about 60, alkynes start to look like a pretty acidic compound. So, at a pK_a of 26, terminal alkynes are weak acids in the overall scheme of things, but they are rock stars of acidity among hydrocarbons.
- In fact, there are just a few bases available to us in the laboratory—albeit very strong ones—that are capable of deprotonating terminal alkynes. Most notable of these is the amide ion, the conjugate acid of ammonia, which has a pK_a of about 35. It is not easy to work with, but it is available.

acid	pK_a (class)	acid	pK_a (class)
$\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C} & - & \text{C} & - & \text{H} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$	60 (sp^3 carbon)	$\text{CH}_3\text{CH}_2\text{-O-H}$	16 (alcohol)
$\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{C} & = & \text{C} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$	44 (sp^2 carbon)	$\begin{array}{c} \text{O} \\ \\ \text{H}_3\text{C} & - & \text{O} & - & \text{H} \end{array}$	5 (carboxylic acid)
NH_3	35 (conj acid of NH_2^-)	H-Cl	-7 (H-X)
$\text{H-C}\equiv\text{C-H}$	26 (sp carbon)		

- So, what is the source of this acidity in compounds like acetylene and propyne? The answer is that alkyne carbons are sp hybridized. Heterolytically breaking the carbon-hydrogen bond means that both bonding electrons will go to the carbon. This means that the hybrid orbital into which the bonding electrons go has about 50% s character, as opposed to about 33% s character for an alkene and 25% s character for an alkane.

- s orbitals hold their electrons tighter and closer to the nucleus than do p orbitals of the same principle energy level. So, more s character in a hybrid orbital means a more stable lone pair in that orbital. And a more stable conjugate base means a more acidic conjugate acid.
- These deprotonated alkynes are remarkably reactive compared to neutral hydrocarbons, and they can prove very useful reagents in the synthesis of other organic compounds.

Cyclic Alkenes and Alkynes

- Just as alkanes can be cyclic, so can alkenes and alkynes. Cyclic alkenes and cyclic alkynes follow many of the same rules as cyclic alkanes, but with two important considerations. First, just like with linear and branched hydrocarbons, the presence of the π system usually makes them much more reactive than similar alkane counterparts.
- Second, the inclusion of a double bond (with sp^2 carbons and angles of about 120 degrees) or a triple bond (with sp carbons and a bond angle of 180 degrees) can significantly affect the ring strain of a cyclic hydrocarbon.
- Cyclization of small alkenes also has the important effect of stabilizing the *cis* isomer.

Suggested Reading

Lewis, D. E., "Aleksandr Mikhailovich Zaitsev (1841–1910): Markovnikov's Conservative Contemporary," *Bulletin for the History of Chemistry* 17/18 (1995): 21–30.

McMurry, *Fundamentals of Organic Chemistry*, Chap. 3.

Wade, *Organic Chemistry*, Chaps. 7.1–7.7, 9.1–9.7.

Questions to Consider

1. Are alkenes and alkynes higher or lower in free energy than alkanes of similar size? Explain.
2. Terminal alkynes in the presence of a moderately strong base can isomerize to a more stable internal alkyne. Propose a mechanism for this process involving the use of an alkoxide, whose conjugate acid pK_a is about 16.

Alkyl Halides

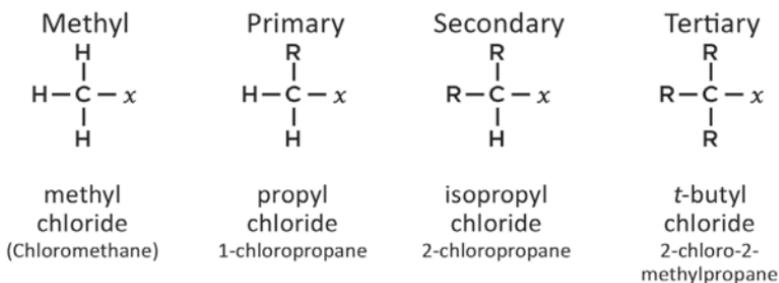
Lecture 10

This lecture will introduce a new class of atoms to the structural mix by expanding the inventory of compounds to include the halogens fluorine, chlorine, bromine, and iodine in a class called alkyl halides—which can be thought of as hydrocarbons in which one or more hydrogen atoms are replaced by a halogen substituent. You will examine both common and IUPAC systems for naming these compounds. In addition, you will learn how the presence of larger, more polarizable halogen atoms decreases the volatility of alkyl halides. You will also learn about the reactivity of alkyl halides. Finally, you will be introduced to the phenomenon of carbocation rearrangements.

Nomenclature of Alkyl Halides

- We commonly refer to simple alkyl halides as alkyl fluorides, chlorides, bromides, or iodides, depending on which halogen is attached. However, the halogens are not ionized like they are in inorganic materials like sodium chloride in your table salt. They are, in fact, covalently bonded to the carbon atom.
- In addition to classifying alkyl halides by which halogen is attached, organic chemists frequently classify alkyl halides based on the substitution of the carbon bearing the halogen (we call this atom the alpha carbon). If there are no other carbons, we call them methyl halides.
- One alkyl group attached to the alpha carbon is a primary alkyl halide. Two attached groups are called a secondary alkyl halide, and three would be called a tertiary alkyl halide. When the exact identity of an alkyl group is not of consequence, we sometimes use the abbreviation “R” to indicate a general alkyl group.

- So, the molecule commonly called propyl chloride would be considered a primary alkyl halide because of its single R group. Next is isopropyl chloride, which has two R groups attached to the carbon bearing the chlorine. So, this would be a secondary alkyl halide. Finally, the simplest tertiary alkyl halide is *t*-butyl chloride.
- From an IUPAC naming perspective, halogens are treated exactly as any alkyl substituent would be, using the prefixes “fluoro-,” “chloro-,” “bromo-,” and “iodo-” to define them. Using the IUPAC naming convention, propyl chloride becomes 1-chloropropane, isopropyl chloride becomes 2-chloropropane, and *t*-butyl chloride becomes 2-chloro-2-methylpropane.



Physical Properties of Alkyl Halides

- Halogens are much larger and more electronegative than hydrogen, and their presence on the molecule has two important effects. First, the size of the halogen atoms means that their large electron clouds are more polarizable. This makes them better suited to create the intermittent dipoles needed to form strong London dispersion forces, increasing their boiling point when compared to their alkane cousins.

- Second, the electronegativity of the halogen produces a permanent dipole in the carbon-halogen bond. The halogen will have a permanent partial negative charge, and the carbon will have a permanent partial positive charge. The dipoles of each type of carbon-halogen bond are very similar because the bond dipole is a function not only of electronegativity, but also of the bond length.
- The addition of a single halogen to an alkane backbone leads to a molecule with a much larger electron cloud. These large electron clouds lead to greater polarizability and, thus, stronger London dispersion forces. This trends when we increase the size of the bonded halogen. This principle also leads us to the conclusion that the number of bonded halogens will have an effect.
- Methane is a gas commonly used as a fuel with a boiling point of -161 centigrade. Add just one chlorine atom to this scaffold and you obtain the molecule methyl chloride, which boils at -24 centigrade. This trend continues as we add yet another chlorine and form dichloromethane, which boils at 40 centigrade.
- This trend continues with chloroform at 140 centigrade, and finally, we have completely saturated the carbon with four chlorines, creating tetrachloromethane, also known as carbon tetrachloride. This behemoth boils at 170 centigrade.
- Carbon tetrachloride is a liquid at standard temperature and pressure and was a popular garment dry-cleaning solvent in the late 1900s, which has fallen out of favor due to environmental and health concerns. Perhaps ironically, its popular replacement, perchloroethylene, looks very similar, and its use in dry cleaning is currently under scrutiny for its potential health and environmental impacts as well.
- The first occurrence of alkyl halides in this application was methyl chloride, put into use near the beginning of the 20th century. But methyl chloride's toxicity and flammability meant that a leaking refrigerator compressor could easily spell disaster.

- Near the end of the 1920s, a researcher named Thomas Midgely, Jr. working for the Frigidaire division of General Motors devised a new alkyl halide compound. Midgely's contribution was a method used to synthesize dichlorodifluoromethane. In doing so, he managed to create a compound with the useful physical properties, but that was also not flammable or appreciably toxic.
- Midgely and his contemporaries dubbed this class of refrigerants CFCs. Lauded as a revolution in refrigeration technology, Midgely's creation became the gold standard of refrigerants. Before long, the era of mass-scale ice shipping was over as thousands of refrigerators were using, and leaking, these compounds around the world.

Environmental Impact

- CFCs can have a potentially calamitous environmental effect in the upper atmosphere. This may be one of chemistry's greatest ironies. These compounds were designed to make life on the ground safer in the form of refrigerators that will not poison or incinerate us, but they ultimately began to produce a hole in one of the most vital protective layers of the upper atmosphere: the Earth's ozone layer.
- After carcinogenic carbon tetrachloride, flammable and toxic methyl chloride, ozone-depleting CFCs, and super-greenhouse hydrofluorocarbons, why do we keep turning to compounds like alkyl halides for such applications? The answer is the "tunability" of alkyl halide volatility. Their relative stability and our ability to methodically and predictably modify the boiling points



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Modern household items and refrigerants are now made without the use of carbon-chlorine bonds.

of these organic solvents have made them a very difficult option to abandon in a number of applications, not the least of which is refrigeration.

Reactivity of Alkyl Halides

- Alkyl halides are also valued in synthetic organic chemistry for their balance of stability and reactivity. Many alkyl halides will keep in a bottle on a shelf for years but can be converted into other useful reagents in a matter of minutes or hours in the lab.
- The key to this balance of stability and reactivity lies in the fact that carbon-halogen bonds are inherently fairly strong but polarized. Average carbon-fluorine and carbon-chlorine bond enthalpies are similar to that of a carbon-carbon bond. Even carbon-bromine bonds are quite strong. This means that in the absence of other reagents, most alkyl halides have a long shelf life.
- But unlike carbon-carbon bonds, carbon-halogen bonds are polar. The more electronegative halogen pulls the bonding electrons closer to itself, creating a mild permanent charge separation across the bond.
- Although some alkyl halides that contain many bonded halogen atoms are exploited for their physical properties, synthetic organic chemists more frequently use alkyl halides containing only one or a few halogens so that subsequent chemical reactions are more site-directed.
- Furthermore, in the low-pressure, high-energy environment of the troposphere, radicals can easily form, but they are far less common in the lab. Organic chemists much more frequently rely on the tendency of halogens to accept the full bonding pair in a process known as heterolytic bond cleavage. Accepting both electrons from the bond produces a halide ion (which is much more stable than a halogen radical) and a positively charged hydrocarbon species known as a carbocation.

- The tendency of this process to happen spontaneously in an alkyl halide is a result of two factors: the stability of the halide ion and the stability of the resulting carbocation. So, the key to predicting how a particular alkyl halide will react lies in being able to understand the factors contributing to the stability of those two products.
- Let's focus on the halide ion. Fluoride, chloride, bromide, and iodide all have a single charge and a complete octet in their outermost energy level. So, they are all fairly stable from an octet-rule perspective. However, there is a steady trend of increasing stability in this set as we go from smaller to larger ions. In general, *t*-butyl iodide more rapidly dissociates into a halide and a carbocation than does *t*-butyl bromide, which is faster than *t*-butyl chloride, which outpaces *t*-butyl fluoride.
- Next, we have to consider the resulting carbocation and its substitution. Carbocations contain a positively charged carbon atom with only three bonds to itself. So, the charged carbon has only six valence electrons; therefore, it does not have a complete octet. Instead, it has three coplanar sp^2 hybridized orbitals bonded to hydrogens or R groups, and it has a vacant *p* orbital.
- We observe in the lab that just like radicals and alkenes, carbocations of higher substitution are more stable. In other words, tertiary carbocations (those having three R groups, like the *t*-butyl cation) form more readily than do secondary carbocations (like the isopropyl cation). Similarly, primary carbocations (like the ethyl cation) are rarely ever seen in the lab. Finally, methyl cations, which have no R groups, are least stable of all. The reason for this trend in carbocation stability is hyperconjugation.
- The rate of formation of a carbocation by an alkyl halide has two important influencing factors: It gets faster as the halogen gets larger, and it gets faster as the carbocation gets more substituted. It should be emphasized that this is a general rule and that there will be exceptions—particularly when we start to consider the effect that solvents can have on reactions.

Carbocation Rearrangements

- Carbocations and species like them make regular appearances in many common reaction mechanisms, so it is worth shining the spotlight on them. One very unusual property of these species is their ability to rearrange one or more of their bonds to increase their stability.
- The substitution of a carbocation can have a profound effect on its stability, with tertiary cations being more stable than secondary, and so on. Molecules have a natural tendency to take on lower energy forms through chemical processes, and carbocations are no exception to this rule.
- Carbocations sometimes can alter their own structure through a process known as rearrangement. These arrangements can take place in two ways: secondary (meaning that it takes place after the carbocation forms) or concerted (meaning that it takes place as the carbocation forms). They can also take place by two mechanisms: hydride shifts and alkyl shifts.
- Carbocation rearrangements can be either a supreme annoyance, against which we must guard, or a clever trick, used to devise ingenious pathways to desired products. In either case, when they are possible, they must be accounted for during synthetic design. Whether these processes are friend or foe, they can have a profound impact on the outcome of a synthesis.

Suggested Reading

Giunta, C. J., "Thomas Midgely, Jr., and the Invention of Chlorofluorocarbon Refrigerants: It Ain't Necessarily So," *Bulletin for the History of Chemistry* 31, no. 2 (2006): 66–74.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 7.1–7.2.

Wade, *Organic Chemistry*, Chaps. 6.1–6.6, 6.15.

Questions to Consider

1. Explain why at room temperature carbon tetraiodide (CI_4) is a solid, carbon tetrachloride (CCl_4) is a liquid, and carbon tetrafluoride (CF_4) is a gas.
2. Carbocations can rearrange by more than just one hydride shift, alkyl shift, or ring expansion. Propose an alkyl halide that is expected to form a carbocation that undergoes more than one sequential rearrangement.

Substitution Reactions

Lecture 11

In this lecture, you will learn about nucleophilic substitution and how nucleophilic substitution mechanisms are divided into two classes— S_N2 and S_N1 —based on the rate laws for each pathway. In addition, you will learn the two most important factors influencing a substitution pathway: Strong nucleophiles and low-substitution substrates favor the S_N2 , while weak nucleophiles and highly substituted substrates favor the S_N1 . You will also learn the effect each pathway has on the retention of chirality in substrates as they undergo substitution. Finally, you will consider solvent selection for substitution reactions.

Substitution Reactions

- Any substitution reaction will have the same basic cast of characters: a nucleophile, a substrate, an electrophile, and a leaving group. Nucleophiles are defined as species that easily donate an electron pair to form a new chemical bond with another nucleus. Their name, in fact, means “nucleus loving.” An electrophile is a nucleus that, unlike the nucleophile, is deficient in electrons and is capable of receiving the electrons from the nucleophile. Their name means “electron loving.” In contrast to nucleophiles, leaving groups are those groups that easily withdraw their bonding electrons to become a separate, stable species. Finally, the entire molecule undergoing substitution is the substrate.
- With a nucleophile and a leaving group both in the mix, there are three potential permutations of a substitution reaction: one in which the nucleophile *first* attacks, and then the leaving group departs; one in which the nucleophile attacks *as* the leaving group departs; and one in which the nucleophile attacks only *after* the leaving group departs.

- The first of these three situations is impossible, because it would require that a transition state form in which the electrophilic carbon has more than eight valence electrons. But the other two are equally valid possibilities still remaining: one in which simultaneous attack and departure maintains a balance of eight valence electrons around carbon throughout the transition, and one in which initial departure of the leaving group produces a carbocation intermediate with only six valence electrons.
- One of Christopher Ingold's great contributions to the discipline of organic chemistry is his 1933 description of these two possible pathways by which substitution may take place. We call these reaction pathways S_N2 and S_N1 (substitution-nucleophilic-bimolecular and substitution-nucleophilic-unimolecular, respectively).
- Any mechanism, no matter how complex, will have what is called a rate-limiting step. This is the slowest elementary step in the mechanism, and it defines the rate of the reaction. Just as a chain is only as strong as its weakest link, a reaction is only as fast as its slowest step. The rate-limiting step and all steps before it are affected to some extent by the concentrations of reagents involved in those steps.
- In other words, the rate of a reaction is proportional to the concentration of reagents in the rate-limiting step but is unaffected by the concentrations of reagents that participate after that. In chemistry, we use a rate proportionality constant, k , to produce the rate law for a reaction.
- So, a reaction in which two reagents react in a single, concerted step should have kinetics that are proportional to the concentration of both reagents. We call this a second-order reaction. But if one reagent slowly undergoes a change all by itself in the rate-limiting step before reacting with the second reagent, then the rate will only depend on the concentration of the dissociating reagent. We call this a first-order reaction, because its kinetics depend on just one reagent concentration.

- Ingold's work with substitution reactions demonstrated that one of these two situations was almost always true: Either the reaction rate depended equally on the nucleophile and substrate concentrations, leading to a second-order rate equation, or the rate depended solely on the substrate concentration, leading to a first-order rate equation. Moreover, his work demonstrated a correlation between certain structural features of nucleophiles, substrates, and leaving groups that could be used to predict which pathway a certain reaction would take.
- Ingold began the process of linking molecular structure with function and reactivity. He observed that not only did two substitution pathways exist, but also that the tendency of reactions to proceed by one or the other was predictable based on correlated structural features in the starting materials.

The S_N2 Reaction Pathway

- The second-order nucleophilic substitution pathway, S_N2 , is characterized by a bimolecular reaction in which a nucleophile attacks and a leaving group departs simultaneously. Because it is the nucleophile's attack that initiates the leaving group's departure, the attack must take place from the opposite side of the substrate in order to break the bond to the leaving group. We call this orientation a backside attack.
- This type of reaction is expected to take place in a single, concerted step. With only one elementary step in this reaction, we expect that the reaction rate will be affected equally by the concentration of both starting materials.
- The key to a reaction running by the S_N2 mechanism lies primarily in two factors: strong (reactive) nucleophiles, like hydroxide, and less-substituted electrophiles, like methyl chloride. Let's consider each one of these factors individually.

- A strong nucleophile like hydroxide is inherently unstable. The high density of negative charge around the oxygen atom is the source of this instability, and hydroxide will seek to relieve it at its earliest chance. Another crucial feature is the degree of substitution at the electrophile. Hydroxide may be poised to attack, but it cannot attack what it cannot get to.
- Methyl chloride is an excellent choice of substrate for an S_N2 reaction, because the three hydrogen substituents leave the region of the molecule opposite the leaving group exposed. Consider the analogous reaction with *t*-butyl chloride—a tertiary substrate. Nucleophiles simply cannot get to the electrophilic carbon of a tertiary substrate, no matter how badly they may want to react.

The S_N1 Reaction Pathway

- What if we attempt to react a weak nucleophile with a highly substituted substrate, instead of reacting a strong nucleophile with substrates of low substitution? Let's consider water reacting with *t*-butyl chloride. Water is clearly a weaker nucleophile than hydroxide. It has lone pairs of electrons on its oxygen but lacks the negative charge that made the hydroxide attack with such urgency. And *t*-butyl chloride has three methyl substituents on the electrophilic carbon, making attack difficult even for a strong nucleophile.
- A patient nucleophile like water with nowhere to attack will simply wait, biding its time until something more accessible and reactive presents itself. In the case of *t*-butyl chloride, this happens when the chloride ion departs on its own, leaving behind a carbocation.
- A *t*-butyl cation is a distinctively more attractive substrate for two reasons: The electrophilic carbon now has only six valence electrons and a full positive charge, and its new planar arrangement of substituents means that it is much more accessible to nucleophiles. This cation is practically begging to be attacked by even the weakest of nucleophiles.

- Water obliges in short order, attacking the carbocation and completing the reaction, producing a protonated alcohol that quickly deprotonates to form a neutral molecule.
- So, in this case, it is the formation of a carbocation that is the first (and rate limiting) of two steps in the reaction process. Because the nucleophilic attack happens after the slow formation of the carbocation, the nucleophile's concentration no longer affects the rate of this reaction.
- S_N2 reactions take place in one concerted step, requiring that the nucleophile attack the carbon bearing the leaving group—and only that specific carbon. But now we have arrived at our first example of carbocation intermediates, so we have to consider the possibility that carbocation rearrangements might occur.

Substitution and Chirality

- S_N2 reactions must take place via backside attack, but S_N1 reactions produce a planar carbocation intermediate that can be attacked from either side with equal efficiency. This leads to a difference in product composition from a stereochemical standpoint. If we were to react a chiral substrate by S_N2 —for example, enantiopure (*R*)-2-chlorobutane—we can expect an enantiopure product to form. The identity of the substrate is not only changed, but the stereochemistry has been inverted as a consequence of backside attack, producing (*S*)-2-butanol.
- In contrast, let's consider the S_N1 reaction between water and (*R*)-2-chlorobutane. Our substrate must first convert into a carbocation, which can then be attacked by the nucleophile from either side, leading to a racemic mixture of 2-butanol.

Solvent Effects on Substitution Reactions

- Ingold proved long ago that the concentration of the nucleophile affects the rate of S_N2 , but not of S_N1 . This is a consequence of its absence in the rate-limiting step of the S_N1 pathway. But reagent concentration is not the only way to alter the rate of the S_N1 and S_N2 reactions to our benefit.
- Because the S_N1 and S_N2 mechanisms differ in the chemistry of their rate-limiting steps, it stands to reason that their rates can be affected differently by changes in the surrounding chemical environment. Usually, this environment is a liquid solvent in which they are dissolved.
- S_N2 is a nice, concerted mechanism taking place in a single step. S_N2 reactions are characterized by the presence of strong nucleophiles, which tend to have high negative charge density—species like hydroxide. Let's consider the effect of running an S_N2 reaction between methyl chloride and hydroxide starting materials.
- The starting material includes a hydroxide with a full, localized negative charge. The reaction then proceeds through a transition state in which that negative charge is spread out across the nucleophile and the leaving group. So, the transition state has less charge density. Of course, there are other factors making it less stable than the starting materials, such as the two bonds in the process of breaking and forming.
- But the fact remains that the activation energy of the reaction is simply the difference in energy between the two states. So, anything that we can do to close that energy gap will speed up the reaction. Anything we can do destabilize the starting material more than the intermediate will accelerate the reaction.

- One of the easiest ways to do this is to choose the right solvent. As you might imagine, solvents of low polarity, like the hydrocarbon hexane, do not interact well with charged nucleophiles, leaving them highly reactive and, therefore, more likely to attack. The problem that sometimes arises in this situation, however, is that charged nucleophiles simply aren't soluble in nonpolar solvents, so we have to choose carefully.
- We sometimes classify solvents based not only on their polarity, but also on their acidity. We call solvents like acetone, dimethylsulfoxide, and acetonitrile "polar aprotic," because they lack any acidic hydrogens. Conversely, solvents like isopropanol, ethanol, and water are called "polar protic." All of these solvents have a strong molecular dipole, but the real difference is in the orientation of that dipole.
- All of the aprotic solvents have their dipole oriented with the negative end at the surface of the molecule, while all of the protic solvents have their dipole oriented with the positive charge density at the periphery of the molecule and the negative end buried deep within.
- While low-polarity, or polar aprotic, solvents tend to accelerate S_N2 reactions, polar solvents in general accelerate S_N1 reactions. This is a good general rule for prototypical substitution mechanisms, but there are many exceptions to this rule.

Suggested Reading

Barton, D. H. R., "Ingold, Robinson, Winstein, Woodward, and I," *Bulletin for the History of Chemistry* 19 (1996): 43–47.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 7.4–7.6.

Wade, *Organic Chemistry*, Chaps. 6.7–6.16.

Questions to Consider

1. When conducted with a chiral substrate, some S_N1 reactions (particularly those with moderately good leaving groups and nucleophiles) proceed with partial retention of stereochemistry. Propose a reason for this observation.
2. Secondary substrates like 2-chlorobutane can react by either S_N1 or S_N2 pathways. Under which conditions of solvent polarity and nucleophile strength will each pathway be favored?

Elimination Reactions

Lecture 12

This lecture covers the second major class of organic reaction: elimination. You will learn about second-order (E2) and first-order (E1) elimination reactions. You will also learn how the strength of the base dictates the order of the reaction and how extremely bulky bases combined with more-substituted beta carbons can lead to a situation in which Zaitsev's rule fails to accurately predict the major product. Finally, you will discover that substitution and elimination frequently compete with one another and that certain reaction conditions—most notably temperature—can be altered to promote the desired mechanism.

The Elimination Reaction

- Alkyl halides and other compounds containing good leaving groups need not necessarily undergo substitution reactions. There is another class of reactions in which these types of compounds often participate. Instead of substituting a new group in place of the leaving group, a pi bond is formed by the loss of an adjacent proton, which we call the beta proton.
- Elimination reactions always proceed with the production of a by-product formed by the leaving group but do not consume a nucleophile molecule in the process. So, in contrast to substitution reactions, elimination reactions are not entropically neutral but, rather, proceed with an increase in entropy, making two or more molecules from one.
- This is a good thing, because the exchange of sigma bonds for a pi bond means that the enthalpy of this reaction is not usually favorable. So, elimination reactions are driven by factors like increased heat and time as well as the formation of stable leaving groups and alkene products. Eliminations are always a possibility and are usually competing pathways in substitution reactions. It is

when this competing pathway becomes dominant that we call the reaction an elimination.

E1 and E2 Reactions

- Completing an elimination reaction requires that two things be removed from the starting material: a stable leaving group and a beta proton from an adjacent carbon. Russian chemist Aleksandr Zaitsev's theory that more-substituted alkenes would form in these reactions proved true. Vladimir Markovnikov instead hung his hat on a theory called microscopic reversibility. Having observed that alkyl halides of low substitution could be used to prepare alkenes, he theorized that reversing the reaction should produce the original starting material.
- But Markovnikov and Zaitsev lacked the tools to probe these mechanisms much, if at all. Decades later, Christopher Ingold once again left his mark on organic chemistry by recognizing that there were three potential mechanisms that had to be considered: departure of a leaving group after deprotonation, departure of a leaving group during deprotonation, and departure of a leaving group before deprotonation.
- In the first possibility, removal of a beta proton from an alkyl halide would require a very strong base. We know that protons don't just fall off of molecules on their own; they need a suitable base to accept them. Because alkyl halide beta protons have a pK_a of about 50, any base strong enough to accomplish this would be practically unusable in a laboratory environment. We would be hard-pressed to find a solvent that was polar enough to dissolve such a base without being acidic enough to be deprotonated by it as well.
- The second possibility—simultaneous deprotonation and leaving group departure—is entirely feasible, because the highly unstable conjugate base in our first mechanism is avoided. The third possibility is also acceptable, generating a carbocation intermediate that gives our electron pair holding the beta hydrogen a place to go without creating a carbanion.

- So, just as in the case of substitution, we are left pondering two believable mechanisms for the elimination of an alkyl halide to form an alkene: one with a rate dependent only on substrate concentration and another dependent on both substrate and base concentration.
- Just as with substitution, both are correct. Ingold realized that in each potential reaction mechanism was a base accepting the beta proton from the substrate, but in one mechanism the base participated in the rate-limiting step, while in the other it did not. Kinetic studies were the key to unlocking the rules governing these two mechanisms.

The E2 Reaction Pathway

- The E2 reaction pathway involves simultaneous deprotonation and leaving group departure. Nucleophiles are electron-rich species that have high negative charge density and lone-pair electrons to donate in heterogenic bond formation. Another type of reagent that has a very similar set of properties to nucleophiles is a Lewis base. Because nucleophiles and bases have similar properties, it is possible for nucleophiles to also act as bases.
- S_N2 reactions take place when strong nucleophiles attack a substrate of low substitution. But what happens if the nucleophile is strong like hydroxide but the substrate is of high substitution, like *t*-butyl chloride? The nucleophile, unable to attack the obstructed electrophile, will not wait to react. When nucleophilic attack is not possible, it will instead react as a base.
- Deprotonation of a beta carbon seems like the next-best alternative to satiate this reactive species, but simple deprotonation would be a highly disfavored reaction because of the low pK_a of alkyl halide beta protons.
- But there is a second process that can be coupled to beta proton removal: the departure of the leaving group. It is this simultaneous removal of the beta proton, departure of the leaving group, and

formation of a new double bond that all come together to form a single-step process that results in the formation of an alkene.

- A beta proton that is at opposition to the leaving group is the one that will be removed. Remember that leaving groups in second-order reactions depart when electrons move in from the backside of the electrophilic carbon. In order to accomplish this in an E2 substrate, the bond holding the acidic proton must be on the backside of the molecule from the leaving group. This orientation is achieved when the beta proton has a 180-degree dihedral angle relative to the leaving group. We call this orientation anti-coplanar.

The E1 Reaction Pathway

- A different situation that might lead to a first-order reaction is one in which an alkyl halide of high substitution is placed in the presence of a very weak base. In a situation like this, any elimination that might occur would likely fall into the E1 class of reactions.
- A very weak base is a species that can accept a proton only under extreme conditions. Usually, this means a neutral compound, such as a molecule of solvent, or one that is negatively charged but has lots of resonance to help stabilize that charge.
- So, let's consider the same substrate as before but with a weak nucleophile like water. In this situation, carbocations should form quite easily from something like *t*-butyl chloride, but even so, there is no strong nucleophile to be found. So, what is a carbocation to do?
- Under the circumstances, the only way to produce a product is to lose an adjacent proton and form an alkene. In the case of *t*-butyl chloride, the elimination product is exactly the same as that obtained in our E2 example, but there are examples where this is not true.
- The distinguishing property of E1 reactions is that they tend to run best under acidic conditions (no good nucleophile) and at high temperatures (favoring systems of greater entropy).

Regiospecificity in Elimination: Zaitsev's Rule

- One consideration that sets second-order elimination, or E2, reactions apart from second-order substitution, S_N2, is the wide variety of possible products that might form from the same combination of reagents. For example, unlike the S_N2 pathway—which involves the attack of a nucleophile on the carbon-bearing leaving group, giving it only one potential reactive site—the E2 reaction requires the abstraction of an adjacent proton, of which there may be many.
- All of the beta protons of a *t*-butyl halide are equivalent, eliminating this consideration. But most substrates for elimination reactions are not so convenient. Issues of regiospecificity and stereospecificity arise quickly.
- Let's consider an elimination reaction that can produce two different products. Take the example of 2-bromo-3-methylbutane. If we were to react this secondary alkyl halide with hydroxide ion, there would be two chemically distinct types of beta protons. Removal of a primary proton leads to 3-methyl-1-butene, but removal of the secondary beta proton leads to 3-methyl-2-butene. So, which is the main product of the reaction?
- In situations like this, the more-substituted alkene product tends to be the major product of the reaction. Zaitsev's rule states that the major product of an elimination reaction will be the most substituted alkene possible. So, applying Zaitsev's rule to our problem of 2-bromo-3-methylbutane with hydroxide gives us the trisubstituted product in greater abundance than the monosubstituted product. By extension, Zaitsev's rule accurately predicts the major products of these elimination reactions as well.
- We can safely apply Zaitsev's rule for E2 reactions when the base is particularly small, like the hydroxide in the previous example. The picture can, however, become a bit more complicated when we use

bulkier bases like *t*-butoxide. When we attempt to react *t*-butoxide with 2-bromo-3-methylbutane to obtain an elimination product, we run into a little snag.

- In fact, *t*-butoxide is much larger than hydroxide, and sterics make it tough for this powerful base to physically get into contact with the tertiary beta proton. With no access to the electrophilic carbon for backside attack—nor to the tertiary beta proton—the base is forced to take its third choice: the methyl proton, leading to the less-substituted alkene as the major product. We sometimes refer to this type of regioselectivity as anti-Zaitsev or Hoffman products.
- Next, let's consider regioselectivity in the E1 mechanism. Just as with E2 reactions, we need to be careful to consider how an E1 might produce multiple products of varying stability. We have already established that E1 reactions are expected to proceed through a carbocation intermediate. This has two important influences on the products formed by this reaction.
- First, the carbocation is planar, which means that they form a planar intermediate, making even more sterically obstructed beta protons accessible to the weak base. This means that E1 reactions are less prone to form Hoffman products.
- So, the reaction of water with 2-bromo-2-methylpentane forms 2-methyl-2butene just as the analogous E2 reaction. But reaction with *t*-butanol—a bulky, weak base—has little effect. We still get the Zaitsev product as the major species. But there is another consideration that always comes with first-order reactions: carbocation rearrangements.
- So, the reaction of water with 2-bromo-3,4-dimethylpentane will produce a carbocation that can not only undergo a secondary rearrangement, but will then form the tetrasubstituted Zaitsev product.

Stereochemistry of Elimination Reactions

- When we work with elimination reactions, just like with substitution reactions, we must not only consider regioselectivity, but also the possible effects on the stereochemistry of the products. Because the product of this reaction is an alkene, of course there is no potential for a chiral center to form in the product, but a stereocenter may yet be produced in the form of cis-trans isomers.

Elimination in Cyclic Alkyl Halides

- Just as with cyclic alkanes, there is an associated ring strain in smaller cyclic alkyl halides that means that the carbon-carbon bonds making up the ring cannot freely rotate. This can pose a serious problem. The ring restricts rotation of the bond between alpha and beta carbons and simply will not allow the tertiary beta proton to achieve the necessary anti-coplanar alignment. The ability of cyclic alkyl halides to undergo E2 reactions is also severely limited by the need for the halide to be in an axial position for the proper orbital alignments.

Competition between Substitution and Elimination

- Substitution and elimination reactions are seldom found occurring exclusively, and they often compete with one another. The key to divining which mechanism will prevail is in the reaction conditions. Recall that the Gibbs free energy equation is a function of temperature. So, the extent to which entropy contributes to a process's spontaneity is a function of temperature. Higher temperature means that entropy has a greater role.
- Increasing temperature makes the increased entropy of the elimination products more favored. So, if we have a reaction with competing substitution and elimination pathways, one way to tip the scales in the direction we want is to use heat.
- Strong bases favor second-order reactions. Lower temperatures favor substitution. Higher temperatures with small, strong bases favor elimination to form the Zaitsev product, while higher temperatures with bulky bases favor the anti-Zaitsev elimination product.

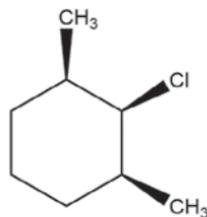
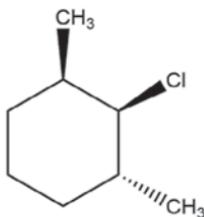
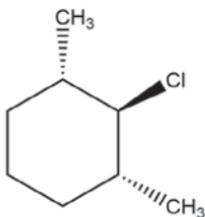
Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 7.7–7.9.

Wade, *Organic Chemistry*, Chaps. 6.17–6.21.

Questions to Consider

1. Some elimination reactions (such as dehydrations of alcohols) are acid-catalyzed. Why are sulfuric and phosphoric acids preferred over hydrochloric or hydrobromic acids for this purpose?
2. Of the three substituted cyclohexanes below, which will react the fastest in an E2 reaction? Which will react the slowest?



Addition Reactions

Lecture 13

This lecture completes the tour of the three general classes of reactions most often encountered in organic chemistry: substitution, elimination, and addition. In this lecture, you will work your way through the basics of how addition reactions occur. In addition, you will learn about the mechanism of hydrohalogenation of alkenes and alkynes. Furthermore, you will learn how two chemists developed a chemistry that is used to modify oils and fats to produce food additives. Finally, you will learn about the methods used to halt hydrogenation of alkynes at the alkene stage.

Addition Reactions

- Addition reactions involve the replacement of a pi bond with new sigma bonds to new substrates, meaning that these reactions tend to be entropically disfavored, creating fewer molecules than they consume. But from an enthalpic standpoint, they are usually favored, because the newly created sigma bonds are lower in energy and more stable than the pi bonds in the starting materials.
- Consider the reactivity of unsaturated hydrocarbons—alkenes and alkynes. The presence of a pi bond gives them an ability to act as nucleophiles themselves instead of a substrate, using their pi electrons to attack electrophilic species.
- Let's consider what happens when an alkene like propene attacks a generic electrophile. The propene molecule sees an opportunity to convert its pi-bonding electrons into more stable sigma-bonding electrons by attacking the electrophile, but doing so means that the resulting species must take on a positive charge, becoming a carbocation. So, the tables have turned; the original nucleophile is now an electrophile. The adjacent carbon is electron-deficient, positively charged, and ready to be attacked itself by anything nucleophilic enough to do so.

Addition of Hydrogen Halides to Alkenes

- Before his epic clash with Aleksandr Zaitsev over the regiochemistry of elimination reactions, Vladimir Markovnikov had already made a name for himself by publishing his famous rule governing the regiochemistry of addition reactions. These addition reactions can be used to produce alkyl halides from alkenes. We call this class of reactions hydrohalogenation because the reaction involves adding a molecule of HCl or HBr across a double bond.
- Even though he was never quite certain exactly how it happened, Markovnikov was able to demonstrate that anytime an alkene with sp^2 carbons of differing substitution, like propene, was reacted with a hydrogen halide like hydrochloric acid, the newly added halogen is always added preferentially to the more-substituted carbon of the alkene, and the hydrogen ended up on the less-substituted carbon.
- The key to understanding exactly why Markovnikov's rule holds only became available some 30 years later, when the carbocation structure was first proposed. When propene attacks hydrochloric acid, its nucleophilic pi electrons naturally seek out the most electrophilic species in the mix. In this case, the target is the hydrogen of HCl, which is very electron-depleted, owing to the presence of the electronegative chlorine.
- In essence, the alkene is acting as a base, accepting a proton from the strong acid HCl. But this is a very special nucleophilic base, because its conjugate acid is an electrophilic carbocation, which means that its formation will naturally favor a product following the rules of carbocation stability. Hyperconjugation provided by additional alkyl groups around the carbocation provide extra stability, making carbocations of higher substitution more stable.
- So, given the choice between a primary and secondary carbocation, propene will choose to become the latter. In a second step, the tables have turned, and the propenyl cation is attacked in turn by the somewhat nucleophilic chloride ion to produce 2-chloropropane.

- Further evidence of this mechanism is evident in the stereochemistry of this class of reactions. When addition of a hydrogen halide produces chiral centers in a new product, all possible stereoisomers are formed equally, forming a racemic mixture. The reason for this is the same as that for racemization in S_N1 reactions—that a planar carbocation intermediate can be attacked with equal efficacy from either side by the nucleophilic chloride ion.
- The final piece of evidence for this mechanism is the tendency for rearrangement products to form during hydrohalogenation.
- Although Markovnikov's rules originally were focused on addition of hydrogen halides like hydrochloric acid, they are remarkably consistent when applied to many more reactions.

Hydrohalogenation of Alkynes

- A very similar chemistry takes place in the case of hydrohalogenation of alkynes, which can be hydrohalogenated either once or twice. In this case, the major difference is that to complete the first addition would require the formation of a vinyl cation. It is difficult to say if this is in fact how the reaction proceeds, but what is undeniable is that it proceeds much more slowly than does hydrohalogenation of an alkene.
- Nonetheless, it can be achieved, creating what we call a vinyl halide in accordance with Markovnikov's rule. Of course, in the presence of excess hydrogen halide, this is of little consequence because any stereochemistry will be wiped out when a carbocation does form in the second hydrohalogenation.
- When this takes place, Markovnikov's rule holds yet again, but even in situations involving equally substituted sp^2 carbons, the halogen will end up on the same carbon atom as its predecessor. This is because the attached halogen atom stabilizes the carbocation by resonance on its way to becoming what we call a geminal dihalide. "Geminal," meaning "twins," implies that the two halogens are

on the same carbon. The alternate possibility—called a “vicinal” dihalide, from the Latin word for “neighbor”—indicates that the halogen atoms are on adjacent carbons and does not form in this type of reaction.

Addition of Halogens to Alkenes

- Another commonly used addition reaction is the addition of molecular chlorine, bromine, or iodine to alkenes. Unlike radical halogenation of alkanes, we don't have to resort to extremes like photoactivated radical chemistry to halogenate alkenes and alkynes. This reaction is typically accomplished using molecular halogens like chlorine or bromine in a non-nucleophilic solvent like dichloromethane. When these reagents are combined, one halogen atom is added at each side of the double bond.
- Chlorine, bromine, and iodine all have fairly large electron clouds, meaning that their valence electrons are not held very tightly by the nucleus. This makes it relatively easy for other charged species (like attacking pi electrons) to induce a dipole in the halogen molecule by electrostatic repulsion of its electron cloud.
- Once this attack begins, the polarization continues until the halogen-halogen bond is broken, producing a halide ion as a by-product. But the truly intriguing product of this step of the reaction is what becomes of the alkene. The first step of this reaction involves not the addition of a hydrogen, but that of a much larger halogen atom to the carbon scaffold offered by the alkene.
- Unlike hydrogen, large halogen atoms need not remain locally bonded to a single carbon, but rather, they can sit between the two alkene carbons, creating a cyclic halonium ion. The formation of this ion is driven energetically by the distribution of the positive charge among three atoms, rather than isolating it on a carbon, as in a traditional carbocation.

- The reaction completes when a chloride ion, for example, attacks the halonium ion, alleviating the positive charge completely and producing a vicinal dihalide. The attack can come from any halide ion in the mix.
- During hydrohalogenation, a planar carbocation intermediate ensures that we will produce an equal mixture of all potential stereoisomers in such a reaction. But the halonium intermediate of the halogenation reaction is not planar. In fact, it is quite far from it.
- The cyclic motif created by the first halogen atom addition blocks the second from attacking from the same side. Attack can only take place from the opposing face of the intermediate. Because addition must take place on opposite sides of the plane of the molecule, we call this an “anti” addition.
- The consequences of this anti addition become more important when we consider halogenation using a more complex alkene. Because the starting material is planar, the chloronium ion can form from either side.

Halogenation of Alkynes

- Alkynes can undergo halogenation in a similar reaction, first forming an alkene with two halogens trans to one another because of the anti addition, followed by a second halogenation to form a tetra-halogenated alkane. When the product of a single halogenation is desired, carefully controlling the amount of halogen added is all that is required.
- Adding just one molar equivalent of halogen will produce the 1,2-dihaloalkene almost exclusively. This works because the resulting 1,2-dihaloalkene has two electronegative halogen atoms attached, withdrawing electron density from the pi bond, making it less nucleophilic and, therefore, much less reactive than the alkyne starting material. So, we do not expect the second halogen addition to take place until all of the starting alkyne has been consumed.

Addition of Hydrogen to Alkenes

- In the 1890s, American chemist James F. Boyce Sr. developed a method for processing cottonseed oil into a material of greater viscosity, more suitable for use in soap and food products. He discovered that the addition of a small amount of nickel to the mixture facilitated the addition of hydrogen molecules to the product, thereby changing its properties favorably.



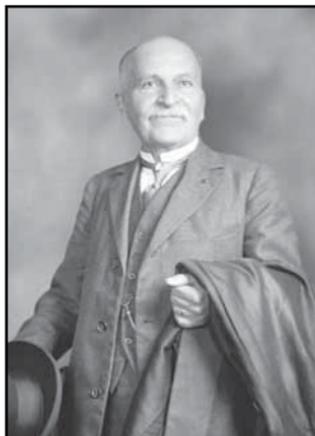
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The discovery of a method to make more suitable soaps and food products led to the production of partially hydrogenated vegetable oils.

- This work was also picked up by renowned French chemist Paul Sabatier, who refined the process into the catalytic hydrogenation that earned him a Nobel Prize and today bears his name.
- Boyce and Sabatier were after a process that would convert less saturated (and less expensive) plant oils into molecules more closely resembling animal fats. This is because animal fats have a higher degree of saturation, making them solids near room temperature and increasing their shelf life. Because animal fats are more expensive, converting a cheaper source into a similar material was good business.
- Their success in this endeavor led to the production of partially hydrogenated vegetable oils, which we are so accustomed to seeing listed on the back of food packages today. The double bonds of hydrocarbons can be saturated using molecular hydrogen at or near room temperature. But, importantly, the reaction is painfully slow.
- Boyce and Sabatier realized that the solution to this was the use of a catalyst to weaken the bond in the hydrogen molecule, thereby promoting the reaction without the need for excessive temperatures.

Fortunately, such catalysts exist. Unfortunately, these catalysts are very rare and expensive metals like platinum and palladium, and Sabatier's method uses heterogeneous catalysts, meaning that the catalyst itself is a solid, while the reagents are in the liquid or gas phase.

- Even though the metal catalyst is not consumed in the reaction, a mass of precious metal would cost a great deal and only have a small exposed surface area on which the chemistry can take place. This potentially prohibitive cost issue is often circumvented by producing the catalyst not as a pure material, but as a thin veneer of the precious metal adhered to a highly porous carbon support. This tremendously increases the amount of surface area which can be generated per gram of catalyst, making the process much more useful.



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Sabatier's work on catalytic hydrogenation earned him a Nobel Prize.

Hydrogenation of Alkynes

- Hydrogenation of alkynes is yet another versatile set of reactions. The process developed by Sabatier is very effective for the complete hydrogenation of an alkyne to an alkane, but it is very difficult (if not impossible) to halt the reaction at the intermediate alkene.
- This challenge was of particular interest to Swiss chemist Herbert Lindlar, who published his work on selective catalytic hydrogenation of alkynes to alkenes in 1952. He succeeded in creating a palladium catalyst that had been deliberately poisoned with (among other things) lead. This intentional contamination of the catalyst reduced its catalytic power to the extent that it could only facilitate a single syn hydrogenation, leading to conversion of alkynes to cis alkenes.

- So, one could employ Lindlar's catalyst in order to stereoselectively produce *Z*-2-butene from 2-butyne. But what if the *trans* (or *E*) isomer were the intended product of the synthesis? Lindlar's catalyst would not achieve the correct stereochemistry because of the mechanism inherent to the reaction.
- In this case, we must turn to more drastic methods like the metal-ammonia reduction method. In this technique, a strong reducing agent like sodium metal is used to convert the alkene into a radical anion. These ions will preferentially form in a *trans* configuration because of steric considerations. After abstracting a proton from an ammonia molecule, the resulting vinyl radical repeats the process of reduction—and protonation, leading to a *trans* product.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 4.1–4.6.

Wade, *Organic Chemistry*, Chaps. 8.1–8.8.

Questions to Consider

1. Which alkenes would be the best starting material to produce the following alkyl halides by hydrohalogenation?
 - a. 2-chloro-2-methylbutane
 - b. 2-chloro-3-methylbutane
2. How many stereoisomers can be produced from the halogenation of the following?
 - a. *cis*-2-butene
 - b. *trans*-2-butene
 - c. Explain any difference in your responses to a. and b.
3. What is the smallest alkene that can produce a chiral compound when hydrogenated using the process developed by Sabatier?

Alcohols and Ethers

Lecture 14

In this lecture, you will learn about the atomic structure and bonding behavior of oxygen, focusing on the oxygen atom in the sp^3 -hybridized state. In addition, you will learn how alcohol groups have that special designation of “functional group” in IUPAC nomenclature and how their less reactive ether cousins don’t enjoy the same distinction. You will also learn techniques for synthesizing alcohols and ethers. Furthermore, you will explore the reactivity of alcohols. Finally, you will be introduced to the activation of alcohols by converting their hydroxyl groups into more reactive leaving groups.

Oxygen

- Oxygen is element number eight on the periodic table and, therefore, has a ground-state electron configuration $1s^2 2s^2 2p^4$. This means that oxygen has a strong tendency to form two covalent bonds to complete its octet: either two single bonds in an sp^3 -hybridized state with bond angles of approximately 109.5 degrees or a double bond in an sp^2 hybridized state. In either case, the oxygen atom will have two lone pairs of electrons completing its octet.
- The only heteroatoms that we have significantly explored are halogens, which tend to form only one bond to complete their octet. This means that for halogens, reacting almost always requires that the halogen be removed from or added to a chemical scaffold. But the two bonds that oxygen can form allow it to remain connected to an organic scaffold by one bond as it reacts with the other, making its chemistry much richer and even more useful than that of halogens.

Alcohols and Ethers

- Alcohols are defined as hydrocarbons that contain an oxygen covalently bonded to a hydrogen and an alkyl group. We call this OH group a hydroxyl group. When the hydrocarbon portion of the alcohol is saturated, we sometimes refer to them as aliphatic alcohols.
- Alcohols are named using IUPAC rules designating the hydroxyl group as a functional group, meaning that it has a higher priority than ordinary substituents. For simple chain alcohols, the standard IUPAC prefix is followed by a location and the suffix “-ol.” For example, attachment of a methyl group to a hydroxyl produces the structure of methanol, while an ethyl group creates ethanol and a propyl group propanol.
- Just like with alkyl halides, once we reach propanol, multiple distinct locations are available to support the attached hydroxyl, requiring that we number the location of this functional group. Placing the hydroxyl at the end of the chain gives us propan-1-ol (also called 1-propanol), while placing it at the middle gives us propan-2-ol (also called 2-propanol).
- Addition of one more carbon to the mix gives us four potential isomers with the IUPAC names butan-1-ol, butan-2-ol, 2-methylpropan-1-ol, and 1-methylpropan-2-ol. But these IUPAC names are a bit unwieldy, so chemists have applied common names of *n*-butanol, *sec*-butanol, isobutanol, and *t*-butanol to these four, respectively.



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The use of ether as an anesthetic changed the practice of surgery forever.

- In contrast to alcohols, ethers do not have a hydrogen directly bonded to an sp^3 oxygen. Instead, ethers are defined by the attachment of two alkyl groups, using the oxygen atom as a bridge of sorts. This has the effect of significantly reducing the reactivity of ethers, meaning that IUPAC nomenclature systems do not treat them as functional groups. Instead, the smaller of the two alkyl chains becomes an alkoxy substituent.
- Another very important consideration with respect to ethers is that their lack of a hydroxyl hydrogen means that they cannot hydrogen bond to other ether molecules. This significantly reduces their boiling points.

Acidity and Boiling Points

- Alcohols are great hydrogen bonders, because the hydroxyl group is capable of both donating and accepting electrons to form such an interaction. This means that alcohol molecules stick to one another much better than analogous hydrocarbons.
- The presence of a hydrogen atom bonded to a heteroatom means that alcohols are also amphoteric, being capable of releasing the hydroxyl hydrogen as a proton, forming a species known as an alkoxide, or accepting a proton to form what we call an oxonium ion. In all but the most acidic or basic of environments we expect aliphatic alcohols to remain neutral.

Synthesis of Alcohols

- Alcohols are used widely in organic chemistry as both reagents and solvents. Most of the world's ethanol is prepared by the fermentation of sugars by the bacterium *Saccharomyces cerevisiae*, or yeast. This little organic chemist is without equal when it comes to creating ethanol, but what about other, more complex alcohols?

- When larger, more complex alcohols are needed, we must often turn to the tools of organic chemistry to create them. There are many ways in which to do this. For example, they can be produced by nucleophilic substitution of alkyl halides using hydroxide ions. But there are many, many more ways.
- We will now focus on how alcohols are produced using alkenes as the starting materials by the addition mechanism. To accomplish this, we will discuss three types of reactions: hydration of alkenes, a technique called oxymercuration-demercuration, and a technique known as hydroboration-oxidation. Each of these reactions has specific advantages and challenges associated with them, and in many cases, they will produce various structural isomers of the product alcohol.
- Let's begin with a special kind of addition reaction: acid-catalyzed hydration of a very simple alkene, propene. As the name implies, we will need three ingredients: an alkene, a mineral acid, and water. In order to complete the reaction, we'll need to acidify the sample using an aqueous solution of mineral acid with a non-nucleophilic conjugate base—something like phosphoric or sulfuric acid.
- A strong acid like sulfuric acid protonates the alkene, but there are two possible carbocations that might form: a primary propyl cation or a secondary isopropyl cation. Hyperconjugation causes the secondary carbocation to be strongly favored. This is one of the driving forces behind Markovnikov's rule, and this reaction will be no exception.
- If we follow the reaction with the isopropyl cation to completion, we see that our acid selection has produced a non-nucleophilic base, leaving only water to act as a nucleophile, attacking the carbocation and forming a new bond. So, we have created a species known as an oxonium ion.

- Oxonium ions are very acidic and quickly lose their acidic proton to a molecule of solvent or to another alkene, thus perpetuating the reaction. If we evaluate the product obtained, we see that the extension of Markovnikov's rule has held, with the added hydrogen on the less-substituted carbon of the product and the hydroxyl group on the more-substituted carbon.
- So, if the goal of our synthesis is to convert an alkene into an alcohol without stereoselectivity and obeying Markovnikov's rule, acid-catalyzed hydration seems to be the ticket. But just as with all reactions involving carbocations, we have to be vigilant of the possibility for rearrangements in the intermediate.
- For example, what happens when we try to hydrate 3-methyl-1-butene with aqueous sulfuric acid, ostensibly to form 3-methyl-2-butanol? Protonation of the alkene leads to a secondary carbocation, but there is an adjacent tertiary carbon. This spells trouble, because a hydride shift can lead to formation of a more stable tertiary carbocation in the intermediate. This leads to a rearrangement product: 2-methyl-2-butanol.
- So, how do we cope with this problem? This question no doubt vexed Markovnikov and was taken up by Karl Andreas Hofmann and Julius Sand in 1900. They were investigating the phenomenon that metals, though rare in organic chemistry, are present and can form bonds to carbon.
- The reaction that Hofmann and Sand developed involves the use of mercuric acetate—a compound consisting of one atom of mercury bonded to two acetate groups. Hofmann and Sand realized that if this compound was used in place of a mineral acid to initiate hydration of an alkene, no rearrangement took place.
- What if it were necessary to hydrate an alkene to produce the anti-Markovnikov product? American chemist Herbert C. Brown published his first paper on the hydroboration of alkenes in 1950.

- What makes boron hydrides so interesting is that boron has a very low electronegativity—so low, in fact, that the hydrogen atoms of boron trihydride are at the negative end of the bond dipole. The unusual orientation of the bond dipole in boron trihydride causes it to interact with the pi system of the alkene in such a way that the hydrogen preferentially positions itself above the more-substituted carbon. More-substituted carbons tolerate positive charges better, and this is exactly what happens as a result of the nearby hydride.
- At this point, a single, concerted step breaks the boron-hydrogen bond, producing what is called an alkylborane. Because of this arrangement of atoms in the transition state, it is clear that hydroboration must take place with syn stereochemistry.
- Finally, the borane group is reacted with hydroxide and hydrogen peroxide to replace the borane with a hydroxyl group. So, the hydroboration and oxidation of our alcohol leads to an anti-Markovnikov hydration of an alkene to an alcohol with syn stereochemistry.
- A final distinction between ethers and alcohols is the lack of an acidic hydrogen in ethers. Because ethers do not act as acids under common laboratory conditions, they find use much more frequently as solvents than as reagents, but they are critical materials nonetheless.
- Ethers can be synthesized using analogues of two of the complex mechanisms while simply substituting the desired alkyl group for the appropriate hydrogen. For example, instead of acid-catalyzed hydration to form 2-methyl-2-butanol, we can simply replace water with an alcohol, leading to the corresponding *sec*-butyl ether. Similarly, oxymercuration and demercuration in an alcohol solvent rather than water leads to a Markovnikov ether product without rearrangement.

- Unfortunately, the complexities of the oxidation step in hydroboration and oxidation make it impossible to produce ethers from alkenes using this method, but there is a solution to this problem.

Reactions of Alcohols

- Although alcohols, and particularly ethers, are most frequently used as solvents in organic chemistry, there are situations in which alcohols can be reactants. The difference in the utility of these chemical cousins lies in their most obvious difference: the presence of an acidic hydrogen. Most simple aliphatic alcohols have a pK_a of about 16. This makes them very weakly acidic, but acidic nonetheless. So, in the presence of a suitably basic environment, alcohols can be deprotonated to form their conjugate bases called alkoxides.
- Organic chemists sometimes use a reagent known as sodium hydride to accomplish this. This is a great technique because not only is it already so strongly favored, but the effervescence of the hydrogen gas by-product also makes the reaction truly irreversible, because the hydrogen gas just bubbles away.
- Just as deprotonation of water forms the more nucleophilic hydroxide ion, deprotonation of the alcohol increases its nucleophilicity substantially by producing alkoxide ions. This nucleophile, mixed with the appropriate alkyl halide, can produce an ether through a process known as the Williamson ether synthesis: an S_N2 reaction.
- Because Williamson ether syntheses are S_N2 , a methyl or primary alkyl halide is expected to react well to form a new ether and a halide ion by-product. So, reacting ethanol first with sodium hydride and then with 1-chloro-3-methylbutane is a suitable route to our ether of lowest substitution. Unfortunately, highly substituted substrates are less likely to be effective, instead producing elimination products with double or triple bonds.

Substitution Reactions of Alcohols

- But remember that alcohols are amphoteric, meaning that they can also accept a proton to become a conjugate acid. Protonation of an alcohol under very acidic conditions changes what would be a poor hydroxide leaving group into a much more stable water leaving group. What was the nucleophile in basic solution is instead the substrate under acidic conditions.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 8.1–8.6.

Wade, *Organic Chemistry*, Chaps. 10.1–10.7, 8.4–8.7, 14.1–14.6.

Questions to Consider

1. Although we refer to the alcohol products of hydroboration and oxidation as anti-Markovnikov products, is the process truly a violation of the underlying principles governing his rules for addition reactions?
2. Which alkyl halide would be expected to react fastest in a given Williamson ether synthesis, alkyl chlorides or alkyl bromides?

Aldehydes and Ketones

Lecture 15

In this lecture, you will explore the properties and reactivity of some simple carbonyl compounds. Specifically, you will learn about aldehydes and ketones, including how these compounds can be produced. In addition, you will consider the reduction of aldehydes and ketones using the familiar reaction catalytic hydrogenation. Furthermore, you will discover how carbonyl compounds react in substitution reactions. Finally, you will learn how aldehydes and ketones can be reacted with alcohols under basic conditions to form hemiacetals and hemiketals or under acidic conditions to prepare acetals and ketals.

Synthesis of Aldehydes and Ketones

- In your body, ethanol, also known as beverage alcohol, is recognized by your liver as a toxin. Whether or not your brain agrees, as soon as the ethanol hits your bloodstream, enzymes in your liver go to work preparing to eliminate it from your system. In order to attenuate the neurotoxic effects of ethanol and prepare it for removal from the body, an enzyme known as alcohol dehydrogenase converts the offending intoxicant into a more oxidized state—that of acetaldehyde.
- The process of enzymatic oxidation is complex and involves the assistance of large, complicated biomolecules, but it essentially consists of removal of the hydroxyl proton and one of its neighbors, thereby producing a double bond between the carbon and oxygen.
- Essentially, this is an oxidative elimination reaction. We call it oxidation because the central carbon is gaining additional attachment to oxygen atoms—in this case, trading a single bond to oxygen for a double bond.



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The process of enzymatic oxidation that rids the body of alcohol also contributes to hangovers.

- The product aldehyde is eventually metabolized further as this process continues, but in the meantime, it interferes with mitochondrial activity, liver function, and a host of other biological mechanisms, contributing to the condition that we colloquially refer to as a hangover.
- In the laboratory, ketones and aldehydes can be produced using various oxidizing agents that accomplish the very same task that the alcohol dehydrogenase does in your body. A classic example of this technique is the oxidation of a secondary alcohol to ketone using chromic acid.
- In this multistep reaction, the secondary alcohol is substituted for one of the OH groups on the chromic acid, creating a compound known as a chromate ester. The mechanism by which this happens is complex and, frankly, still somewhat debatable.
- What is clear, however, is that the chromate ester has something that chromic acid itself does not: alpha protons. One of those alpha protons is removed in an E2 reaction, with chromous acid (H_2CrO_3) acting as the leaving group to produce the final ketone.

- So, this mechanism depends on the presence of an alpha hydrogen on the starting material. A secondary alcohol has only one of these. So, this oxidation can only take place once, ending at the ketone stage in which the carbonyl carbon has no more hydrogens to give up.
- In the case of primary alcohols, however, two oxidations can occur, leading not to the desired aldehyde, but rather to a more oxidized compound called a carboxylic acid. For now, our goal is to make an aldehyde, so how do we stop the oxidation at the desired point?
- The key to stopping the oxidation selectively at the aldehyde stage is in remembering that aldehydes in aqueous solution tend to form reactive hydrates called geminal diols (“gem” diols for short). It is these geminal diols that can form a new chromate ester and undergo additional oxidation by chromic acid to form the carboxylic acid.
- So, if we want to stop the oxidation at the aldehyde stage, we have to stop this gem diol from forming. As you might expect, the easiest way to avoid hydration of anything is to not have water around. But removing water poses a second problem: Chromic acid is not significantly soluble in most organic solvents.
- So, to achieve our goal, we have to substitute a different oxidizing agent that is soluble in an organic solvent. Pyridinium chlorochromate (PCC) is one reagent that proves very useful in the oxidation of primary alcohols to aldehydes in particular, because of its solubility in solvents like methylene chloride.
- This reaction of primary alcohols with PCC in organic solvents is the organic chemistry equivalent of the biological effects of the drug disulfiram, more commonly known by its trade name, Antabuse. Antabuse is often prescribed to discourage alcohol abuse in alcoholic patients. It does so by inhibiting the enzyme aldehyde dehydrogenase—that enzyme that continues the process of oxidatively breaking down the alcohol metabolite acetaldehyde into the more manageable, and far less toxic, acetic acid.

- Antabuse binds to and shuts down enzymes in the liver that further oxidize acetaldehyde and move it along in the natural process of removal. Stopping the oxidation process for ethanol at the aldehyde step like this causes an unusually high level of acetaldehyde to build up in the patient's bloodstream. This in turn causes what is best described as a super hangover.
- PCC simply accomplishes the same effect on the lab bench. The difference is that it does so by preventing aldehyde hydrate formation instead of enzyme inhibition, and it can be done not only for ethanol, but also for practically any primary alcohol starting material we can imagine.

Reactions of Ketones and Aldehydes: Reduction to Alcohols

- Catalytic hydrogenation of carbonyls leads to an addition product in which hydrogen gas is added across the carbonyl double bond. To do this, we use a special catalyst called Raney nickel to form the corresponding alcohol. Raney nickel is a specially prepared, highly porous nickel-aluminum alloy that has a tremendous surface area and catalytic activity for hydrogenation. This catalyst was invented in 1926 by American engineer Murray Raney and is so effective that it is still in use industrially today.
- The mechanism is completely analogous to hydrogenation of alkenes. In fact, Raney nickel was first developed for use in hydrogenation of vegetable oils, just like Sabatier and Boyce's nickel catalysts.
- This method is often chosen in industrial settings, where gas-handling equipment is available and inexpensive hydrogen gas offsets the cost of this equipment. But in the laboratory, where we usually want to perform reactions on a smaller scale, we often turn to the use of hydride reagents.
- Both sodium borohydride and lithium aluminum hydride can accomplish this modification when added to a ketone or aldehyde in a protic solvent. The boron or aluminum in these reagents are

extremely electropositive and make bonded hydrogens act more like hydride ions. These hydride ions are very nucleophilic and will attack a carbonyl very efficiently. The resulting alkoxide simply removes a proton from the solvent to become the neutral alcohol product.

Reactions of Ketones and Aldehydes in Acidic or Basic Environments

- Just as with alcohols, aldehydes and ketones are amphiprotic, so we must consider the possibility that ketones and aldehydes might act as nucleophiles or electrophiles, depending on their pH environment. Just like alcohols, compounds containing carbonyl groups are prone to reactions under conditions of extreme pH—either high or low.
- Basifying and acidifying are both viable strategies for activating ketones and aldehydes, inducing them to react. No reaction is a better example of this than the aldol condensation, a reaction between two carbonyl compounds that can be conducted under either basic or acidic conditions with similar efficiency.
- The first report of an aldol condensation was given by French chemist Charles-Adolphe Wurtz in 1872. What Wurtz didn't know, but we know today, is that the reaction of one ethanal with another takes place when a portion of the sample becomes protonated at the carbonyl oxygen. So, a mixture of both neutral aldehyde and protonated aldehyde needs to be present.
- The protonated aldehyde has a resonance contributor with positive charge density at the carbonyl carbon, and the neutral aldehyde can tautomerize to form a species known as an enol (for the alkene and alcohol motifs that combine to make it up).
- In this system, we have an electrophilic protonated aldehyde and a nucleophilic enol—all the ingredients necessary for an addition reaction to take place. As the enol attacks the protonated carbonyl, a new alcohol group forms. The enol then quickly deprotonates to reform a carbonyl group.

- The aldol condensation is complete, and a beta-hydroxy-ketone has formed. It is this product that Wurtz first created in 1872, initiating a vein of research into a mechanism that is still in use today.

Reactions of Aldehydes and Ketones in Basic Conditions

- Wurtz first accomplished this reaction by increasing the *electrophilicity* of a portion of aldehyde with *acid*. It wasn't long, however, before it was realized that the same result could be accomplished by instead increasing the *nucleophilicity* of a portion of the aldehyde by addition of a suitable *base*.
- Addition of a base like hydroxide or methoxide can cause a portion of ethanal to become deprotonated at its alpha carbon, which can participate in resonance to form a resonance-stabilized enolate. One of the resonance contributors to this compound has negative charge density at the alpha carbon, making it a nucleophile.
- So, the enolate nucleophile, best represented by the contributor with the negative charge on the alpha carbon, attacks a neutral, but electrophilic carbonyl carbon, breaking its pi bond and promoting a series of steps that lead to the same product as in Wurtz's acidic reaction.

Acetals and Ketals

- Carbonyl-containing compounds don't just react with themselves. They make great electrophiles for attack by a large library of nucleophiles. Another commonly used reaction employing ketones and aldehydes as electrophiles is their reactions with alcohols. When we do this, we get compounds reminiscent of hydrates like methylene glycol, but one or both of the OH hydrogens is replaced with an alkyl group.
- In the case of an aldehyde like formaldehyde, replacement of one OH leads to what we call a hemiacetal, while replacement of both give us an acetal.

- When the carbon bearing the two groups was instead derived from a ketone (having two R groups), we call the resulting compounds hemiketals and ketals.
- The formation of hemiacetals and hemiketals from aldehydes and ketones is accomplished in exactly the same way that their hydrates are made, but we simply substitute an alkoxide in place of the hydroxide nucleophile. After one nucleophilic attack has taken place, there is no good leaving group to depart and make room for a second attack. Therefore, the reaction stops at the hemiacetal or hemiketal stage.
- We can instead create acetals and ketals by mixing aldehydes and ketones with an alcohol under acidic conditions. Under these conditions, the carbonyl group can be protonated, making it a good electrophile. It is then attacked by the weakly nucleophilic alcohol through an S_N1 reaction. This forms a protonated ether that quickly loses its proton to solvent.
- But under acidic conditions, a second attack is possible, because the hemiacetal or hemiketal formed can be protonated to create an oxonium ion in which a water leaving group can be displaced by another alcohol nucleophile. This leads to the acetal or ketal, depending on whether the starting material was an aldehyde or a ketone, respectively.
- Both acetals and ketals are very stable to strong bases and nucleophiles, but they can be easily converted back into their ketone or aldehyde counterpart using acidic hydrolysis, essentially reversing the reaction by adding water. These characteristics make acetals and ketals useful as protecting groups in synthesis, masking reactive carbonyl sites that can be unmasked later after chemically modifying other regions of a molecule.

Suggested Reading

Kragh, H., "From Disulfiram to Antabuse: The Invention of a Drug," *Bulletin for the History of Chemistry* 33, no. 2 (2008) 82–88.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 9.1–9.8.

Wade, *Organic Chemistry*, Chaps. 18.1–18.14, 22.1, 22.2, 22.7–22.9.

Questions to Consider

1. Would water be a suitable solvent for a base-catalyzed aldol condensation reaction? Explain.
2. Between neutral aldehydes and neutral ketones, which has the more electrophilic carbon? Explain.

Organic Acids and Esters

Lecture 16

This lecture concludes the tour of oxygen-containing compounds by covering carboxylic acids and esters. You will discover that both of these motifs contain an sp^3 oxygen connected to a carbonyl carbon. In addition, you will learn about the two ways to prepare carboxylic acids. You also will learn about the Fischer esterification, which allows us to produce esters from an organic acid and an alcohol. Furthermore, you will discover that ester chemistry can be incorporated into this class of compounds, creating products that have significantly improved bio-availability. Finally, you will be introduced to the age-old process known as saponification.

Carboxylic Acids

- The complex esters and acids from a perfect bottle of wine as well as the acetic acid that ultimately causes its demise are members of a subset of organic compounds that contain two oxygen atoms. But these two types of compounds don't find their only home in the beverage industry. Carboxylic acids are a primary component of compounds that we come into contact with every day, including many detergents, the non-steroidal anti-inflammatory ibuprofen, and the commonly used food preservative benzoic acid.



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The complexity of wine starts with chemical processes that take place during fermentation.

- Esters include compounds like isoamyl acetate, the fragrance and flavor component of bananas and also a signaling hormone that is released from the stinger of an attacking bee to call for backup. Esters also find use in the drug industry in a cleverly designed class of compounds known as prodrugs, which include heart medications, antivirals, and more.
- Because they are the end of the line in many natural oxidative processes, simple carboxylic acids were discovered early in the history of science. So, some of them have common names that actually serve as the basis for their more modern IUPAC substituent prefixes.
- Formic acid, containing a single carbon, gets its name from the Latin word for “ant,” because this is the compound that gives fire ant bites their sting. Acetic acid, with a two-carbon chain, gets its name from the Latin word *acetum*, meaning “acid.” Propanoic acid, with a three-carbon chain, is sometimes also called “propionic acid,” from the Greek terms for “first” and “fat,” because it is the smallest acid that has the properties of fats. Butyric acid, with a four-carbon chain, is named because it was first isolated from rancid butter.
- Much like in the case of aldehydes, IUPAC nomenclature treats the entire COOH as a functional group, but we still count the carbon in the chain used to determine the prefix of the name. This makes the names of these compounds methanoic acid, ethanoic acid, propanoic acid, and butanoic acid, respectively. Numbering the carboxylic acid group’s location is unnecessary because it is incapable of extending a chain, instead always terminating a chain.
- Replacing the acidic hydrogen of a carboxylic acid with an R group has three profound effects on esters. First, they are not remotely as acidic as their predecessors. Second, their functional group polarity is much lower. Finally, the fact that they can only accept hydrogen bonds, not donate to them, makes them more volatile and less water soluble than carboxylic acids of similar size.

- Common names of esters sometimes use the prefix for the chain containing the carbonyl, followed by “-ane,” and then the prefix for the R group without the carbonyl with the suffix “-ester.” An example compound is butane methyl ester.
- Alternatively, the IUPAC system treats esters as alkylated carboxylic acids. For the same example compound, we state the prefix of the R group bonded directly to the bridging oxygen, followed by the prefix for that bonded to the carbonyl and ending in the suffix “-ate.” The same compound can also be called methyl butanoate.
- Neutral carboxylic acids contain both an sp^2 oxygen from the carbonyl and an sp^3 oxygen as a hydroxyl. The dual nature of the oxygen atoms in this motif makes acids excellent at hydrogen bonding to themselves, giving them relatively high boiling points. It also leads to strong interactions with water, leading to good water solubility when their carbon frameworks are relatively small.
- Perhaps what sets organic acids apart from analogous alcohols and aldehydes is their higher acidity. The key to this elevated acidity is the way the two oxygen atoms work in concert to offer resonance and stabilize the conjugate base that forms when the acidic proton is removed. We call this deprotonated carboxylic acid a carboxylate ion.
- Removal of a proton from a carboxylic acid produces an anion with two identical resonance contributors, both of which place some of the negative charge on an electronegative oxygen atom.

Synthesis of Carboxylic Acids

- Carboxylic acids are the end of the line as oxidation of primary alcohols goes. They can be produced using our now-familiar aqueous chromic acid reaction in which one round of oxidation produces an aldehyde, followed by hydration and a second round of oxidation. So, when treated with aqueous chromic acid, ethanol oxidizes to ethanal, which becomes ethanoic acid, or acetic acid.

- But carboxylic acids need not be created from oxygen-containing starting materials. Certain alkenes can also be oxidized to form acids using a suitable oxidizing agent as well. Consider, for example, 2-butene, which can be reacted with potassium permanganate under acidic conditions to produce two molecules of acetic acid.
- This reaction takes place through an intermediate that we would call a vicinal diol. This vicinal diol quickly splits under acidic conditions to form two carboxylic acids. In this case, two molecules of acetic acid are formed. We sometimes refer to this technique as oxidative cleavage of a double bond.

Reactions of Carboxylic Acids and Synthesis of Esters

- Revered German chemist Emil Fischer was one of the most prolific chemists of the late 1800s, and his work on carbohydrates gave us the Fischer projection. Far from being just a carbohydrate chemist, Fischer was driven to synthesize many of the small biologically relevant molecules that we encounter on an almost daily basis, including caffeine and the theobromine found in chocolate. He also is well known for developing a technique for producing an ester from a carboxylic acid under very mild reaction conditions—a reaction that bears his name.
- The Fischer esterification is a condensation reaction, meaning that it forms water as a by-product. It relies on a strong mineral acid catalyst to protonate the carbonyl of a carboxylic acid. Just like ketone and aldehyde carbonyls, in this protonated state, the carbon of carboxylic acids becomes significantly electrophilic and can be attacked by even a weak nucleophile like a neutral alcohol.
- This attack forms a tetrahedral intermediate that can take on two different tautomeric states: one in which the alcohol oxygen is protonated and one in which a hydroxyl is protonated. Departure of an alcohol from the original tautomer constitutes a reversal of the first step, but instead, a water can depart from the second tautomer, thereby leading to a protonated ester that quickly loses the catalytic proton to become neutral again.

- One of the great benefits of Fischer esterifications when compared to other methods of the day is that none of the reagents are sensitive to water, a notoriously difficult substance to exclude from organic reactions. But this benefit comes at a cost—that the reaction is an equilibrium that only very slightly favors product formation. Fischer esterifications, therefore, usually require the use of one reagent in extremely high concentrations to ensure that the other is almost completely converted.
- In yet another twist, the nearly equal energies of reactants and products means that we can turn the Fischer esterification reaction around, reversing the roles of product and reactant. So, we can exploit Le Chatelier's principle and turn a Fischer esterification into an ester hydrolysis simply by changing the solvent from alcohol to water. The product of this reaction should be a nearly complete conversion of ester to acid.

Tamiflu: An Ethyl Ester Prodrug

- The same sort of ester hydrolysis can take place in the body when a prodrug like Tamiflu is ingested. Oseltamivir carboxylate is an effective antiviral drug, but it suffers from a significant drawback. The carboxylic acid motif makes it too polar to be effectively absorbed across the lining of the stomach and into the bloodstream. When taken orally, only about 5% of the active ingredient reaches the human bloodstream, where it can do its work.



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Tamiflu can traverse the stomach lining easily, ensuring that most of the drug reaches the bloodstream.

- So, the best administration route for this drug would be an intravenous injection that would bypass the gastrointestinal tract completely, but this is not the most pleasant method of administration.
- The chemists at pharmaceutical giant Genentech devised a strategy involving the use of oseltamivir. They synthesize the ethyl ester of oseltamivir carboxylate, which is marketed under the trade name Tamiflu.
- Tamiflu itself is not active against influenza, but it is far less polar than its carboxylic acid counterpart. Because of this, it can much more effectively make its way from the gastrointestinal tract across the low-polarity stomach lining into the bloodstream. About 80% of orally administered Tamiflu reaches the blood, compared to just 5% of the free carboxylate form.
- Once the Tamiflu molecules reach the bloodstream, their ester groups are hydrolyzed back into their active antiviral carboxylic acid form with a little help from some enzymes in the liver. This strategy of using modified active compounds that are later chemically converted into their active form by the patient's own biochemistry is in wide use today. These modified active compounds are called prodrugs, and this strategy of dosing patients with esters that later become carboxylic acids is one of the most frequently used designs.

Saponification

- Soapmaking is a process nearly as old as—or possibly even older than—recorded history. Early soapmakers deserve credit as some of the first, albeit unwitting, organic chemists of the human race. The traditional making of soap uses a reaction that accomplishes nearly the same result as an acidic ester hydrolysis reaction, but it does so irreversibly and with remarkable ease and efficiency.
- Animal fats and vegetable oils contain compounds known as triacylglycerides. Sabatier and his contemporaries toyed with the saturation of these alkyl chains using hydrogenation reaction. But

triacylglycerides are useful for much more than just a food source. When the ester bonds are broken in these molecules, several useful compounds result, including those used in soap.

- Instead of relying on acidity to increase the electrophilicity of an ester, saponification relies on the removal of a proton from water to produce a stronger nucleophile in the form of hydroxide. This was easily accomplished even in ancient times by allowing rainwater to percolate through wood ashes to create lye, which modern chemists might call potassium hydroxide.
- The hydroxide from lye is a much better nucleophile than water and attacks the carbonyl of neutral esters easily to form a tetrahedral intermediate. Just as with the acid mechanism, this intermediate is now faced with two options: losing a hydroxide to go back to starting materials or losing an alkoxide as it recovers its carbonyl bond.
- Finally, we can see the secret to the irreversibility of saponification and why it is so easy to run this reaction to completion. The final step in the mechanism involves the transfer of a proton from the resulting acid (pK_a of about 5) to the resulting alkoxide (pK_a of about 16).
- With pK_a values this drastically different, clearly proton transfer is fast and irreversible, and the products obtained are alcohol and the carboxylate salt of an organic acid. This carboxylate salt is no longer reactive and can be isolated from the resulting glycerol. Our soap preparation is complete.
- But saponification is not limited to hydrolysis of fats. It can be used to disassemble a range of esters into carboxylates and alcohols, giving us yet another tool to break down small organic esters.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 10.1–10.4, 10.9.

Wade, *Organic Chemistry*, Chaps. 20.1–20.4, 20.10.

Questions to Consider

1. How might methyl butyrate be converted into ethyl butyrate using a reaction similar to those covered in this lecture?
2. Why are organic acids more closely associated with flavors in wines while esters are more closely associated with aromas?

Amines, Imines, and Nitriles

Lecture 17

In this lecture, you will learn how crucial nitrogen is to many biological molecules and how it typically has three bonds, making it a structurally diverse atom. In addition, you will learn about the simplest of nitrogen-containing compounds, amines, and how they are classified as primary, secondary, and tertiary. You also will be introduced to the structure and classification of imines, in which the nitrogen contains a pi bond to an adjacent carbon. Finally, you will consider nitriles, in which two pi bonds are present, and you will discover that the simplest and most well-known nitrile is hydrogen cyanide.

Structure of Nitrogen

- Nitrogen has an electron configuration of $1s^2 2s^2 2p^3$. So, nitrogen's valence shell will be filled when it shares three covalent bonds with other atoms. This makes nitrogen quite an interesting structural twist, because unlike oxygen, in its sp^3 -hybridized state, it can perpetuate chains and also bear one additional functional group or substituent.
- The library of nitrogen-containing motifs can get unwieldy very quickly, so we'll focus on just the simplest of these groups—those consisting of only one nitrogen atom bonded to one or more hydrocarbons. Within this narrow group of compounds, nitrogen can take on an sp^3 -hybridized state, forming three single bonds to distinct partners, creating what is known as an amine. It can also take on an sp^2 hybridization state, making a double and a single bond, forming an imine, or it can be sp , creating just one triple bond, commonly called a nitrile.

- This means that the family of simple nitrogen-containing compounds is larger and more complex than oxygen. We now have to consider not just how our heteroatom can terminate or perpetuate a chain, but also how it can modify that chain, introducing branching in ways that oxygen simply can't.

Structure and Nomenclature of Amines, Imines, and Nitriles

- Aliphatic amines can be thought of as saturated hydrocarbons containing at least one bonded sp^3 nitrogen atom. Just as oxygen had two bonding partners, nitrogen will have three, meaning that it may be bonded to just one alkyl group, creating a primary amine; two alkyl groups, creating a secondary amine; or three alkyl groups, producing a tertiary amine.
- Amines can be thought of as cousins to alcohols and ethers in which an NR group has been substituted instead of an OR. Alkylamines are somewhat less reactive than their alcohol brethren, leading to their frequent use as weak bases in reactions involving more reactive starting materials. The pK_a of a protonated alkylamine (or alkylammonium ion) is about 11. This makes them suitable bases for the removal of protons from species like carboxylic acids, phenols, and others.
- IUPAC nomenclature of amines is a bit more complicated than that for oxygen-containing compounds, owing to the branched nature of the sp^3 nitrogen. Amine motifs are treated as functional groups, with their longest attached alkyl chain as the parent hydrocarbon. Examples of primary amines are 1-hexamine, 2-hexamine, and 3-hexamine.
- In the case of a secondary or tertiary amine, the nitrogen is treated as its own address on the parent molecule, and its substituents are listed with *N* as the location. An example of a secondary amine is N-ethyl-1-hexylamine, while an example of a tertiary amine is N,N-diethyl-1-hexylamine.

Synthesis of Amines

- When it comes to organic synthesis, the human race has been bested time and time again by single-celled organisms. Just as was the case with synthesis of acetaldehyde, acetic acid, and other oxygen-containing compounds, it would seem that the extra 3 billion years of practice afforded to microorganisms has made them far more prolific at synthesizing nitrogen-containing compounds.
- Amines are the simplest starting point from which Haber-Bosch ammonia (named for Fritz Haber and Carl Bosch) can be injected into the organic chemistry realm. One very simple example of this is direct alkylation of ammonia using alkyl chlorides.
- Ammonia is a fairly good nucleophile, and it can be coerced to react by an S_N2 reaction with a primary or methyl alkyl halide like ethyl chloride.
- When mixed, a nucleophilic substitution reaction takes place, generating a primary amine and one mole of hydrochloric acid. So, here we run into a potential problem. The product amine is also nucleophilic and, in theory, can react with yet another alkyl halide to form a secondary amine, which could again react to form a tertiary alkyl halide.
- So, it is rather easy to make a tertiary alkyl amine by direct alkylation—just use a large excess of alkyl halide. Conversely, we can force the reaction system in the direction of primary alkyl halides by using a large excess of ammonia, limiting the chances that an already-formed primary amine will productively collide with another alkyl halide before they are all consumed.
- But this requires a very large excess of ammonia. The solution to this problem in making primary amines was actually worked out well ahead of Haber's time by one of his countrymen, Siegmund Gabriel, who used what we commonly refer to as a protecting group to temporarily render two sites on ammonia unreactive and then restore them to their original state after alkylation.

- Gabriel used a compound called phthalimide in place of ammonia, activating it with potassium hydroxide to create a more nucleophilic phthalimide ion. This ion attacks the alkyl halide to form the N-alkyl phthalimide intermediate. But there are no more NH protons to lose, which is a requirement for the reaction to proceed.
- After this step, a molecule known as hydrazine is used to remove the protecting group. Hydrazine contains two potentially nucleophilic nitrogens, and the phthalimide motif has two electrophilic carbonyl carbons. The hydrazine first attacks one carbonyl, and then the next, forming the very stable by-product phthalimide hydrazide and our primary amine.
- Direct alkylation is an easy way to make tertiary amines, and primary amines can be made using phthalimide protecting groups and the Gabriel synthesis. But what about secondary amines? They cannot be favored by stoichiometric control, nor can the Gabriel synthesis be easily modified to protect only one bond to nitrogen.
- The simplest solution to this problem is a technique known as reductive amination. In this reaction, a primary amine formed by direct alkylation, the Gabriel synthesis, or other means is reacted with a ketone or aldehyde under acidic conditions.
- Under these conditions, an N-substituted imine is formed. Once this imine intermediate is formed, the product is reduced using a familiar reagent: lithium aluminum hydride. This adds hydrogen across the double bond to produce a secondary amine. In the case of ketones, a branched alkyl group is obtained, whereas aldehydes yield straight-chain secondary amines.

Structure and Nomenclature of Imines

- Imines contain an sp^2 nitrogen and, therefore, share a great deal of structural similarity to their ketone and aldehyde brethren. In fact, we take their names—ketimine and aldimine—from similar carbonyl-bearing structures.

- Imines are most easily synthesized by the reaction of ammonia or a primary amine with ketones or aldehydes using a strong, non-nucleophilic mineral acid like sulfuric acid to activate the ketone. In this situation, the nitrogen acts as a nucleophile, attacking the carbonyl that uses one of the amine protons to tautomerize to a β -hydroxyamine. Finally, a second tautomerism occurs, leading to departure of a water molecule and formation of the imine.
- Of course, imines can always be reduced to their analogous amines using lithium aluminum hydride or palladium and carbon. Just as with creating a secondary amine, a linear primary amine can be made by reduction of a primary aldimine. Branched primary amines can be prepared by reduction of primary ketimines. Linear secondary amines can be prepared from secondary aldimines, and branched secondary amines can be prepared from secondary ketimines.
- But imines are so much more than just intermediates in the synthesis of amines. They hold their own as a commercially useful class of materials. Imines have the ability to do something that no other functional group we have yet examined can accomplish: They can be used to connect two large pi systems together through resonance. Of all the motifs we have considered so far, imines are the only heteroatom motif that has the ability to perpetuate the overlap of pi orbitals from one side of the functional group to the other.
- A perfect example of this motif's occurrence in commercial products is their presence in dyestuffs. Phenazine, for example, contains two of these groups. They link the two neighboring rings by resonance, creating a huge volume through which the pi electrons can move. Phenazine serves as the backbone for a number of commercial stains and dyes.

Structure and Nomenclature of Nitriles

- Nitriles, the simplest compounds containing an *sp* nitrogen, have a terminal nitrogen triple-bonded to a carbon, the most simple of these probably being the most well known: hydrocyanic acid, better known as hydrogen cyanide, the gas commonly used in executions decades ago.
- Hydrogen cyanide is a weak acid, and it dissociates partially in the bloodstream, creating protons and the cyanide ion. This small ion is a powerful binder to certain proteins involved in the electron transport chain that our bodies use to process energy and stay alive.
- The cyanide ion is not only very toxic, but is also very nucleophilic, prompting many to brave this potentially lethal compound in pursuit of their chemical goals. For example, cyanide was, and in some cases still is, used as an agent to extract gold from low-grade ore.
- Cyanide and gold form a strong complex known as aurocyanide. This complex is far more water-soluble than gold itself; gold can be leached from rock using strong solutions of cyanide in water. Naturally, this process must be very carefully monitored and controlled, and its by-products must be thoroughly treated for disposal.
- We also use cyanide to produce much larger nitrile compounds from primary and secondary alkyl halides in a simple S_N2 reaction. Using cyanide as a nucleophile, carbon chains can be conveniently extended by one carbon, creating larger nitriles. These nitriles have many uses, including an alternative to the Gabriel synthesis to manufacture primary amines without concern of over-substituting the product.

- Having pi bonds to their heteroatoms means that nitriles can be thought of as being similar to carbonyls, just like their imine cousins. They have a very electrophilic nitrile carbon and are susceptible to nucleophilic attack at that location. So, we can design syntheses in which the electrophilic nitrile carbon is attacked, leading to strategies to create many other functional groups.
- Probably the most familiar use of the term “nitrile” is its reference to functional groups used in certain rubber products, the best example of this being nitrile examination gloves. The polymer used to produce nitrile rubber is created from a reaction using acrylonitrile as one of its starting materials.
- The result of the process is a polymer that is decorated with repeating nitrile groups, giving it greater resistance to oils than natural rubber latex. Another benefit of nitrile latex is that it is prepared synthetically and, therefore, contains no plant material, like natural rubber latex does. This is why nitrile products do not fall prey to the same allergy-related issues as natural rubber latex.



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The production of nitrile rubber results in a polymer with greater oil-resistance than natural rubber latex, which makes for efficient examination gloves.

Suggested Reading

Hager, *The Alchemy of Air*.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 10.11, 12.1–12.5.

Wade, *Organic Chemistry*, Chaps. 19.1–19.8, 19.19.

Questions to Consider

1. How does the third bond available to nitrogen atoms increase the structural complexity of nitrogen-containing compounds?
2. In what ways does the lack of an N-H bond cause tertiary amines to have different chemical and physical properties?

Nitrates, Amino Acids, and Amides

Lecture 18

In this lecture, you will discover some slightly more complex functional groups involving both nitrogen and oxygen. You will learn about nitrate esters, a very unstable functional group that can be produced by reacting nitric acid with alcohols. You also will explore nitro compounds and amino acids. In addition, you will learn how the amide functional group can be prepared by heating a carboxylic acid in the presence of ammonia, driving off water to push the reaction forward. Finally, you will learn how amino acids can be joined together through an amide bond.

Nitrate Esters

- Fritz Haber contributed the starting material for the synthesis of, among other things, nitric acid. The importance of nitric acid in the field of explosives was secured much earlier. One day in 1846, according to legend, German-Swiss chemist Christian Friedrich Schönbein spilled a bit of nitric acid onto a table.
- After wiping up the spill with a cotton apron, he hung the apron on a stove door to dry. After drying, the apron suddenly and vigorously burst into flames. After extinguishing the fire and carefully considering what had happened, Schönbein realized that it was the combination of nitric acid and the carbohydrate fibers in the apron that had formed the explosive material.
- Very interesting functional groups decorate the long polymer known as carbohydrates. These functional groups are called nitrate esters, and they aren't present in the naturally occurring plant fibers.
- The arrangement of nitrogen and oxygen atoms in the nitrate ester groups makes it impossible to draw a resonance contributor in which all atoms have zero charge. This makes the group very

unstable. Add the fact that all of the oxygen needed for combustion is already present in the nitrate ester group, and you have a very explosive substance.

- The same nitrate group is present in nitroglycerine, the explosive prepared by nitration of glycerine by-product recovered from soapmaking. Nitroglycerine is a much smaller molecule than gun cotton fibers, making it a liquid at room temperature.

Nitrates

- A somewhat more stable functional group containing both nitrogen and oxygen is the nitrate functional group. Compounds containing this group are collectively referred to as nitro compounds. Probably the most famous nitro compound is trinitrotoluene (TNT).
- Most commercially relevant nitro compounds are synthesized by reacting small hydrocarbons with nitric acid at very high temperatures. This reaction is complex, proceeding through radicals and usually producing mixtures of nitrated compounds. But these compounds are of such great value that we frequently overlook this inefficiency.
- One particularly useful application of the nitro group in synthesis is that it can be reduced to an amine functional group using the familiar hydrogen and metal catalyst developed by Sabatier, or acidic solutions of certain metals. This can be a very handy synthetic tool when an amine group is desired in a particular location on a product, but attachment of a nitro group is easier to accomplish.



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TNT contains organic motifs that combine nitrogen and oxygen with organics to form an extremely reactive compound.

- A classic example of this utility is the synthesis of the anesthetic Novocain. The reaction requires the use of thionyl chloride to convert the carboxylic acid group to an acid chloride. A secondary amine is then reacted with that activated site to produce the needed tertiary amine.
- The problem is that the amino group from the ring can also react with the activated acid chloride. The solution is to start with an unreactive nitro group, completing the tertiary amine formation before reducing the nitro group to the desired amine.

Amino Acids

- We have examined nitrate esters and nitrates, both of which contain nitrogen-oxygen bonds, and—not so coincidentally—both of which can be used to make high explosives. But there are other organics that contain both of these elements joined not directly to one another, but through one or more carbons. When we make this very small structural change, we find ourselves making molecules that have a very different but equally versatile chemistry and can be used safely and reliably in organic synthesis.
- When a carboxylic acid motif is connected to an amine group via at least one intervening carbon, we call the resulting molecule an amino acid. Amino acids combine an acidic carboxylic acid group with a basic amine group, so they are often found in a state in which the acid is deprotonated but the amine is protonated. We call species like this—ones with a positive and negative charge in separate regions—zwitterions.
- The most famous group of amino acids is the 20 amino acids used by your body and all other living systems to produce proteins and enzymes that moderate your biochemistry. All of them share a common amino acid motif—one in which the two groups are separated by only one carbon. We call these alpha amino acids.

- But amino acids can have more than one carbon separating their acid and base groups. Two carbons in between produces a beta amino acid. Three carbons in between leads to a gamma amino acid, the simplest of which is gamma aminobutyric acid, a powerful neurotransmitter and integral part of your central nervous system.

Amides

- Yet another pervasive motif in organic chemistry that contains oxygen and nitrogen is the amide functional group. You can think of an amide as a carboxylic acid or ester with an sp^3 nitrogen, rather than an sp^3 oxygen. The lower electronegativity of the amide nitrogen means that it is significantly less acidic than organic acids, with a pK_a somewhere around 25 compared to 5 for a typical organic acid.
- Primary amides have an NH_2 group and can be synthesized from carboxylic acids by reaction with ammonia gas. A favorable proton transfer forms carboxylate and ammonium, which are heated to drive off the water by-product of the amide bond formation. It is this condensation reaction that forms the primary amide.
- Primary amides are named using the “R-” group prefix followed by an “-amide” suffix. An example of a two-carbon primary amide is ethanamide. Just as carboxylic acids are similar to esters, varying only by replacement of the acidic hydrogen with an R group, primary amides can be changed to secondary and tertiary amides in which one or both hydrogens are substituted with an R group.
- When there are R groups present, we name them as substituents of the parent primary amide. Examples are N-methylethanamide and N,N-dimethylethanamide. You may see these names shortened by dropping the “N” designation and simply calling them methylethanamide and dimethylethanamide.

The Hofmann Rearrangement

- In addition to being a biologically relevant structural motif, amides give us a useful alternative to the direct amination route to create amines. Amines can be synthesized easily when the R groups of the alkyl chloride substrate are primary or secondary. But an S_N2 reaction is essentially impossible when the alkyl halide substrate is tertiary.
- So, we are left wondering how we might create something like *t*-butylamine, in which the amine nitrogen is attached to a tertiary carbon. If we were to try to direct amination of *t*-butyl bromide or *t*-butyl chloride, we expect a preponderance of the elimination product to form (if anything forms at all).
- One solution to this problem is the Hofmann rearrangement, named for German chemist August Wilhelm von Hofmann. He discovered that primary amides could be converted into amines by reaction with a molecular halogen like chlorine or bromine and an aqueous base like sodium hydroxide solution. This reaction works even if the adjacent carbon is tertiary.
- Let's go through this reaction using *t*-butyl amide, molecular bromine, and aqueous sodium hydroxide. Under these conditions, just a small amount of the amide is deprotonated, forming a nucleophilic species that attacks the bromine molecule. The important difference is that the R groups are already attached to the nucleophile, not the substrate, in the initiating event of the reaction.
- This process forms an N-bromo amide, which is deprotonated a second time. Then, the bromide group is displaced from the amide nitrogen in an alkyl shift. This effectively reverses the carbon and nitrogen ordering in the chain, creating what we call an isocyanate.
- Hydroxide ion then catalyzes the conversion of isocyanate to a motif known as a carbamic acid, which is essentially just a carboxylic acid bonded directly to a nitrogen, rather than a carbon. Carbamic acids have a strong tendency to decarboxylate under basic conditions, leading to an amine.

- So, we have used the Hofmann rearrangement starting with *t*-butylamide to produce *t*-butylamine. About 30 years later, Theodore Curtis improved on this reaction using azide ion to convert an acyl chloride to acyl azide. This species reacts by a similar mechanism to form isocyanate, which decarboxylates to form an amine.

The Peptide Bond

- Perhaps the most interesting chemistry involving amides is their use to link together dimers and short oligomers (meaning a chain of a few subunits) of amino acids to form some consumer goods with which you might be familiar, including the artificial sweetener aspartame. Aspartame is actually the union of two amino acids—phenylalanine and aspartic acid—via an amide bond. The carboxylic acid portion of the phenylalanine is esterified with methanol.
- This molecule tastes sweet—hundreds of times sweeter than sugar—as it crosses your lips. But what concerns some is what happens to the aspartame afterward. In the acidic conditions of your gastrointestinal system, the amide bond is easily hydrolyzed to produce aspartic acid and phenylalanine methyl ester.
- The aspartic acid is of little concern, because it has no known ill effects on health. What is concerning to some is that the phenylalanine methyl ester also hydrolyzes into phenylalanine, to which a small percentage of the population is highly sensitive, and methanol, which is metabolized to formaldehyde, which can have toxic effects in the body, including blindness.
- This might sound alarming at first. The good news is that an average diet soda contains about 180 milligrams of aspartame, which is just about enough to produce 18 milligrams of methanol when it reaches your system. By way of comparison, an average glass of beer or wine contains about 50 milligrams of methanol. A similar amount of methanol is also produced by hydrolysis of naturally occurring methyl esters in fruit juices.

- So, based on the numbers, you are no more likely to develop vision problems drinking diet soda than you are by drinking grape juice or beer. To reach acutely dangerous levels of methanol in your system would likely require a diet soda binge the likes of which the world has never seen before.

Suggested Reading

Karpenko, V., "Some Notes on the Early History of Nitric Acid: 1300–1700," *Bulletin for the History of Chemistry* 34, no. 2 (2009): 105–116.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 10.10, 15.1, 15.2.

Wade, *Organic Chemistry*, Chaps. 24.1–24.5.

Questions to Consider

1. Nitrogen atoms are most stable when they have three covalent bonds and one lone pair of electrons. Use resonance structures to explain why organic nitrates and nitrate esters can be so unstable compared to amines and amides.
2. Hydrolysis of amide bonds takes place more efficiently at higher temperatures. How does this help to explain why many people feel the need to add more aspartame to hot beverages than to cold ones to obtain the same level of sweetness?

Conjugation and the Diels-Alder Reaction

Lecture 19

In this lecture, you will be introduced to the phenomenon of conjugation, in which multiple pi bonds in resonance with one another lend extra stability to a compound or ion. You will learn a few structural arguments for why this added stability exists, and you will discover a new way of modeling the energies of conjugated pi systems in alkenes. In addition, you will scratch the surface of conjugated diene reactivity by exploring two reactions. Finally, you will examine a reaction conceived by Otto Diels and Kurt Alder that allows us to quickly and easily form two carbon-carbon bonds.

Conjugation

- The simplest conjugated compound possible in organic chemistry is the hydrocarbon 1,3-butene. Compounds with pi bonds, or the potential to have them, tend to have resonance contributors that can stabilize those compounds; 1,3-butadiene is no different, having resonance contributors that contain pi electron density on the intervening carbon-carbon bond.
- When this resonance involves the commingling of multiple pi bonds, as it does in this case, we refer to this special type of resonance as conjugation. Conjugation in a compound comes with some important structural, physical, and chemical properties.
- The requirement for conjugation is that double bonds are alternating. If the double bonds are more than one carbon-carbon bond apart, then an intervening sp^3 carbon prevents the pi electrons from exchanging by resonance.

Naming Conjugated Compounds

- In spite of what we now know about the remarkable mobility of pi bonds in conjugated compounds, when we try to name these compounds, we revert to the most stable resonance contributor. This is always the contributor with all neutral atoms and alternating pi bonds. The name is constructed in much the same way as simple alkenes, but with the alteration that before the “-ene” suffix we insert a prefix “di-,” “tri-,” “tetra-,” etc.
- For example, what is commonly called vinyl ethylene would be named 1,3-butadiene. Creating ever-larger linear conjugated alkenes produces 1,3,5-hexatriene, and then 1,3,5,7-octatetraene, etc. This analogy extends to cyclic conjugated compounds. For example, 1,3-cyclohexadiene would be a conjugated compound as well.

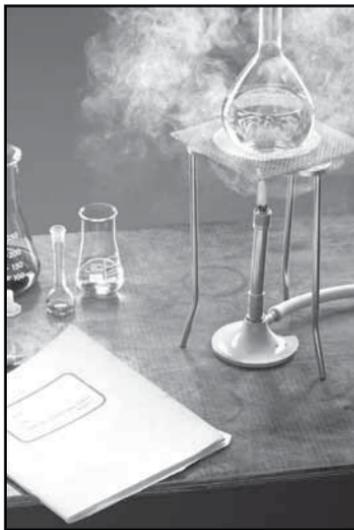
Stability of Conjugated Species

- Just as we did with isolated alkenes, we can also survey the effect of conjugation on stability using heats of hydrogenation. Let's do this using a simple system with only a few isomers, such as pentadienes.
- As a reference, the heat of hydrogenation of 1-pentene is 125 kilojoules per mole. If we add a second double bond that is isolated from the other by multiple carbon-carbon bonds, we create 1,4-pentadiene, which contains two isolated double bonds. Not surprisingly, the heat of hydrogenation doubles because we have essentially added a second bond of exactly the same type.
- But hydrogenation of its regioisomer 1,3-pentadiene releases less energy than the sum of that for two isolated double bonds. It is this observation that first led to our understanding of the stabilizing effect of resonance.
- This stabilizing effect extends far beyond simple diene hydrocarbons. Resonance has similar effects on the stability of compounds containing heteroatoms, such as enols, carbocations, and many more.

Reactivity of Conjugated Alkenes

- Although conjugated systems are somewhat more stable than similar but isolated pi systems, they can and do undergo many of the addition reactions that we discussed previously for simple, isolated alkenes—with a few important caveats.
- For example, the highly connected pi systems of conjugated compounds like alkenes mean that they can often undergo more complex addition reactions with unexpected regioisomers. The classic example of this is the addition of a hydrogen halide to 1,3-butadiene.
- Markovnikov's rule states that the addition of hydrogen halides to alkenes will occur with the halide going to the more-substituted carbon. But what happens when that alkene is conjugated?
- In the reaction between 1,3-butadiene and hydrochloric acid, the pi electrons still attack the acidic hydrogen of hydrochloric acid, producing a secondary carbocation—but the presence of an adjacent *p* orbital means that this carbocation is resonance stabilized, placing some of the positive charge density much farther away from the newly acquired proton than we are accustomed to seeing.
- So, in the second step of our reaction, the chloride nucleophile now has a *choice* of where to react. The two potential results are the products of a 1,2 addition, which produces a terminal alkene in accordance with Markovnikov's rule, and a 1,4 addition, which produces an internal alkene, the likes of which Zaitsev would be likely to predict.
- So, in a single system, we have a microcosm of this classic feud going on. The real winner is probably Zaitsev. The more stable product is, in fact, the internal alkene. But the catch is that Markovnikov's product forms faster, because the nucleophilic attack by chloride in the second step has a lower activation energy barrier at the 2 position than at the 4 position.

- So, if we run this reaction at very low temperatures for very short periods of time, we get more of the 1,2-addition product. This is because the competing process, the 1,4 addition, happens very slowly and doesn't get a chance to take place. We call reactions run under conditions like this kinetically controlled reactions, and the corresponding product is called the kinetic product.
- But if we give the system plenty of heat and lots of time, giving the 1,4-addition a chance to take place, then it will be the major product, because both pathways are accessible to the reagents, giving them a choice. We call reactions run like this, with long run times and high temperatures, thermodynamically controlled reactions.



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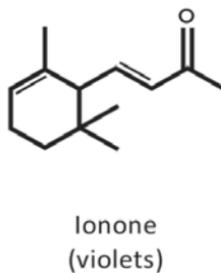
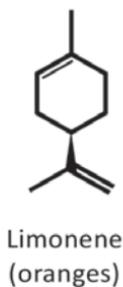
Reactions with long run times and high temperatures are called thermodynamically controlled reactions.

The Diels-Alder Reaction

- In the early decades of the 1900s, synthetic organic chemistry was earning recognition as a powerful field of study with tremendous potential for useful application in medicine, industry, and beyond. But as the 20th century dawned, the library of synthetic techniques available to organic chemists was still lacking.
- A particular challenge facing chemists was the need for techniques to create new carbon-carbon bonds. In 1928, Otto Diels and Kurt Alder devised a reaction scheme that exploited the geometry of conjugated diene molecular orbitals to produce not just one new carbon-carbon bond, but two in a single step.

- The Diels-Alder reaction is actually one of a class of reactions known as pericyclic reactions, which consist of the exchange of multiple pi electrons simultaneously between two molecules to create new sigma bonds between them. The Diels-Alder is designated a [4+2]-pericyclic reaction because it involves such a reaction between a conjugated diene (having 4 pi electrons) and one pi bond from another reagent known as a dienophile (having 2 pi electrons).
- The simplest example that meets these criteria is the reaction between *s-cis*-1,3-butadiene and ethene. To envision how this reaction takes place, let's re-create the molecular orbitals of both molecules. First, 1,3-butadiene has four molecular orbitals, of which the pi 2 is the highest occupied molecular orbital (HOMO) and the pi 3 is the lowest unfilled molecular orbital (LUMO).
- We collectively refer to the HOMO and LUMO as frontier molecular orbitals, because they usually represent the orbitals that will be vacated and occupied, respectively, when a reaction takes place.
- Ethene is a bit simpler because it only has two *p* orbitals in its pi system. So, pi 1 is the HOMO and pi 2 is the LUMO.
- As the two reagents approach one another, the HOMO of the diene and the LUMO of the dienophile are in phase on both sides, and the same is true of the diene LUMO and the dienophile HOMO. This means that the two reagents are perfectly configured to exchange electrons on both sides in a concerted process that produces two new sigma bonds from four of the pi electrons.
- The entropic penalty of making one molecule from two is easily balanced and, in fact, overwhelmed by the enthalpic benefit of trading two pi bonds for two sigma bonds. The new carbon-carbon bond creation is complete.

- What makes the [4+2] reaction so easy to complete is the in-phase alignment of frontier molecular orbitals. Because the geometries of the molecular orbitals are perfectly set up for a reaction to take place, all we need is to mix the reagents and wait for the molecules to collide. We call this a thermally activated reaction.
- If we try to conduct analogous reactions—for example, in a [2+2] cyclization, making cyclobutene from two molecules of ethylene—the frontier molecular orbitals are not properly aligned when the compounds are in their lowest energy states.
- We can resort to a trick called photoactivation, promoting electrons into higher-energy molecular orbitals by shining light of just the right wavelength on them. This essentially changes the identity of the frontier molecular orbitals, artificially creating the overlap that we can get for free in a [4+2]. It is this detail—that Diels-Alder reactions are thermally activated—that makes them so useful.
- In addition, a number of biologically and commercially relevant compounds, such as cyclic terpenes, contain a cyclohexene motif. Compounds naturally occurring in plants, such as limonene in oranges, terpineol in lilac, and alpha lonone from violet, can all be easily synthesized using a Diels-Alder strategy.



- The Diels-Alder reaction can be performed with more complex dienes and dienophiles, leading to products with a more robust stereochemistry than the cyclohexene product from the previous example.
- In the addition of the dienophile to the diene, both new carbon-carbon bonds form on the same side of the newly created ring. In the case of cyclohexene formation, this is purely an academic observation, because all substituents of the newly joined carbons are hydrogen atoms. But what if they are not?
- Let's begin by examining the first step of the Woodward synthesis of cholesterol. Robert Burns Woodward knew that he was trying to make a compound with four fused carbon rings on it from much simpler starting materials, so why not consider the Diels-Alder to start building this scaffold?
- Woodward began his synthesis using 1,3-butadiene to create his first fused ring to a compound known as hydroquinone. The Diels-Alder process ensured that the desired six-membered ring would form. But Woodward faced a new challenge: His bicyclic structure had the wrong stereochemistry. The Diels-Alder forced the addition of his new ring in a *cis* configuration.
- Consider the simpler example of 1,3-butadiene reacting with *cis*-2-butene as the dienophile. The product of the reaction will have chiral centers at the two carbons from the 2-butene. Because we used *cis*-2-butene, we expect to obtain a single meso compound in which the methyl substituents are *cis* to one another on the ring. (*4R,5S*)-4,5-dimethylcyclohexene.
- However, using *trans*-2-butene leads instead to a set of diastereomers in which the methyl groups are on opposite sides of the ring, creating an (*R,R*) enantiomer and an (*S,S*) enantiomer.

Suggested Reading

Berson, *Chemical Creativity*, Chap. 2.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 4.8.

Wade, *Organic Chemistry*, Chaps. 15.1–15.6, 15.11, 15.12.

Questions to Consider

1. For which of the reactions below do you expect different products to form depending on the temperature at which the reaction is run?
 - a. 1,3-butadiene with 1 equivalent of HCl
 - b. 1,4-pentadiene with 1 equivalent of HCl
 - c. 1,3-cyclohexadiene with 1 equivalent of HCl
2. The Diels-Alder reaction between acrolein and 2-methoxy-1,3-butadiene can produce two different isomers. Which would you expect to form in excess, and why? (Hint: Consider charges in the resonance hybrid for each compound.)

Benzene and Aromatic Compounds

Lecture 20

This lecture focuses on characterizing and naming a class of compounds known as aromatics. You will learn how cyclic pi systems of $4n + 2$ pi electrons have a remarkable stability that was recognized very early in the history of organic chemistry. In addition, you will learn about Hückel's rule, which predicts that this trend continues on to larger systems, and the polygon rule. You also will examine how aromaticity can profoundly influence the acid-base properties of organics. Finally, you will consider situations in which aromatic rings fuse together to create a new class called polynuclear aromatic hydrocarbons.

The Structure of Benzene

- It was known for quite some time that a compound of unusual stability and a very low hydrogen-to-carbon ratio could be isolated from torch fuel. Although the compound was clearly a hydrocarbon, its unusual chemical stability and reduced hydrogen content defied explanation until the 1860s, when August Kekule hypothesized that benzene's formula and properties could be explained if the molecule were cyclic.
- We know today that Kekule was right. His theory was not beyond challenge, however, as Kekule's model of a cyclic triene predicts that a molecule of benzene should have two different types of carbon-carbon bonds: three shorter double bonds and three longer single bonds. Yet the compound proved to have six identical bonds, forming a perfect hexagon.
- Also, Kekule's putative structure should generate two possible isomers when replacing two of the hydrogens with other groups, such as chlorine. One isomer has a double-bonded carbon between the substituents, and the other has only a single bond. Kekule attempted to explain this observation as a fast interconversion between the two putative isomers, but he was actually wrong about this.

- In 1925, Sir Robert Robinson published a theory in the *Journal of the Chemical Society* postulating that what he called an “aromatic sextet” of electrons stabilized the ring by moving unrestricted about the entire circular pi system, creating a ring of identical carbons joined by bonds of one and one-half order. This theory leads us to more accurately draw benzene molecules using a circle or dashed interior hexagon to represent the aromatic sextet of electrons.
- In the 21st century, far from just qualitatively observing the stability of benzene, we can use the technique of calorimetry to determine its heat of hydrogenation—this is, the amount of heat released when the unsaturated compound is saturated with hydrogen. If we conduct this experiment using cyclohexene and 1,3-cyclohexadiene as controls, we can determine with relative ease that the double bonds in these systems are nearly equivalent.
- But when we add that magical third pair of pi electrons, the heat of hydrogenation is far less than we would have expected—about 150 kilojoules per mole less. We call this discrepancy the resonance energy for benzene. To put the size of that resonance energy into perspective, it is just less than half the bond enthalpy of a covalent carbon-carbon bond.

Molecular Orbitals of Benzene, Hückel’s Rule, and Frost Circles

- Benzene consists of six sp^2 carbon atoms joined in a ring. This ring is perfectly flat in the case of benzene, which allows all of its p atomic orbitals to combine to form one large pi system with density both above and below the ring.
- But the rule for the formation of molecular orbitals is that six atomic orbitals in means six molecular orbitals out. These orbitals all correspond to the linear addition of p atomic orbitals with varying combinations of phase. For example, when all six p orbitals are in phase, the lowest possible energy molecular orbital is obtained. We call this the pi 1.

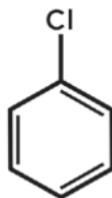
- But it is also possible to form five other permutations of molecular orbitals: two possibilities with a single nodal plane (π_2 and π_3), two possibilities with two node planes (π_4 and π_5), and one possibility in which all six p orbitals are aligned antiparallel, creating three nodal planes and a sixth molecular orbital (π_6).
- So, we are in a situation very similar to that of 1,3,5-hexatriene, with the caveat that some of the molecular orbitals are equivalent in energy. If we orient these molecular orbitals on a vertical energy axis, we can superimpose a six-membered polygon on the energy diagram for a six-membered ring.
- Bisecting this ring with a horizontal line gives us the nonbonding energy for the diagram, and populating the π system with the total inventory of six π electrons from benzene leads us to a situation in which all of those electrons are in a more stable bonding molecular orbital. This is the source of benzene's unusual stability.
- In fact, this geometric coincidence—called the polygon rule or a Frost circle—holds for all simple annulene structures like this one. In fact, they can be used to explain yet another concept, known as anti-aromaticity.
- The molecular orbital diagram for cyclobutadiene predicts that moving its four π electrons into a planar system requires that two of them populate nonbonding orbitals. This arrangement leads not to an energetic benefit, but rather to a penalty for aligning all four p orbitals parallel to one another.
- It is actually more thermodynamically favorable for cyclobutadiene to have two isolated double bonds. Without any aromaticity to offset the tremendous angle and torsional strain it is under, cyclobutadiene is a hopeless proposition.
- Consider the next progression in this type of molecule: 1,3,5,7-cyclooctatetraene. If we inscribe an octagon within a circle, point down, there will be eight π molecular orbitals in the system

for this compound. When we populate these orbitals with eight electrons from its pi system, we see a situation similar to that of cyclobutadiene, in which the last two electrons are in nonbonding orbitals, making 1,3,5,7-cyclooctatetraene anti-aromatic.

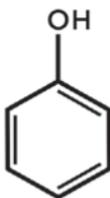
- This fact is evident in the structure of 1,3,5,7-cyclooctatetraene, which has been shown to have four isolated double bonds of shorter length and a distinct pucker, which places alternating pi bonds out of alignment with one another in an attempt to avoid anti-aromaticity.
- If we continue our analysis by expanding the pi system yet again, we see that 1,3,5,7,9-cyclodecapentene is again aromatic, and so on. This trend—that $4n$ pi electrons leads to anti-aromatic systems and $4n + 2$ electrons leads to aromatic systems—is known as Hückel's rule, named for German chemist Erich Hückel.
- But the utility of Hückel's rule extends well beyond just hydrocarbons like benzene; it can be used to explain the behavior of other cyclic systems with aligned p orbitals as well. For example, a polygon analysis of the tropylium ion, which is a carbocation consisting of a seven-membered ring with six pi electrons and a positive charge, shows that it is also aromatic.
- In fact, the effect of resonance on the stability of tropylium is so powerful that it is one of the few carbocations that can be purchased as a stable salt and stored in the laboratory. Those pesky intermediates from first-order reactions have become a starting material, owing to the stabilization provided by resonance. And the same is true for cyclopentadienyl cation, which contains six pi electrons and a system of five pi molecular orbitals. In both instances, all six pi electrons find homes in bonding orbitals, lending extra stability to the ions.
- Hückel's rule can be extended to systems containing heteroatoms—for example, pyridine (C_4H_5N).

Naming Aromatic Compounds

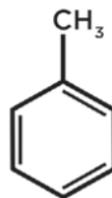
- The revelation that all carbons of benzene are equivalent simplifies the process of naming them when they are substituted. Because all six carbons are identical and the pi-bonding electron density is the same, using the name 1,3,5-cyclohexatriene (per IUPAC) is a bit misleading, so we usually default to describing this ring motif as “benzene.”
- Just as any other carbon scaffold can be modified by replacing its hydrogen atoms with more complex substituents and functional groups, so can those of benzene.
- When a single substituent is attached to a benzene ring, we simply start the name with that substituent’s prefix—for example, chlorobenzene, hydroxybenzene, or methylbenzene. Because all six carbons of benzene are equivalent, the position of the first modification is of no consequence. We get “chlorobenzene” no matter which carbon we attach it to.



Chlorobenzene



Hydroxybenzene



Methylbenzene

- Attaching a single functional group to the ring prompts us to place a modifier at the end of the name—for example, benzaldehyde or benzoic acid.
- Sometimes the groups and the parent get turned on their head, and we describe the benzene ring as a substituent itself, using the identifier “phenyl” or “aryl.” For example, chlorobenzene is also often called “aryl chloride,” and hydroxybenzene is called “phenol.”

- But what really spices up the nomenclature of benzene rings is when we have two or more attached substituents and functional groups, because the attachment of a single substituent renders the remaining unmodified carbons different from one another.
- Take methylbenzene, for example. There are three chemically distinct locations on the ring. One of them is a single bond away, another is two bonds away, and a final position is three bonds away.
- Where we place the second group makes a profound difference in the identity and chemistry of the compound. For example, dimethylbenzene, commonly called xylene, can form three different isomers: 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene.
- We often use a more common method of nomenclature to indicate which regioisomer of the compound we are discussing, using the prefixes “ortho-,” “meta-,” and “para-” in place of the numbered locations of the groups. The prefixes are often shortened to a single italicized letter—for example, the three isomers *o*-xylene, *m*-xylene, and *p*-xylene.

Large Polynuclear Aromatics

- Aromatics need not exist as an isolated benzene ring. Although most, if not all, of the compounds we will be investigating will have isolated benzene motifs, a newer class of compounds has gathered considerable interest in recent decades.
- Picture two benzene rings fused along one edge, essentially sharing a carbon-carbon bond. We call this compound naphthalene. By fusing the rings, we create two aromatic systems that share a common pair of *p* orbitals, so it should come as no surprise that naphthalene’s resonance energy is about 252 kilojoules per mole—slightly less than two separate benzene rings, but substantial nonetheless.

- For planar compounds, this trend continues through the tricyclics anthracene and phenanthrene all the way up to graphite, which is essentially a never-ending sheet of fully fused benzene rings. This allotrope of carbon benefits from such significant resonance stabilization that at standard temperature and pressure, it is even more stable than diamond.
- In the 1980s, chemists began devising ways to endow curvature to these so-called graphene sheets by changing which edges each ring shares with others, creating new allotropes of carbon in the form of spheres. The most famous of these is the truncated icosahedron C_{60} molecule buckminsterfullerene, affectionately referred to as “buckyballs” and named for the famous architect, inventor, and futurist R. Buckminster Fuller.
- One can also envision how the buckyball motif could act as endcaps connecting a graphene sheet that is rolled up on itself. This structure is commonly called a carbon nanotube. These materials show some promise in some very exciting applications—such as gas storage, media, and building materials to electronics, engineering, and medicine—but much of that potential is yet to be realized.

Suggested Reading

Berson, *Chemical Creativity*, Chap. 3.

Davenport, D. A., “Observations on Faraday as Organic Chemist Manqué,” *Bulletin for the History of Chemistry* 11 (1991): 60–65.

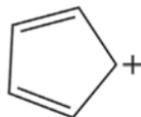
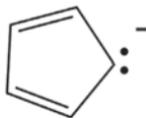
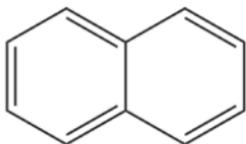
McMurry, *Fundamentals of Organic Chemistry*, Chaps. 5.1, 5.2.

Thomas, J. M., “The Royal Institution & Michael Faraday: A Personal View,” *Bulletin for the History of Chemistry* 11 (1990): 4–9.

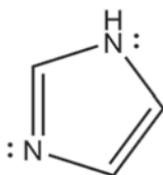
Wade, *Organic Chemistry*, Chaps. 16.1–16.14.

Questions to Consider

1. Which of the species depicted below are aromatic?



2. Imidazole is a frequently used organic base. Which nitrogen from imidazole is more basic, and why?



Modifying Benzene—Aromatic Substitution

Lecture 21

This lecture will build on your understanding of the structure of benzene by investigating a very useful class of reactions known as electrophilic aromatic substitution reactions. You will investigate the general mechanism by which it takes place, and you will learn how other reagents often need to be activated to make them reactive enough to entice the substantially stabilized benzene ring to react with them. In addition, you will learn about a handful of the many modifications that can be made to benzene. Finally, you will consider how already-modified benzenes can be further modified to produce ortho, meta, and para isomers.

Electrophilic Aromatic Substitution

- In 1873, at the University of Strasbourg in Germany, Adolf Von Baeyer was supervising a graduate student named Othmar Zeidler, whose graduate project included the synthesis of a substituted benzene compound known as dichlorodiphenyltrichloroethane (DDT). Zeidler's synthesis of this compound was accomplished using chlorobenzene and chloral under acidic conditions. Under these conditions, the two chlorobenzene rings are joined by substituting the chloral for hydrogens in the para position of each ring.
- The Swiss chemist Paul Muller is credited with later discovering, documenting, and obtaining a Swiss patent for the insecticidal use of the compound, after which the U.S. government tested and used the compound to combat infectious disease abroad. Shortly after the conclusion of World War II, the U.S. government began to allow commercial use of DDT for pest control in domestic crop production.
- Unfortunately, DDT lasted so long in the environment that it could be transmitted from insects to fish, and from fish to birds. Many bird species suffered tremendous population declines due to the

presence of DDT in their food sources. In 1972, the United States banned the use of DDT in agricultural applications. Today, it only finds use in emergencies as a vector control agent to prevent the spread of disease.

- The synthesis of DDT is a shining example of an electrophilic aromatic substitution reaction, which is so named because the newly attached motif starts out as an electrophile (unlike nucleophilic substitution, in which the newly added group is nucleophilic).
- In the reaction of benzene and a generic electrophile, for example, the pi electrons of benzene are not held as tightly as most sigma-bonding electrons, even though they are in an aromatic system. Although it takes an extraordinarily electrophilic reagent to coax them into attacking, it can be accomplished.
- When an adequately electrophilic reagent is added to benzene, the pi electrons of benzene simply can't resist attacking, and in doing so, they generate a tetrahedral center adjacent to a resonance-stabilized carbocation. We call this intermediate a sigma complex because we have traded two of our aromatic pi electrons to make a new sigma bond to the electrophile.
- Even with the newly formed, more stable sigma bond, the sigma complex is of much higher energy than the starting material. This is mainly because the ring has lost its aromaticity, and the associated stability, at this point.



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Though now banned in the United States, DDT is a shining example of an electrophilic aromatic substitution reaction.

- Under conditions like this, the intermediate will immediately begin to look for ways to dispense with the positive charge of the carbocation and recover its aromaticity. The simplest way to remove the newly acquired positive charge is to lose a proton to the solvent.
- If we remove one of the substituents about the tetrahedral center that we generated in the first step of the reaction in a heterogenic bond cleavage, we can repopulate the aromatic ring using the bonding electrons that were holding that substituent in place. Removal of the electrophile would produce an uninteresting result, because we simply return to the starting materials. But what if instead we remove the proton on the same tetrahedral center?
- A molecule of solvent or another weak base is usually all it takes to abstract that proton, leading to a return to aromaticity (and therefore stability), while leaving the new benzene-electrophile bond intact. Our substitution reaction is complete.

Generating Electrophiles

- As simple as the electrophilic aromatic substitution mechanism seems, getting such a reaction started can be complicated because it requires a species so electronegative—so hungry for electrons—that it can compensate for the temporary loss of aromaticity during the reaction's first step. Indeed, the key to a successful substitution is to generate an adequately electrophilic substitution reagent.
- With regard to Zeidler's synthesis of DDT, chloral itself is not electrophilic enough to react with the aromatic electrons of chlorobenzene. This is why Zeigler added a small amount of sulfuric acid to his reaction. Sulfuric acid is strong enough to protonate a carbonyl group like that of chloral, increasing the electrophilic character of its carbonyl carbon. It is this protonated carbonyl species that was key to starting the reaction that ultimately produced this history-changing compound.

- Over the past two centuries, many researchers have devised ways to substitute benzene using many familiar functional groups, including nitration, halogenation, and alkylation. In all three of these cases, simply mixing benzene with nitric acid, molecular bromine, or an alkyl halide will not achieve the desired reaction. We need to find ways to make each of these three reagents even more electrophilic than they already are.
- Nitration of benzene is typically achieved by adding a bit of sulfuric acid to the mixture. The purpose of this sulfuric acid is to protonate the nitric acid, which acts as a base. Sulfuric acid is extremely strong, with a pK_a of about -2 , and can protonate just enough nitric acid to get the process started.
- Once protonated, nitric acid can lose a water molecule to form a species known as nitronium. The electron cloud around nitronium is exactly the same as that of carbon dioxide, but it has a central nitrogen atom instead. That extra proton in the nucleus of nitrogen means that the nitrogen now has a $+1$ charge associated with it. This dense region of positive charge, complete with oxygen atoms ready to accept pi electrons as the attack occurs, is all it takes to make an effective electrophile for nitration.
- Halogenation of benzene is another highly desirable goal, but it is one that cannot be achieved simply by mixing benzene and molecular halogens like chlorine. In this case, inorganic complexes like aluminum(III) chloride or iron(III) chloride are used to induce a strong dipole in the molecular halogen bond. This method of chlorination is so effective that when taken to extremes, all six hydrogens from a benzene can be substituted with chlorine, producing hexachlorobenzene.
- The same type of catalyst can be used to enhance the dipole of an alkyl halide to produce an alkylation. Alkylated benzene compounds produced in this way can be used to produce such useful products as synthetic detergents.

Substitution of Substituted Benzenes

- When we substitute one hydrogen from benzene, like its nitration, or when we substitute all of its protons, like we did using chlorine and aluminum(III) chloride catalyst, only one possible isomer of the intended product exists. But what about when we replace some, but not all, of the hydrogens around a benzene ring?
- Once a substituent has been placed on the ring, the remaining hydrogens are no longer equivalent. We have two ortho positions, two meta positions, and one para position around the ring. Will the second substitution take place preferentially at one of these positions, or will we get a statistical mixture of all three possibilities?
- This consideration is well illustrated by Zeidler's successful DDT synthesis. If his electrophilic aromatic substitution methodology caused substitutions at random locations around the ring, we would expect that any given sample of chlorobenzene molecules should produce a mixture of products that are 40% ortho, 40% meta, and only 20% para.
- Moreover, the chances of a second substitution occurring at the para position are only 20%, leaving a paltry 4% of the final product in the preferred configuration. However, when Zeidler's synthesis is performed, the desired regioisomer is the major product obtained. So, how did it come to be that chlorobenzene selectively undergoes electrophilic substitution at its para position?
- This tendency for a reaction to occur at one particular position among several similar positions is called regioselectivity. Functional groups attached to benzene rings alter not only the reactivity of the ring, but also the regioselectivity of subsequent additions.
- Recall that there are three different positions available to react on a substituted benzene ring: two ortho positions, two meta positions, and one para position. Based on this distribution, one might expect

that, for example, brominating a nitrobenzene molecule would yield a mixture of products that is 40% ortho-, 40% meta-, and 20% para-substituted.

- However, when we conduct this reaction, we find that this distribution of products is rarely the case! In fact, we usually find a preponderance of one product with just a small amount of the others. So, how does this preference to substitute at a particular location on the ring happen? The answer lies in the stability of the sigma complex transition states of all three reaction pathways.
- Let's start by analyzing the three possible pathways for the electrophilic aromatic substitution of chlorobenzene. When an electrophile finds itself at the meta position, we see a transition state form in which three resonance contributors form, all of which look very similar to those in a simple benzene ring undergoing substitution.
- However, when an electrophile attaches to the para position or the ortho position of the ring, we can draw a fourth resonance contributor. More contributors mean a more stable species. Hammond's postulate, named after chemist George S. Hammond, says that a more stable intermediate in the rate-limiting step leads to a faster reaction.
- In terms of the three possible products of any electrophilic substitution of chlorobenzene, the meta-intermediate is similar in energy to substitution of benzene, but the ortho- and para-intermediates are lower in energy, thus lowering the activation energies of the pathways for these two products.
- So, the meta position of chlorobenzene is less reactive than the ortho and para positions. In fact, chlorine is part of a class of substituents called ortho/para directors. To explain why the para position is substituted more than the ortho requires that we look to our second consideration: ring activation and deactivation.

- The second consideration is that the already-attached group may withdraw or donate electron density to the ring. Reducing electron density within the ring makes it less likely to attack, because doing so would only increase the magnitude of charge generated in the intermediate. Conversely, donating additional electron density to the ring would be expected to activate the ring and make it even more reactive.
- One of the traits that makes chlorine and bromine so interesting in this reaction type is that they withdraw electrons from the ring inductively. This means that the electronegativity of chlorine causes it to pull electrons out of the ring. Unlike resonance, inductive effects attenuate with distance.
- This gives us an explanation for the strong preference for the para position over the ortho position. The higher positive charge on the ortho atoms of chlorobenzene simply makes them less likely to attack an electrophile and take on even more positive charge.

Common Substituents and Their Effects

- Activating ortho/para directors include groups such as the amine group of aniline, the hydroxyl group of phenol, and the methoxy group of anisole. Groups like these have the ability to donate electrons to the ring by resonance.
- Deactivating ortho/para directors include halogens like fluorine, chlorine, and bromine. These groups direct by donating electrons in resonance but deactivate because of the strong dipole they create in the C-X bond.
- Deactivating meta directors, such as nitrates, carboxylic acids, and aldehydes, all withdraw electrons strongly by resonance. All of these groups contain a heteroatom two bonds away from the ring.

Suggested Reading

Casron, *Silent Spring*.

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 5.3–5.7.

Wade, *Organic Chemistry*, Chaps. 17.1–17.3, 17.5–17.8.

Walker, *Blizzard of Glass*.

Questions to Consider

1. Is it possible for a benzene ring to undergo substitution with a nucleophile instead of an electrophile? If so, what structural features must the ring have (leaving groups and ring substituents)?
2. Propose a strategy to convert benzene into 1-bromo-2,4-dinitrobenzene using electrophilic aromatic substitution. What by-product do you expect to form in this synthesis?

Sugars and Carbohydrates

Lecture 22

From the sweet ingredient of soda, to the cell walls making up a fibrous piece of wood, to the tough shell of a crab, all of the members of this extraordinarily diverse group of materials have one thing in common: They are all made up of the same general class of organic compound—carbohydrates. In this lecture, you will learn about these and other biologically important materials crafted from carbohydrates from the perspective of an organic chemist.

Definition and Classification of Carbohydrates

- Carbohydrates are compounds with the molecular formula $C_n(H_2O)_n$. Some simple examples of members of this class of compounds are the simple sugars erythrose, ribose, glucose, and fructose. Despite having a carbon-to-hydrogen-to-oxygen ratio of 1:2:1, carbohydrates are complex, polyhydroxylated species.
- Probably a more modern definition of carbohydrates would be polyhydroxyaldehydes and polyhydroxy ketones with the formula $C_n(H_2O)_n$ —and also the products produced by linking them together. Today, the term “carbohydrate” is used interchangeably with the terms “saccharide” and “sugar” to refer to all of these materials collectively.



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We are trained to think of carbohydrates as not much more than a dietary source of calories, but they are actually much more than that.

- In 1861, Aleksandr Butlerov published a paper entitled “Formation of a Sugar-Like Substance,” in which he detailed a synthesis using formaldehyde and a base to form what he believed to be simple sugars. He named his new substance “formose,” for the formaldehyde starting material and the class of sugar that he believed he had created. In fact, Butlerov had created a mixture of carbohydrates that interconverted through a series of aldol reactions.
- Carbohydrates are broadly classified by the number of subunits that comprise them. Individual simple sugar molecules can be connected to one another in one of several ways to produce chains of varying length. These chains are still referred to as carbohydrates and are classified based on their length.
- Sugars that cannot be hydrolyzed into simpler compounds are called monosaccharides. When two such units are joined together in a condensation reaction, we get a disaccharide. Polysaccharides can have anywhere from just a few to thousands of condensed monosaccharide units.

Monosaccharides

- Monosaccharides can be of varying length and organization but must meet the requirement of having a molecular formula of $C_n(H_2O)_n$. If we simply have a chain of carbons each with its own hydroxyl group, then we miss the required ratio of atoms just slightly—we have two hydrogens too many. To fix this, we reduce the compound to get a carbonyl at one end.
- The inclusion of just one carbonyl solves the problem and gives us a framework on which to build our simple sugars. When the requisite carbonyl is placed at the end of the chain, we call these sugars aldoses (for the aldehyde group). If instead the carbonyl is on an interior carbon, we call this a ketose (for the ketone motif it produces).

- We name monosaccharides based on the number of carbon atoms contained therein. So, a six-carbon sugar with a terminal carbonyl is an aldohexose, whereas a six-carbon monosaccharide with an interior carbonyl is a ketohexose. This system is applied to all commonly occurring monosaccharides, which tend to have anywhere from three to seven carbons, with most ketoses having the carbonyl on the second carbon.
- But simply defining the number of carbons in the chain and the location of the carbonyl bond in a simple sugar isn't enough to let us unambiguously identify carbohydrates. All along a chain of hexoses, pentoses, tetroses, and even the triose glyceraldehydes, there are one or more chiral centers. Particularly in the case of longer monosaccharides like hexoses, chirality can generate a large number of potential stereoisomers.
- The drawing method known as Fischer projections is used to investigate stereoisomers. Fischer projections are created by drawing a compound so that all of the horizontally depicted bonds are coming out of the plane of the page and vertical bonds are falling back behind it.
- Herman Emil Fischer won his Nobel Prize in part for his characterization of the structure of glucose, and a large part of his technique for this was to use his systematic form of projection, which made all of the stereochemical relationships in these complex molecules evident.
- As a general rule, we draw monosaccharides in a Fischer projection with the terminal carbonyl at the top of the drawing. We can then number carbons of the chain from top to bottom to facilitate discussion.

Cyclic Hemiacetals and Glycosides

- A carbonyl activated by acid in the presence of an alcohol forms a motif called a hemiacetal. In the case of monosaccharides, we have both a carbonyl and an alcohol available to participate in such chemistry intramolecularly.
- When this reaction takes place between the carbonyl of a carbohydrate and its terminal hydroxyl group, a relatively stable ring of five or six atoms can sometimes form.
- We call these cyclic sugars furanose in the case of a five-membered ring and pyranose in the case of a six-membered ring, each named for the cyclic ether that makes up its backbone. The result is an equilibrium between the acyclic aldose or ketose form and the cyclic furanose or pyranose form.
- The anomeric C1 of pyranose and furanose molecules is a crucial site for modification in both the lab and in nature. Close inspection of glucopyranose reveals that the C1 is the only carbon bonded to a pair of electron-withdrawing oxygen atoms. Thus, it is the most electrophilic and most likely to participate in substitution reactions, such as the reaction between alpha-D-glucopyranose and acidified methanol.
- This mixture generates an equilibrium mixture of both the alpha- and beta-functionalized monosaccharide. When the C1 is functionalized, we call the product a glycoside, and the newly added group is called an aglycone.
- Glycosides turn up in a long list of biologically relevant materials, including salicin from willow bark used to treat headaches in ancient times. Glycosides even appear covalently bonded to specific protein side chains in a special class of enzymes called glycoproteins. There, they serve several functions, including protecting certain proteins from enzymatic degradation and enhancing their water solubility.

Disaccharides

- Although theoretically it is possible for any hydroxyl of one monosaccharide to form a glycosidic linkage with another, there are three arrangements that we principally see in nature. We distinguish these linkages by numbering the monosaccharide acting as the “aglycone” with prime notations ($'$). Following this system, $1,1'$ to $1,4'$ and $1,6'$ linkages are found in nature.
- A familiar disaccharide with a $1,4'$ linkage is maltose, which is formed by the glycosidic linkage of two glucose units through an alpha anomer. One glucose acts as the glycoside, bonding through its $C1$, and the other acts as the “aglycone,” bonding through its $C4'$. This leaves the $C1'$ to interconvert between enantiomers through an equilibrium process.
- Maltose is most familiar as the starting material for beer, made by the hydrolysis of starches in the first part of the process. Much of the maltose is consumed by the yeast that is used to brew the beer, but a small amount is retained in the beverage.
- Although they do exist in a few disaccharides, $1,6'$ linkages are less common. They are actually more relevant to polysaccharides. One example of this type of linkage is gentiobiose, a $1,6'$ disaccharide between two glucose units. By connecting to the aglycone at its $6'$ carbon, additional conformational flexibility is introduced, making a nice building block for branched polysaccharides.



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The starting material for beer is the disaccharide called maltose.

- A prime example of a 1,1' linkage is the familiar sweetening agent sucrose, which consists of a glucose and a fructose unit linked by a bridging oxygen through one another's anomeric carbon. So, in this unusual case, both sugars are acting as glycosides for themselves and as aglycones for their bonding partner.
- Because both anomeric carbons are occupied by the glycosidic linkage, sucrose has no free anomeric carbon to open back up in equilibrium with the cyclic form. This is important because sugars are much more prone to oxidative degradation when in their acyclic forms. This makes sucrose much slower to oxidize than other disaccharides and a popular choice for use in preserves.

Polysaccharides

- Polysaccharides are simply longer chains of sugars in which most of them are acting both as glycosides and as aglycones, perpetuating a polymer built from monosaccharide subunits. Many materials with which we are familiar are made from polysaccharides. For example, cellulose in cotton fibers is made up almost exclusively of D-glucose units attached by beta-1,4'-glycosidic bonds.
- The same material makes up about half of the mass of dried wood. Cellulose combines into closely packed fibrils that interact with one another via hydrogen bonding, forming a strong, tough, insoluble material. Certain animal species, most notably cows and termites, have symbiotic bacteria living in their digestive tract that help them break down the cellulose in cotton and lumber and use them as a food source.
- By contrast, switching the beta linkage to an alpha linkage gives us amylose, a starch that curves on itself into a helix. It can be digested and used as a source of nutrition for higher-order animals—even those without bacterial help to break it down.
- If we take amylose and branch it about every 30 subunits or by cross-linking another chain at a 6' position, we get amylopectin, a water-soluble thickening agent used in cooking applications.

- More extensive branching of the same kind leads to glycogen, one of the human body's primary energy stores. If you have enough glycogen stored up in your muscles, you are just a hydrolysis reaction away from additional glucose molecules for use as energy to help you run that marathon or finish that workday.
- A final example of polysaccharides is the remarkable armor that protects insects and arthropods such as cicadas and crabs. Chitin—the material from which these exoskeletons are made—is a polymer of a glucose derivative called N-glucosamine, which is a pyranose form of glucose with an amide functional group substituted at the C2 position of the ring.
- Polymerize this molecule through beta-1,4'-glycosidic bonds and you have chitin, a material so tough that once formed, it cannot grow with the animal. This is why crabs and insects periodically molt, shedding their chitin armor and producing a whole new, slightly larger coat of armor once the old one is shuffled off.



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The same class of materials used to sweeten soft drinks can also make up the armor that protects insects and sea creatures from predators.

- The secret to chitin's strength is not only in the glycosidic linkages, but also in the amide functionality added to the sugar ring. The amide nitrogen and carbonyl from one chitin chain can hydrogen bond to others on a separate strand. The result of this H-bond network is a material of remarkable strength.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chap. 14.

Wade, *Organic Chemistry*, Chaps. 23.1–23.7, 23.18, 23.19.

Questions to Consider

1. Is cyclization of carbohydrates driven by enthalpy or entropy? In light of this, how is temperature expected to affect the equilibrium between open-chain and cyclized forms?
2. Draw the two chlorinated monosaccharide subunits comprising sucralose (discussed in Lecture 11), indicating stereochemistry where appropriate.

DNA and Nucleic Acids

Lecture 23

Elegantly simple in its library of just four letters, but stunningly complex in the size and organization of those four letters, DNA and its chemical cousin RNA are familiar biopolymers that form the basis of life itself. Our understanding of DNA and the biochemical processes surrounding it has altered our perception of what it is to be a living thing. Scientists endeavor to study it, understand it, and ultimately manipulate it in ways that improve life. None of this understanding is possible without tearing this beautiful complex down into its most basic constituent parts—which is the focus of this lecture.

RNA

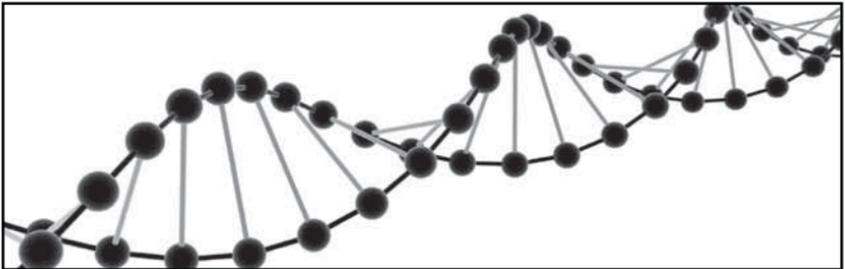
- Ribonucleic acid (RNA) serves several critical roles in converting your genetic code, or genome, into the proteins essential to life, or proteome. In addition to other roles, one of RNA's most important jobs is to transport the information in the DNA of your cells to areas where proteins are made. The “ribo-” part of the name refers to the carbohydrate ribose.
- Like any other aldopentose, ribose can undergo cyclization to form the associated ribofuranose, with its anomeric carbon in one of two positions: alpha or beta. It is the beta form that is the central building block of RNA.
- To produce the building blocks of RNA, the anomeric hydroxyl in beta-ribofuranose is replaced with an organic base through a nitrogen atom. In the case of RNA, these four bases are cytosine, uracil (as opposed to the thymine of DNA), adenine, and guanine. These units are further subdivided into the class of pyrimidine bases and purine bases, based on their backbone structure.

- Using one of these four bases as the aglycone in beta-ribofuranose produces one of the four subunits of RNA, collectively called nucleosides. Not surprisingly, these nucleosides have names similar to those of the bases that give them their identity. An aglycone of cytosine forms the nucleoside cytidine. Uracil leads to uridine. Adenine produces adenosine, and guanine produces guanosine.
- The glue that holds the nucleoside subunits together into a chain—so that there is a sequence to the collection of C's, U's, A's, and G's that will make up the information in the RNA molecule—is a phosphate functional group.
- By attaching a phosphate group at the 5' position on the sugar of our nucleoside, we create a motif called a phosphoester. The phosphoester group will be the linkage through which our nucleosides are connected to give our collection of information order.
- This collection of three crucial elements—information in the base, the backbone of the ribose, and the glue of the phosphoester—make up what is called a ribonucleotide, which is one complete subunit of RNA, ready to be linked to others to create a useful code.
- RNA is nature's messenger molecule, transporting information from the genetic code stored in DNA and assisting in the conversion of that information into the vast library of proteins that our bodies use to regulate its chemistry.
- Because the role of RNA is transmission of information, which is carried out on a fairly rapid time scale, RNA itself does not need to endure for long periods of time to effectively perform its duties in living systems. In fact, it is part of RNA's design that it can be broken down easily and its components recycled for use in creating more RNA as it is needed.

- RNA has a pretty stable backbone, but there is a chink in the armor at the 2' hydroxyl group. This nucleophile hangs out next to the phosphate ester group, which has an electrophilic phosphorus atom. The 2' hydroxyl of RNA just can't help but attack the phosphorus, initiating a mechanism that ultimately expels the next ribonucleotide in the sequence, breaking the chain that gives RNA its information-carrying ability.
- RNA can carry huge amounts of information back and forth, being broken down and rebuilt as the organism needs it. But there would be no information to transport or translate if there were no method of storing that information indefinitely until it is called upon. This task falls to a close chemical cousin of RNA, the famous DNA.

DNA

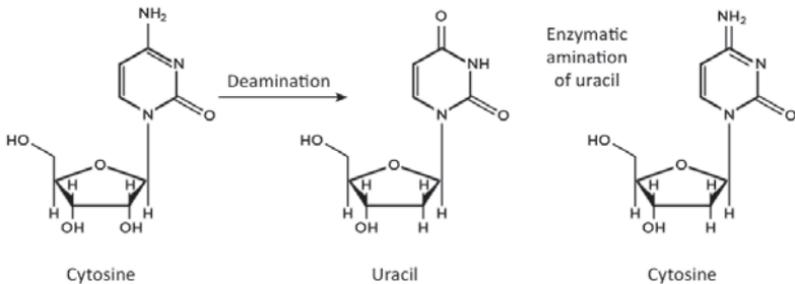
- Deoxyribonucleic acid (DNA) is another ribose-based biopolymer that serves a very different purpose. DNA is very similar to RNA, consisting of a phosphate, sugar, and base to form what we call a deoxyribonucleotide.
- There are two key structural differences that make DNA more robust than RNA. First is the removal of the 2' hydroxyl group of the beta-ribofuranose sugar. Instead, this group is replaced with a hydrogen, which is non-nucleophilic. This removal of one very specific oxygen from the ribose is the source of the “deoxyribo-” portion of DNA's name.



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Mapping genes and sequencing DNA helps us understand the chemical basis on which life evolves and changes in response to environmental stimuli.

- With this nucleophile out of the picture, DNA hydrolyzes about 100 times slower than RNA. This makes DNA a much better choice not for a short-lived messenger, but for the storage of the genetic code that needs to last you the rest of your life.
- A second feature of DNA that makes it a more robust system is the replacement of uracil with thymine, a methylated version of uracil. The reason for this difference is that cytosine itself can deaminate spontaneously to become uracil. When this happens to your DNA, this is bad news, because it means that your DNA mutated.



- But your body has a defense mechanism for this—a complex molecule called an enzyme that finds that uracil in your DNA and re-aminates it to recover the original cytosine. This incredible repair mechanism comes with a problem, however. If DNA actually used uracil, it wouldn't know which uracils to alter and which ones to leave alone. So, it uses thymine instead as the complementary base for cytosine.

Base Pairing

- DNA's double-helical structure was first proposed by James Watson and Francis Crick. But the discovery of the DNA double helix was the result of a concerted effort on the part of many talented researchers.

- In 1869, Friedrich Miescher first isolated DNA from the nuclei of cells. It was this biological source that prompted him to name it nuclein—a name that was later revised to DNA to better reflect its chemical composition.
- Russian researcher Phoebus Levene was able to identify the individual components of DNA, including the sugars, phosphates, and bases that comprised it. But he lacked the necessary tools to properly explain exactly how each of these pieces came together to form a structure for DNA.
- In the 1940s, Erwin Chargaff developed a method for isolating the bases from DNA samples. He found that the number of cytosine bases in any given sample closely matched the number of guanine bases. He also determined that the number of adenine bases closely tracked that of thymine.
- In the 1950s, the X-ray crystallography lab of Maurice Wilkins and Rosalind Franklin at Kings College finally reached a milestone in genetics. They were able to use a technique called X-ray diffraction to determine the spatial arrangements of atoms in the DNA molecule.
- In the end, it was Watson and Crick, however, who made it to press first with their model of the double helix, earning them their place in history. What Watson and Crick proposed explained every observation to date: The sugar, phosphate, and base molecules found by Levene were all accounted for; the equal amounts of purine and pyrimidine bases from Chargaff's experiments were easily explained; and the crystallography data from Wilhelm and Franklin's labs, as well as Watson and Crick's, clearly showed that a helical structure held them all together.
- The key to putting it all together was that the two pyrimidine bases (adenine and thymine), when held in place by the helix proposed, formed a network of two hydrogen bonds, causing them to pair up. Guanine and cytosine formed a similar set of three hydrogen

bonds when placed on adjacent strands. These base pairs and their non-covalent interactions (now called Watson-Crick pairs) are what hold the two strands of DNA together in an antiparallel alignment with one another.

- There is even more interaction going on with the base pairs. The pi systems of neighbors stack against each other, creating a strong, contributing dispersion force that holds them together. This interaction has been successfully targeted as a site for antitumor drugs, which can slip in between adjacent bases in rapidly growing cancer cells, causing kinks in their DNA strands, inhibiting their ability to replicate their genetic code and grow.

DNA Fingerprinting

- In recent decades, DNA research has gone well beyond simply characterizing this fascinating structure. Ingenious molecular biologists and chemists have devised new applications using the understanding of DNA. Probably the most well known of these is the art of DNA profiling—identifying an individual and linking him or her to even the smallest hair, skin, or fluid sample, usually for the purpose of forensics.
- There is a common misconception that DNA fingerprinting is statistically irrefutable and that it involves characterizing the entire genome of an individual and comparing it to yet another entire genome from a sample found elsewhere. But this is not the case. The truth is that a DNA fingerprint is a bit less reliable, but only slightly so.
- DNA testing relies on a special protein called a restriction enzyme, which cuts DNA only at very specific sequences of base pairs. The contents of the cut DNA are analyzed by a technique called gel electrophoresis. Essentially, the negatively charged DNA is dragged through a thick gel using an applied voltage. In this environment, larger fragments are impeded more, and smaller ones are less impeded. So, the fragments fan out in a pattern specific to the individual.

Protein Manufacturing

- Another incredible use found for DNA is in the production of proteins for chemical research and as medical therapies. For example, human insulin is a relatively small protein, but it is critical to proper blood sugar management. Adults with type 2 diabetes suffer from an inability to produce the insulin needed to properly manage this critical solute in their blood.
- For decades, sufferers had to inject themselves with solutions of insulin taken from the pancreas of pigs, which is a great solution for most of the population. But a small variation in the pig version of insulin elicited an allergic reaction in a fraction of patients.

- Enter DNA and the world of microbiology. For the past few decades, patients requiring insulin get not the porcine version of the protein, but an exact copy of human insulin—and it does not come from the pancreas of a person, either.



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- Scientists take the DNA making up the gene for human insulin and insert it into the DNA sequence of *E. coli* bacteria—a non-pathogenic strain. The bacterial DNA is modified in three important ways. First, genes coding for enzymes to chew up foreign materials are removed. Second, the gene coding for the desired protein is inserted. Third, a special trigger is placed next to that gene. In the presence of the proper signaling molecule, this sequence triggers the bacteria to produce huge quantities of the inserted gene.

Human insulin is a relatively small protein, but it is critical to proper blood sugar management.

- With no protective enzymes to clean up the huge quantity of protein being created, the bacteria are helpless. They express and express and express, until eventually they are not much more than microscopic bags of human insulin. These “bags” are then broken open, and their contents are collected for use in human insulin therapy.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 16.5, 16.6.

Wade, *Organic Chemistry*, Chaps. 23.20–23.24.

Watson, *DNA*.

Questions to Consider

1. Ribonucleotides can mis-pair in DNA when mutations occur. For example, a G-T mismatch can take place when the thymine adopts its enol tautomer. Draw this base pairing between guanine and the thymine tautomer, showing the hydrogen bonds that stabilize it.
2. Before the double helix was proven, what were some of the other proposed structures of DNA? How were they disproven?

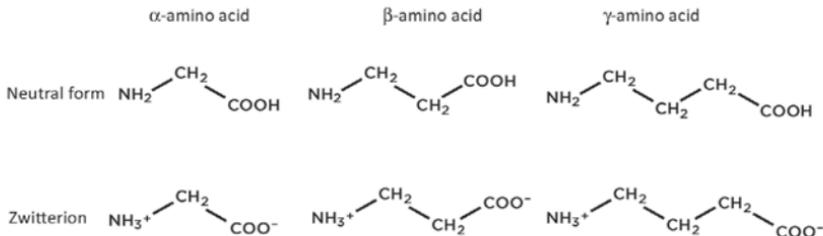
Amino Acids, Peptides, and Proteins

Lecture 24

In this lecture, you will learn about a class of materials that not only make up 20% of the mass of your body, but that find use in medicine, materials, drug chemistry, detergents, and many more functions. This class of materials is proteins. Usually associated with skin, hair, and muscle fibers, proteins make up a class of catalysts that mediate every chemical reaction that your body carries out. But before you can develop an appreciation for these large, complex kings of catalysis, you have to become familiar with their building blocks—amino acids.

Amino Acids

- Amino acids are so named because this class of compound always has two distinct functional groups: an amine and an organic acid joined by one or more carbons. The simplest possible example is an amino acid in which amine and acid groups are joined by a single CH_2 (methylene) group. When only one carbon separates the functional groups, we call these “alpha” amino acids.
- Extending the chain by one more methylene creates a “beta” amino acid, and yet another insertion creates a “gamma” amino acid, and so on. Alpha amino acids are the ones that were chosen by nature as the basis for proteins; they are a very special set of compounds that carry out the chemistry of life.



- The simple alpha amino acid glycine has two different methylene hydrogens on its alpha carbon. It is this position that is modified to create a short library of 20 alpha amino acid compounds used to produce nearly all of the proteins and enzymes that drive the chemistry of life. When something other than a hydrogen is present in one of these positions, we refer to the group as a side chain.
- Of course, there is really no side, front, back, top, or bottom to a molecule, but when we align various amino acids for the purposes of comparison, we usually line up the amino acid portion of the molecule and treat the side chain as a motif branching off to the side. Even so, these bonds can twist and rotate and do not necessarily exist locked in a specific configuration.
- Side chains can be broken down into several classes based on their chemistry. For example, aliphatic (or hydrocarbon) side chains are present in the amino acids alanine, valine, leucine, and isoleucine. Acidic side chains are available on aspartic acid and glutamic acid. Hydroxyl groups make an appearance in threonine and serine. Nitrogen-containing side chains are on lysine as well as arginine and histidine.
- Aromatic side chains include phenylalanine, tyrosine, and tryptophan. Asparagine and glutamine have terminal amides. Methionine and cysteine contain sulfur atoms. Finally, proline is a curious amino acid whose side chain wraps back around and bonds to its own amine nitrogen.
- All but glycine contain a chiral center at the alpha carbon, meaning that there are two possible enantiomers of each compound. Remarkably, all 19 amino acids with a chiral alpha carbon take on the same stereochemistry in living systems. So, only one enantiomer of each amino acid is useful biologically.
- The reason for this is twofold. First, chiral RNA is responsible for sequestering and using these amino acids to build proteins, so only one handed form interacts properly with the ribosomal RNA. The

other reason is that many amino acids are manufactured from one another in the body. Only 8 of the 20 are absolutely essential in your diet. The rest can be made by chemically modifying some of the 8 essentials.

Synthesis of Amino Acids

- There are quite a few ways to produce amino acids from non-biological sources, though biological sources are very attractive because amino acids make up a very large percentage of the biomass of living systems.
- In 1850, German chemist Adolph Strecker devised a way to produce amino acids from aldehydes using ammonium chloride and potassium cyanide. His process generates an amino nitrile via an iminium intermediate. Ammonia is then eliminated with the use of an aqueous acid.
- The most noteworthy amino acid synthesis was the one carried out by young graduate student Stanley Miller in the 1950s at the University of Chicago. Miller was a student of Harold Urey, who had a keen interest in the origin of life and had asked if it were possible for simple, vital organic compounds to form under the reducing, stormy conditions of the Earth's early atmosphere.
- Miller designed a system that simulated the early Earth's atmosphere in closed conditions on a lab bench. He enclosed water, methane, ammonia, hydrogen, and formaldehyde in a sealed vessel and allowed an electrical current to arc through the mixture for an extended period of time.
- After running his apparatus for a week, Miller tapped the circulating solution and analyzed it. When he did, he found a broad range of amino acids. Miller himself detected 11 of the 20 amino acids necessary to support life as we know it. In later years, sealed samples from his experiments have been analyzed and shown to contain all 20.

Peptides and the Amide Bond

- When we put amino acids together via a series of condensation reactions that form chains of amide bonds, the polyamides that result are called either peptides or proteins. The distinction between the two is one of size, with the former generally referring to polymers of less than 100 residues and the latter encompassing larger molecules.
- For example, if we could condense two glycine residues together in an end-to-end relationship, we would create a very short chain consisting of two glycines, minus a water. The loss of the water is important, because it balances what would be an entropically disfavored reaction.
- We can continue the process, condensing another to make triglycine, then another, and so on. The result is a chain of glycine residues. We call them residues, instead of amino acids, because they have lost one equivalent of water when they are in the chain.
- Biochemists like to arrange their polyamides so that the nitrogen-containing terminus is at the left, and the sequence can be read like a sentence from left to right—N terminus to C terminus.
- Our polyglycine peptide is pretty boring as peptides go, but nature has provided us with 19 more options for each slot in the peptide. It is this variety that leads to stunning complexity in the possible sequences for peptides. We call each unique sequence of condensed amino acids a primary structure.
- Furthermore, when amino acids condense to form an amide bond, the amine nitrogen from one residue and the carbonyl from the preceding residue participate in a resonance that locks in a plane defined by the N, H, C, and O of the amide bond. We call this collection of atoms the amide plane.

- But that leaves the alpha-carbon bonds free to rotate, and this gives proteins a tendency to twist and collapse on themselves in very specific arrangements that maximize intramolecular attractions created by backbone atoms and side chains as well. Not only do alpha carbon backbone bonds rotate, but they tend to do so in just a few specific geometries, called secondary structures. These structures include many different versions of three basic motifs: helixes, strands, and turns.

The Folding Process

- Higher-order elements of structure—secondary, tertiary, quaternary—are in theory dictated simply by the sequence, or primary structure, of a protein. If we simply construct the linear protein for nearly any naturally occurring enzyme, we often find that the protein will most likely fold into its functional form—usually with startling speed.

- In rare instances, however, the functional form of the protein is actually not the most stable fold. Proteins can become misfolded and trapped in a topology that will not allow them to fold properly. Ordinarily, it wouldn't be too alarming if a single protein in your body misfolded. After all, you have millions and millions more to get the job done.



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The misfolding of proteins is responsible for the buildup of plaque in the brains of Alzheimer's victims.

- But it does become disconcerting when one misfolded protein encourages the misfolding of others, producing plaques of proteins with potentially devastating health implications. This situation most notably happens when amyloid plaque builds in the brain of an Alzheimer's disease victim.

Protein Synthesis

- Biologically synthesized proteins can be produced using complex RNA machinery within cells, but what do chemists do when they want to make highly purified peptides and proteins in the laboratory for study? Several techniques are available, including the use of special strains of *E. coli* bacteria as manufacturing plants for proteins.
- The genome of a very special, already genetically modified *E. coli* is altered to encourage the bacteria to produce massive quantities of just one desired protein. This technique is startlingly effective when large proteins containing naturally occurring amino acids are the target.
- There is a method for synthesizing even peptides and proteins with exotic side chains using organic chemistry. The developer of this method, Bruce Merrifield, won the 1984 Nobel Prize in Chemistry for his development, which is called solid phase peptide synthesis. It is sometimes also called the Merrifield synthesis.
- Merrifield's technique starts with an insoluble polymer resin to which a single amino acid is attached. The connection to resin is made through the C terminus, and the N terminus is available for reaction. Merrifield then turned to a classic technique for making amide bonds—an active ester coupling. By mixing amino acids with a special reagent that turns them into esters, the exposed amine of the growing chain can be enticed to attack the carbonyl of amino acids in solution.
- This is a problem when the amino acids in solution have amine groups of their own. If unchecked, the growing peptides will extend in an uncontrolled fashion. So, Merrifield applied a special protecting group to the N terminus of the amino acids prior to reacting them with the growing peptide on resin. Merrifield used a group called a *t*-butoxycarbonyl motif.

- When present, this N-terminal protecting group prevents more than one amino acid from attaching to the growing peptide in a single reaction. The excess reagent can then be washed away from the resin, and the N-terminal protecting groups can be removed before introducing the next coupling. In this way, Merrifield was able to produce peptides in sufficient yield and purity to be used in experimentation.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, Chaps. 15.3, 15.4.

Wade, *Organic Chemistry*, Chaps. 24.8–24.13.

Questions to Consider

1. Although some peptides and proteins hydrolyze easily under acidic conditions, some are remarkably stable. Why?
2. Some enzymes become inactive or insoluble in water at different pH values. Why?

Metals in Organic Chemistry

Lecture 25

It is just about impossible to deprotonate an alkane under any kind of sensible laboratory conditions. But there is a class of compounds that can be made to act like carbanions. In order to do this, we have to abandon the safety and comfort of the first two rows of the periodic table. We have to use a remarkable marriage between the usual suspects of organic chemistry and metals. In this lecture, you will investigate a small slice of a field known as organometallic chemistry.

The Birth of Organometallic Chemistry

- Organometallic chemistry got its start in the lab of Aleksandr Butlerov at the University of Kazan in Russia in the 1800s. Butlerov had noticed that dialkyl zinc reagents, chemicals containing two organic alkyl groups bonded directly to a zinc atom through their carbons, could be used to produce alcohols from ketones by transferring their alkyl group to the carbonyl carbon of the ketone.
- Excited about the prospect of developing a new method for the formation of carbon-carbon bonds, Butlerov passed this project on to his protégé, Aleksandr Zaitsev, who was able to apply its chemistry to several new substrates, but always with limited success. These zinc-based reagents proved to be unpredictable and difficult to work with.
- Then, in 1900, a young French graduate student by the name of Victor Grignard blew the lid off of organometallic chemistry by devising a powerful, versatile, and adaptable organometallic reagent for use in producing new carbon-carbon bonds.
- In the late 1890s, in Philippe Barbier's lab at the University de Lyons in France, while Grignard was conducting experiments for his doctoral dissertation, he acted on a hunch. He replaced the zinc

from the only known class of organometallics of the day with what he believed would be more reactive magnesium. His work not only earned him his doctorate, but one-half of the Nobel Prize 12 years later. His corecipient was Paul Sabatier, for his metal-catalyzed hydrogen-addition reaction.

The Grignard Reaction

- So, what had Grignard accomplished? He mixed an alkyl halide with magnesium metal in ether. This combination of reagents produced what we would call an alkyl magnesium halide, in this case an alkylmagnesium bromide. This process involves two distinct radical reactions that take place when the alkyl halide bond spontaneously and breaks, sending one electron each way.
- So, we have two radicals, hungry for a partner for that unpaired electron. We also have neutral magnesium metal, with two valence electrons that it is more than willing to give up to establish its own octet. The magnesium strikes a deal with the two radicals and inserts itself between the alkyl group and the halide, forming two new covalent bonds—one to the halide radical, and then one to the alkyl radical. From an octet perspective, everyone is happy again.
- But in regard to the covalent bond between the carbon and magnesium, magnesium has a very low electronegativity—so low, in fact, that we usually refer to it instead as having high electropositivity. Its electronegativity being so much lower even than carbon, the new carbon-magnesium bond has a dipole oriented with the negative end of the dipole on the carbon.
- It is this increased negative charge density that made Grignard reagents act much like analogous aliphatic carbanions, but without the hassle of using some of the strongest bases to get it.
- If we mixed isoamyl anion with carbon dioxide, what would we get? How about a nucleophilic attack on the carbon of CO_2 , followed by a quick workup in acid to protonate the carboxylate

we just formed? If we do this, we get isocaproic acid, the exact compound that Grignard had produced using isoamyl bromide, magnesium, and CO_2 .

- Of course, when Grignard made it, his reagent was not a carbanion, but an alkyl magnesium bromide reagent, which means that we have to account for the magnesium and bromine. What happens to them during the nucleophilic attack is a bit complicated and case-specific, but the simplest way to model the reaction is with the Mg-Br motif attached to the oxygen of the new carboxylate or alkoxide. Exposing these species to aqueous acid leads to carboxylic acid and magnesium hydroxybromide.
- Grignard's new nucleophile could be used to produce acids from carbon dioxide, secondary alcohols from aldehydes, and tertiary alcohols from ketones. It seems that anything with a carbonyl is fair game for them. Grignard reagents are extremely versatile, offering not only ways to make alcohols and acids, but also aldehydes from amides, tertiary alcohols from esters, and many more.
- But there is much more to the Grignard reaction. Easy though it is to run, there are a few special considerations that must be taken to ensure its success. First, the Grignard reagent itself is only stable in ether solvents like diethyl ether or tetrahydrofuran. Second, the reaction mixture must be kept extraordinarily free of protic solvents, including water.

Ethers and Protic Solvents in Grignard Syntheses

- One of the great limitations of Grignard reactions is that alkylmagnesium halide reagents can only form in ether solvents. But why? The answer lies in the ability of solvents to coordinate metals. The solvent must have oxygen atoms with lone pairs that can stabilize the Grignard by donating electrons to form a stabilizing metal-oxygen interaction in solution.

- That alkyl magnesium halide motif is so polar that it needs a solvent that will be able to arrange its dipole to beneficially interact with the positive charge density at the magnesium. For this purpose, ethereal solvents are just the ticket. Nonpolar solvents like hexanes or benzene are not capable of forming such stabilizing interactions, so they are clearly out.
- Grignard reagents are really polar, so why can't we use more polar solvents like ethanol to dissolve them for reactions? Ethanol has enough polar punch to get this reagent to form in solution, but it is protic, with a pK_a of about 17. Recall that Grignard reagents react like carbanions, whose conjugate acid has a pK_a of about 60. So, a Grignard reagent will form in ethanol—for a split second before reacting with the ethanol to form ethoxide and a hydrocarbon. This is not a good way to make a Grignard.
- Ethers like diethyl ether and THF are special because they strike a balance between their ability to solvate a Grignard with their inability to react with it, and this is why they have been the preferred solvent for this sort of reaction from 1900 until today.
- But using ether and THF isn't enough. Because it is slightly polar, ether can dissolve a small bit of water. Our solution to this is to use ether that has been chemically dried before use. We accomplish this through the use of inorganic drying agents like magnesium sulfate or molecular sieves, which act like sponges, absorbing the water from the ether and trapping it as a solid complex that can be filtered or decanted away.
- A more modern substitution for many Grignard reagents is *n*-butyllithium, which itself can be made by mixing *n*-butylchloride or bromide with lithium metal and is preferred over other alkyllithium reagents for its relative stability. Bottles of this reagent can be purchased and stored for short periods of time, while Grignard reagents usually must be prepared at the time of use.

Organometallic Catalysts

- In addition to the use of metals to activate hydrocarbons and turn them into nucleophiles, another use of organometallic compounds harkens back to Paul Sabatier, who developed a technique for hydrogenating fats using platinum metal.
- In modern laboratories, the reduction of alkenes to alkanes is still a widely used technique, but the heterogeneous nature of Sabatier's methods leaves much to be desired. Hydrogenating double bonds at the surface of a solid catalyst may work well on industrial scales, but in the laboratory, a reaction that takes place in solution is more desirable.
- If we had access to a homogeneous catalyst—one that could be dissolved in organic solvents along with the substrate—we could run reactions much more efficiently and cleanly in the lab. But the problem is that metals themselves are not generally soluble in the kinds of solvents that one would use to dissolve an alkene.
- In 1966, British chemist Geoffrey Wilkinson published a paper outlining a way to solubilize a large transition metal like rhodium by bonding to it organic molecules that we call ligands. These ligands were specially designed to be strong Lewis acids, which would donate stabilizing electron pairs to the metal ion, forming a complex that gave it the solubility characteristics of the ligands while retaining the catalytic activity of the metal.
- Wilkinson's work is generally regarded as the seminal work in the field of organometallic chemistry. His discoveries in this field launched an age of investigation into metal-ligand interactions that continues to this day in labs around the world.
- Wilkinson's work has inspired the creation of some really exciting and exotic-looking complexes. You will see extensions of his work in such life-changing compounds as contrast reagents for MRI.

Biological Organometallics

- Some of the most astonishingly powerful organometallic catalysts are the ones at work in your body right now. For example, if we remove all of the protein atoms from a subunit of the structure of human hemoglobin, left over is a large, cyclic ligand coordinating an iron atom from four planar positions. It is the coordination of these four nitrogen atoms, and also two others in the form of histidine amino acid residues, that gives the molecule its life-sustaining ability to bind, transport, and release oxygen in the body.



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- But nature has gone far beyond just using iron ions to get the job done. For example, hemocyanin—rather than hemoglobin—transports oxygen in crustaceans like crabs and lobsters. This enzyme contains two copper ions coordinated to the protein matrix, giving lobsters, crabs, and many other marine animals a very different blood chemistry than mammals.
- Another of nature's chemists is the nitrogen-fixing Rhizobia bacteria that live in the root nodules of legumes like soy. The molecule that they produce that allows them to fix nitrogen is called nitrogenase, and it is a protein that contains not just one metal ion, but multiple clusters of them in complex with sulfur atoms.
- Scientists have discovered and characterized two different forms of nitrogenase, both of which rely on iron to function— one exclusively, and another in concert with molybdenum. Even though these metalloprotein structures have been well known for decades,

their ability to accomplish the same reaction at room temperature and pressure that Fritz Haber could only accomplish at explosively high pressures and temperatures remains unexplained today.

- When someone finally unlocks the chemistry of these large, powerful organometallic molecules, the impact it will have on world food supply management will likely be as great as cold fusion would be for the power industry.

Suggested Reading

Lewis, D. E., "The Beginnings of Synthetic Organic Chemistry: Zinc Alkyls and the Kazan' School," *Bulletin for the History of Chemistry* 37, no. 1 (2002): 37–42.

McMurry, *Fundamentals of Organic Chemistry*, 7.3.

Wade, *Organic Chemistry*, 10.8, 10.9.

Questions to Consider

1. Propose two ways that you might use a Grignard reagent to prepare 3-methyl-3-hexanol from an alkyl halide and a ketone.
2. What is it about the atomic structure of gadolinium that makes it such a powerful magnet?

Synthetic Polymers

Lecture 26

A tremendous amount of attention has been poured into understanding, designing, and creating useful polymers. From the tires on your car, to the man-made fibers in some clothing, to medical equipment, body armor, and more, the importance of synthetic polymers to our modern lifestyles cannot be overstated. This lecture will provide a short survey of polymer chemistry—how polymers are designed, how they are made, and a few ways in which they have changed the world.

Polymers

- Polymers are defined as large molecules consisting of one or more repeating units known as monomers. Biologically relevant polymers include DNA, RNA, proteins, and starches.
- Synthetic polymers are classified in more than one way, but a typical method is to distinguish them based on how they are prepared. From this perspective, most polymers fall into one of two general classes: addition polymers or condensation polymers.
- Addition polymers are formed when monomers react with the end of a growing chain. Addition polymers tend to be prepared from alkene subunits, trading less-stable pi bonds for the new sigma bonds that link them together. The first wholly synthetic polymer, polystyrene, falls into this class of compounds. The process of creating addition polymers consists of three phases: initiation, propagation, and termination.
- In the case of polystyrene, polymerization reaction initiates when a sample of styrene is heated in the presence of a small amount of benzoyl peroxide. The heat causes the benzoyl peroxide to dissociate into two phenyl radicals, a process encouraged by the loss of carbon dioxide gas.

- In the second step—propagation—as each monomer encounters the reactive radical at the end of a chain, a new sigma bond is formed homogenically, regenerating a radical at the end of the lengthened chain.
- In the case of polystyrene, this process repeats itself several thousand times before the third phase, termination, takes place. In termination, two growing radicals react with one another, forming one last sigma bond that consumes the radicals without generating a new one.
- Addition polymers are very attractive targets for commercial materials because their properties can be tuned by controlling the overall size of the macromolecules produced in the chain-growth reaction. The size of addition polymer molecules can be controlled simply by altering the relative amount of benzoyl peroxide added: Relatively fewer benzoyl peroxide molecules means fewer growing chains, and because growth can only take place at the end of an initiated chain, one expects to obtain longer polymers in such a scenario. Additionally, fewer growing chains equates to a lesser chance that two growing chains will encounter one another in a termination step.
- Another example of an addition polymer is the polyethylene used in plastic bottles, formed by the addition of ethene monomers to one another. Polyvinyl chloride (PVC), most well known as a substitute for metal plumbing pipes, is assembled in a similar reaction using vinyl chloride monomers. Even the once-popular cookware coating Teflon is formed by polymerization of tetrafluoroethylene monomers.
- The second major class of polymers is condensation polymers, which differ from addition polymers in that their growth is driven not by trading of pi bonds for sigma bonds, but by the formation of small molecule by-products.

- A perfect example of this is the formation of nylon-6, in which molecules of 6-aminohexanoic acid are joined together in a reaction that produces not only an amide union between monomers, but also a molecule of water as a by-product.
- Condensation polymers are also called step-growth polymers, because unlike chain-growth polymers, condensation can take place at any time between any monomers or growing polymers.

Copolymers

- When polymers are constructed from multiple monomers, we refer to them collectively as copolymers. Copolymers can take on a vast array of arrangements, including alternating copolymers, in which monomers regularly repeat; random copolymers, in which a statistically random arrangement of monomers exists; block copolymers, which are characterized by large defined regions consisting of one monomer type or the other; and graft copolymers, in which a polymer of one monomer supports polymers of another.
- A familiar alternating polymer is produced when vinyl chloride and vinylidene chloride react in a radical chain-growth polymerization. In this reaction, monomers add in an alternating order, with vinyl chloride monomers reacting at initiated vinylidene termini and vinylidene chloride monomers reacting at initiated vinyl chloride termini. The result is an alternating polymer called saran, which is used to make the very popular food wrap that bears its name.
- But alternating polymers can just as easily be produced using condensation polymerizations. One example of this is the polymer nylon-6,6, which is prepared using equal parts of adipic acid and 1,6-hexanediamine.
- By producing nylon in this way, the orientation of alternating amide bonds is reversed from those in nylon-6. In fact, it is more accurate to say that the amide bonds in nylon-6 are reversed, because nylon-6,6 was actually the first of these to be patented by Dupont in 1935.

- The development of the homopolymer nylon-6 by BASF was an attempt to produce a material with similar properties that did not infringe on Dupont's intellectual property. Both of these polymers were a huge success and are still used today as the backbone for some of the most modern materials produced by both companies.
- Random copolymers are produced by mixing monomers, but unlike alternating copolymers, growing random copolymers can incorporate any of the monomers in any order, leading to a statistically random distribution of monomers in the macromolecule.
- An example of a random copolymer is polybutyrate, which is a polyester compound built from two distinct subunits. The distinction is that these subunits are randomly oriented throughout each polymer strand. Incredibly, polybutyrate is fully biodegradable. Plastic bags and wraps produced from this flexible random copolymer are completely deconstructed by moisture and microbes in the ground.
- One of the more exciting advances in recent decades has been the development of block copolymers, which aim to exploit the best properties of more than one polymer by linking together large regions of each, called domains.
- The block copolymer SBS—which stands for poly(styrene-butadiene-styrene)—is used in many modern applications, including tires and shoe soles. In a single molecule of this block copolymer, a domain of polybutadiene is sandwiched in between two polystyrene domains.
- The polystyrene blocks give this polymer great toughness, while the polybutadiene domain becomes softer under high-temperature conditions, allowing the material to be more easily moldable like softer rubbers. The result is a material that behaves more like plastic at high temperature, but more like vulcanized rubber when cooler.

- Graft copolymers are characterized by a uniform backbone polymer that is decorated by strands of a different polymer attached covalently along its length. In many cases, graft copolymers can be designed to have certain properties of both polymers that make it up.
- Examples include long polysaccharides like cellulose onto which other polymers are grafted. This has the effect of producing a very large molecule with many of the properties of the smaller grafted polymers while retaining the biodegradability of the cellulose backbone.

Cross-Linking Polymers

- Natural rubber is a somewhat complex mixture created by trees to defend themselves from wood-eating insects. It has quite a few minor components, but the big player in its chemical properties is a polyisoprene macromolecule made on long, unsaturated hydrocarbons, making it very thick and insoluble in water.
- The problem is that these polyisoprene macromolecules are only held together by dispersion forces stemming from their electron clouds. These forces are enough to make the molecule viscous, but they can be overcome. So, when we pull on natural rubber molecules, they can slide back and forth with one another.
- In the latter part of the 1830s, Charles Goodyear invented a method for producing a variation of rubber that would be strong enough to produce objects that could be molded into a desired shape but would then retain that shape across a greater range of conditions. His method involved steam heating a mixture of natural rubber with sulfur.
- What Goodyear accomplished by the addition of sulfur was to cross-link the polymer molecules with covalent bonds to sulfur. With these bonds in place, the material can still be deformed slightly, but as soon as it is released, it snaps back into its original position.

- So, the presence of these cross-links is what gives vulcanized rubber its toughness and ability to retain its shape—exactly what you would hope for in a product like an automobile tire. It also, unfortunately, makes the material very difficult to deconstruct, meaning that vulcanized rubbers are difficult to recycle.



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Polycarbonates and Bisphenol A

- Another common polymer motif is polycarbonates. These polymers are found in materials as tough and rigid as bulletproof glass and as soft and supple as commercial water bottles. Both of these products are made from the condensation of carbonic acid with bisphenol A (BPA) to form an alternating copolymer.
- Recently, concern has arisen over the possibility that these polymers can hydrolyze back into their starting materials over time, leaching bisphenol A into the water or beverage that they contain. The reason for so much concern is mounting evidence that bisphenol A imitates estradiol in the body, potentially causing developmental and reproductive problems.
- Some studies suggest that BPA is less than 0.0001 as powerful of a hormone as estradiol is, suggesting that this controversy may be overblown. Still, we simply don't know what the long-term effects of exposure to low levels of BPA might do. Regardless, many people are sufficiently wary of BPA that they are willing to purchase products labeled "BPA-free" without giving much thought to what is actually in the plastic.

Modern tires can be deformed slightly, but will snap back into their original position.

- The polymers industry has responded to these concerns by offering BPA-free plastics with a great deal of fanfare. What they do not tell you, however, is that most of these products are still polycarbonates that are simply made using molecules like bisphenol S or bisphenol F in place of bisphenol A in an analogous reaction.



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Most products labeled “BPA-free” are still polycarbonates.

Plasticizers

- Another hot-button plastics issue is the use of compounds called phthalates. Phthalic acid is a small organic diacid that is easily esterified with a number of aliphatic alcohols to produce small molecules called phthalates.
- Phthalates—like dibutyl phthalate, for example—are sometimes added to polyvinyl chloride to soften the plastic enough to make it useful over a wider range of applications. Plasticizers work by disrupting the packing of the polymer chains—in this case, in the PVC, causing it to soften. That new car smell many people love is caused by these plasticizers, escaping the newly prepared plastics into the air.
- Polyethylenetetraphthalate (PETE) is used in food packaging and does not contain isolated phthalate molecules. The “-phthalate” portion of PETE’s name refers to the monomer that is condensed to prepare the polymer. So, in this case, the phthalate is locked securely in the matrix of this nonbiodegradable plastic, where it cannot easily be released.
- So, PETE doesn’t release phthalates into the environment even though “-phthalate” is in its name, and PVC very often does release phthalates, even though the term “-phthalate” is nowhere to be found in its name.

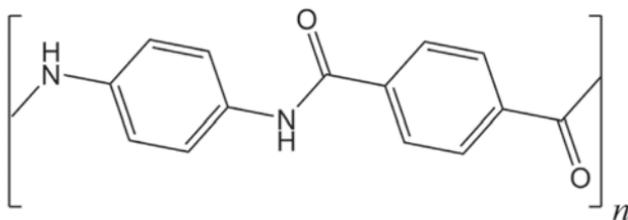
Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 15.3, 15.4.

Wade, *Organic Chemistry*, Chapter 26.

Questions to Consider

1. How will increasing or decreasing the amount of initiating reagent used in chain-growth polymers affect the chain size in the completed polymer molecules?
2. Shown below is the structure of the well-known copolymer Kevlar. Propose two monomers that might be used to produce Kevlar using a condensation reaction.



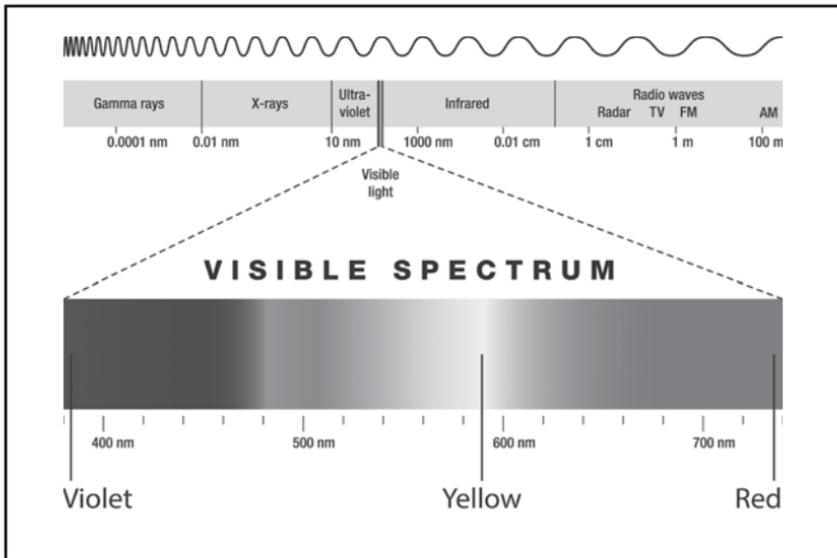
UV-Visible Spectroscopy

Lecture 27

This lecture will discuss the techniques that organic chemists and many others use to identify the products of their work. Specifically, this lecture will explore the science of spectroscopy. Most simply put, spectroscopy is the observation of the interaction of light with matter. Over the next few lectures, you will learn about some of the ways that scientists coax structural information from molecules using spectrometers to sense how they interact with different forms of light. This lecture begins in the visible and ultraviolet regions of the spectrum.

Light

- What we generally refer to as “light” is, in fact, electromagnetic radiation, a form of self-propagating energy composed of perpendicularly oscillating electric and magnetic fields. Exhibiting both wave- and particle-like properties, light carries energy and momentum. It is the wave properties of light and the energy it carries that are most interesting to spectroscopists, and we therefore tend to classify light based on these properties.
- One of the properties associated with waves is the wavelength—the distance from one point on the wave to the next analogous point. Another property of light is velocity. Light has a fixed speed at which it travels in a given medium, regardless of its wavelength. Light in a vacuum always travels at 3.0×10^8 meters per second. The frequency of light is the number of equivalent points along the wave that pass by a given location in a specified time.
- The constant speed of light becomes a proportionality constant for the relationship between wavelength and the reciprocal of the frequency: $c = \lambda\nu$. To put it simply, because of the constant speed of all light, cutting the wavelength in half results in a doubling of the frequency.



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The electromagnetic spectrum includes not only what we can see with the naked eye, but also higher- and lower-frequency wavelengths.

- Another property of light that is crucial to understanding spectroscopy is that light does still have some particle character. We call these particles of light photons. A single photon of light contains an amount of energy that is directly related to its frequency by a factor called Planck's constant (h). A single photon of light has an associated wavelength, frequency, and energy that are all related to one another.
- We classify light according to its frequency or wavelength, which are related to the amount of energy carried by a single photon of that light. The known range of wavelengths is called the electromagnetic spectrum. This spectrum includes, in order of increasing frequency (and energy): radio, microwave, infrared, visible, ultraviolet, X-ray, and gamma ray.

The UV-Visible Spectrometer

- In 1801, Wilhelm Ritter acted on a hunch that there was more to the spectrum than what Sir Isaac Newton had seen with his own eyes more than 100 years earlier. The problem is that Wilhelm was a human, and his eyes couldn't see any farther along the spectrum than Newton's could. Ritter needed a different kind of eye, and he had just the tool for the job—silver chloride.
- Silver chloride is an inorganic compound that is most famous for its use in photographic film. Solutions of silver chloride undergo a chemical reaction in the presence of visible light that causes them to dissociate into a suspension of silver metal and chlorine gas. In other words, the solution turns dark on exposure to light.
- It was known even before Ritter that this reaction did not proceed at the same speed in different colors of light. He could disperse light with a prism, then place vials of silver chloride solution in different parts of the resulting spectrum, and clearly see that the reaction was fastest in blue, slower in green, and slower still in red.
- Ritter's real contribution was that he decided to place a vial of silver chloride solution outside of the blue-colored light from the prism. The solution outside of the blue end of the spectrum reacted even faster than any of the samples within the visible area.
- This experiment is remarkable because it clearly demonstrated the existence of light with a frequency even higher than the violet light at the edge of the visible spectrum—one that was not detectable to the human eye but had even more energy than visible light. Ritter had discovered ultraviolet light.
- Of course, since Ritter's day, the science of spectroscopy has come a long way. We no longer have to move a sample from one band of light to the next to observe how a sample is interacting with light. Instead, we rely on sophisticated instruments called spectrometers.

- All spectrometers have the same basic functional parts. How each part functions can be very different depending on the design and the technique needed to solve a particular problem, but all spectrometers consist of several crucial parts.
- First is a light source that generates a broad spectrum of light. This can be as simple as an ordinary incandescent lightbulb or a more advanced lamp. The light from this source is sent to a device called a monochromator. The simplest example of this would be Newton's prism dispersing sunlight into its constituent parts. Modern monochromators are usually more sophisticated and vary widely in design.
- The most common tool for this purpose is known as a diffraction grating, which accomplishes the same effect as the prism but can be very precisely machined to produce much narrower bands of very specific wavelengths, allowing us to make more detailed measurements.
- The light produced by the lamp and monochromator is passed through a sample one wavelength at a time. The sample can be solid, liquid, gas, or solution. Most commonly in the organic chemistry lab, we want to characterize the interaction of light with a compound in solution, so we use a quartz cell sometimes called a cuvette to hold the sample.
- The sample is held securely in the sample compartment, where light from the monochromator passes through it. As light exits the sample compartment, it strikes a detector that turns the light intensity into an electrical signal that can be interpreted by a computer.
- As the monochromator is adjusted to send different wavelengths of light to the sample, the detector measures the intensity of the exiting light at each wavelength and compares it to the intensity of the original beam when no sample is present.

- One of the first of these devices was built by German physicist August Beer, who is most well known for his law of absorbance, which he proposed in 1852. His law is concerned not with the maximum wavelength of absorption, but with just how strongly a given compound or sample absorbs.
- Beer observed that incrementally increasing the concentration of a chromophore, or colored chemical compound, cut the transmittance by half each time. Similarly, for a given concentration, the transmittance was cut in half when the length of the cell was increased incrementally.
- This relationship produces an exponential relationship. But scientists prefer to work with linear relationships, which are much easier to predict. So, Beer converted transmittance to a new unit, called absorbance. The absorbance is the negative logarithm of a sample's transmittance. The resulting plot is a very simple, very useful relationship in which incremental concentration or path length increases lead to incremental absorbance values.
- Beer's equation relates absorption to three important factors: a property of a given molecule called its molar absorptivity (which is essentially a measure of how well it absorbs at a given wavelength), the concentration of the sample, and the path length of the cell used in the experiment.

Factors Influencing Absorption: Pi-to-Pi* Transitions

- With conjugated alkenes, the frontier molecular orbital energy of conjugated compounds decreases as additional p atomic orbitals join the system.
- A single photon of light carries a specific packet of energy with it, and this energy can be calculated from its wavelength and Planck's constant using the relationship $E = hc/L$. Let's set the rule that this photon will only be absorbed by a molecule when it can promote an electron to a higher energy state when the orbital energy gap is exactly equal to the energy packet of the photon.

- Simple conjugated alkenes have pi systems that overlap very well with one another, creating a virtual superhighway for electrons to move from one orbital to the next. When electrons move from the highest occupied pi molecular orbital to the lowest unfilled pi molecular orbital, we call this transition the pi-to-pi* transition.
- Because of the fantastic geometric overlap of the associated orbits, this absorption occurs nearly every time an electron of sufficient energy strikes the molecule. In other words, the extinction coefficient for this absorption can be very, very large.
- We can construct an energy diagram for the molecular orbitals of a conjugated system, and when we do this for 1,3-butadiene and 1,3,5-hexatriene, we discover that the frontier molecular orbitals are closer in energy in the more conjugated compound. So, there is a distinct correlation between the wavelength of maximum absorption and the extent of conjugation in organic compounds. And this trend continues into the visible spectrum as well.

Ultraviolet Radiation Protection

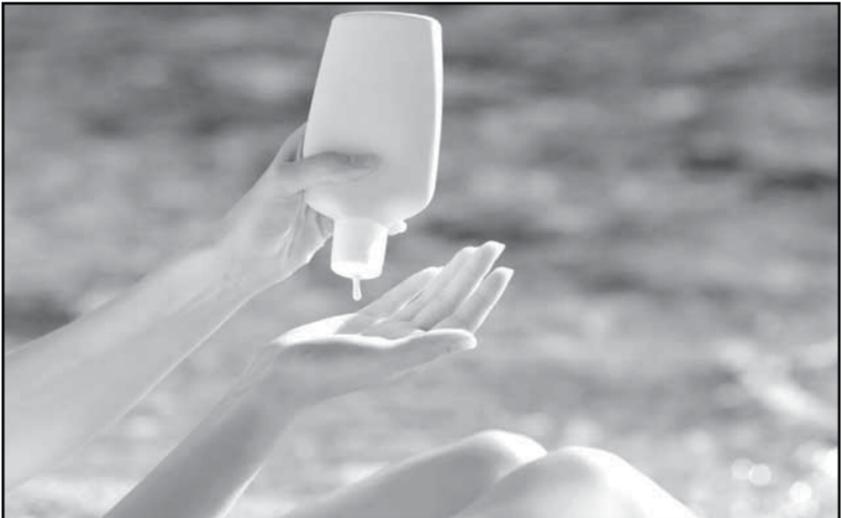
- The single most well-known source of electromagnetic radiation is the Sun. In addition to the intense visible light emitted by the Sun, it is also constantly bathing the planet in strong ultraviolet radiation that is capable of causing damage to cellular DNA. The overall ultraviolet region of the spectrum is defined as the region between 100 and 400 nanometers (nm) in wavelength, but spectroscopists and other scientists break down the ultraviolet spectrum into three general regions: UVA, UVB, and UVC.



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The single most well-known source of electromagnetic radiation is our Sun.

- UVC radiation spans 100 nm to 280 nm wavelengths. UVC is the portion of the ultraviolet spectrum that isn't normally found at the surface of the Earth, because it is naturally absorbed by the gasses in the Earth's atmosphere. This high-energy, potentially damaging radiation is absorbed by two naturally occurring atmospheric gasses in particular: oxygen, which absorbs between 100 nm and 200 nm, and ozone, which absorbs between about 200 nm and 280 nm. These two gasses work in concert to protect us from all of the most dangerous ultraviolet light reaching the planet.
- UVB radiation spans 280 nm to 315 nm wavelengths. It is the portion of the ultraviolet spectrum that reaches the surface and causes reddening of the skin, known commonly as sunburn. Because of this, it was long thought that UVB rays were the only dangerous form of ultraviolet radiation reaching the planet's surface, leading companies to produce sunblock formulations containing compounds like para-aminobenzoic acid (PABA), which absorbs very well right up to the edge of the UVB.



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Modern sunblock formulations are effective against both UVA and UVB rays.

- UVA radiation spans the 315 nm to 400 nm region of the spectrum. For a long time, it was thought that this lower-energy ultraviolet light was not harmful to humans because it did not cause sunburn like UVB. In the later decades of the 1900s, however, medical researchers began to recognize that UVA light can, in fact, cause cellular damage even though it does not cause a reddening of the skin. So, modern sunblock formulations have abandoned PABA in favor of compounds like octocrylene and avobenzone.
- When we look at the ultraviolet spectrum as a whole and at those materials that we use to protect ourselves from it, both man-made and naturally occurring, the trend is that increasing the size of the conjugated pi system in the compounds correlates directly with the wavelength of maximum absorption in the compound. From oxygen, to ozone, to PABA, octocrylene, and avobenzone, each is larger and more conjugated than the next.
- So, using this predictive tool of extended conjugation, these products have been carefully engineered to have very large extinction coefficients at very specific wavelengths to fill in the gaps that Mother Nature left behind.

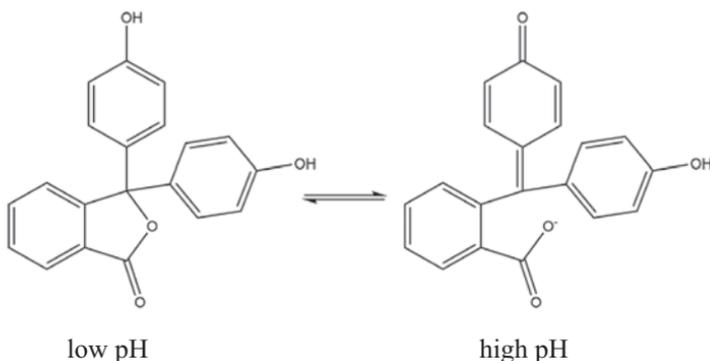
Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 13.5, 13.6.

Wade, *Organic Chemistry*, 15.13.

Questions to Consider

1. Phenolphthalein is a compound often used to detect changes in pH because it changes from colorless to dark purple depending on pH. Under which conditions (low pH or high pH) do you expect phenolphthalein to be colored?



2. Although they usually represent the strongest absorption, the frontier molecular orbitals are not the only pi molecular orbitals that can participate in absorption. Do you expect other transitions within the pi system to absorb longer or shorter wavelengths?

Infrared Spectroscopy

Lecture 28

Just like ultraviolet light, infrared light from the Sun is constantly bombarding us. Unlike ultraviolet light, however, infrared light isn't associated with any particularly dangerous health effects. Infrared is still a very interesting part of the electromagnetic spectrum, though. It interacts with organic molecules by a completely different mechanism, yielding completely different information about their structure. In this lecture, you will learn about the red end of the visible spectrum and what lies beyond.

Infrared Light

- Objects at or near room temperature naturally emit the wavelength of light known as infrared. Scientists like those at NASA have developed cameras and telescopes capable of detecting the infrared emissions of both small objects on Earth and celestial bodies on the other side of the known universe, creating false-color images, in which the detected infrared light has been shown.
- But infrared light isn't just radiated. Like all other parts of the electromagnetic spectrum, it can also be absorbed. And just as a warm object cools by radiating energy as infrared light, an object can be warmed by absorbing it.



Though invisible to the naked eye, infrared light can be captured using sensitive cameras.

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- Wilhelm Ritter’s experiment that resulted from his hunch to look outside of the blue end of the visible spectrum was almost certainly inspired by one conducted earlier that year by Sir William Herschel, who made a truly inspired discovery when he asked a simple question: Which color of light is most effective at heating a surface on which it is shined? To answer this question, he used a prism to diffract sunlight into a spectrum and placed thermometers with blackened bulbs at regular intervals within that spectrum.
- Herschel saw that the temperature indicated by the thermometers increased across the spectrum from blue to red. Knowing what we do about the amount of energy contained in photons of different wavelengths, this may seem counterintuitive at first, but Herschel essentially proved that red light is absorbed more efficiently by objects near room temperature.
- But the pertinent result of Herschel’s experiment wasn’t the trend he saw in the visible spectrum. His real breakthrough came when he wondered if the trend continued beyond the spectrum that he could see. Sure enough, when he placed a thermometer just beyond the red portion of the spectrum, it read an even higher temperature than the one in the red light. Clearly, there was some form of light beyond the red portion of the spectrum, prompting him to call his new discovery “infrared” light.

Infrared Spectrometers

- Modern spectroscopy in the infrared region is conducted using an instrument very similar to those used for UV-visible. Both start with a source lamp, though the infrared source lamp is made of a different material that generates more infrared light.
- The infrared beam is split using a mirror, which sends the beam to two different cells. One is the reference cell, containing no sample, and the other is the sample cell, containing the molecules we want to analyze.

- The beams are then reflected back onto the same path using a device called a beam splitter, which allows only one of the two beams to make it to the detector at a given time. After passing through a monochromator, the intensities of the two beams are compared at the detector to calculate the transmittance of a sample.

Vibrational Modes

- In order to understand infrared spectroscopy, we need to begin to think of molecules in terms of dynamic models, rather than the idealized structures—symmetrical, rigid, unmoving—that are so often depicted in the literature, models, textbooks, and television. Dynamic simulations approximate the random motions of each atom within the molecule. The bonds between and among the atoms stretch, bend, and twist in numerous ways. Put simply, bonds vibrate.
- Consider carbon monoxide—two atoms joined by a triple bond. With only two atoms, there is only one possible bond vibration that can take place: a stretching between the atoms. But when we move on to carbon dioxide, a molecule with three atoms, we can conceive of vibrations involving a symmetrical stretch, an asymmetrical stretch, symmetrical bending, and asymmetrical bending. So, there are four different ways in which CO₂ can vibrate.
- If we continue adding atoms, we find that the total number of vibrational modes possible is equal to $3n - 5$, where n is the number of atoms in a linear molecule—or $3n - 6$ for nonlinear molecules. This means that for a compound as simple as methane, we expect to find 9 different types of vibrations. Ethane has 24, and more complex molecules have dozens or even hundreds of vibrational modes, each with its own frequency.

Infrared Absorption

- What is it that brings these two apparently disparate concepts—how infrared spectroscopy is conducted and the vibration of bonds and sets of bonds in organic molecules—together? The answer is

that many bond vibrational frequencies are the same as those of infrared light, and just as an electronic transition could be promoted by just the right photon in UV-visible spectroscopy, a transition in the vibrations of a molecule can be induced by just the right infrared photon.

- When a bond vibrating at a particular frequency encounters a photon of identical frequency, that photon can be absorbed, increasing the amplitude of the associated vibration. This is the absorption that is measured by the spectrometer. For example, if our spectrometer reports to us that photons with a frequency of 2000 hertz are being absorbed, we know that there must be a bond vibrating at that frequency within the molecule.
- Of course, we have a pretty good idea of the vibrational frequencies of different types of bonds near room temperature. The trend is that larger atoms and weaker bonds lead to slower vibrations. In other words, a C-H bond should vibrate faster than a carbonyl bond, which should vibrate faster than an ether bond. In fact, this is exactly what we see in infrared spectroscopy.

Detecting Functional Groups with Infrared

- There is one more catch to the science of infrared spectroscopy. It is known as the infrared selection rule, which states that a vibrating bond or set of bonds can only absorb a photon of the same frequency if that vibration causes a change in the dipole of the molecule. No dipole change means no absorption; strong dipole change means strong absorption.
- Functional groups, which usually have strong dipoles, are often powerful infrared absorbers, while less-reactive bonds, such as alkyl C-H bonds, tend to absorb very weakly or sometimes not at all.
- Most functional groups contain good, strong polar bonds to at least one hydrogen or double and triple bonds among larger atoms (or both). So, the signatures associated with most common functional

groups in infrared are typically found in the higher-frequency region of the spectrum, whereas the vibrations within the skeleton have a tendency to cause absorptions in the lower-frequency region of the spectrum.

- The few but distinct absorptions caused by functional groups lead us to define the higher frequency region of the infrared spectrum as the functional group region, because it is often where we find the information we need to catalog which functional groups are present in the sample and which are not.

The Fingerprint Region of the Infrared

- The high-frequency region of the infrared spectrum tells us about the presence or absence of functional groups, but what about the low-frequency region? If it is so complex that it defies dissection, why do we bother to collect this information?
- We call the low-frequency region of the spectrum the fingerprint region, because just like fingerprints, the complex set of vibrations within the skeleton of a molecule give it a complex pattern in this region that is unique to that particular molecule. Just as a fingerprint can be compared to a reference to identify its owner, the fingerprint region of an infrared spectrum can be compared to a standard to identify a molecule.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 13.3, 13.4.

Wade, *Organic Chemistry*, 12.1–12.2.

Questions to Consider

1. Infrared spectroscopy samples must be kept exceedingly dry to produce the best spectra. Explain why.
2. Which bonds in hydrofluorocarbons (Lecture 10) give them the potential to be a greenhouse gas, trapping heat by infrared absorption?

Measuring Handedness with Polarimetry

Lecture 29

In this lecture, you will learn about the interaction between light and matter called optical rotation. You will learn that Étienne-Louis Malus is often credited for first observing plane-polarization of light from the Sun using a palace window and a piece of Icelandic spar as polarizers. Modern polarimeters operate on the same basic principles as in Malus's experiment, but the wavelength and plane of polarization of the analytical beam are more controlled. In addition, you will learn about the ability of chiral molecules to rotate plane-polarized light and how their specific rotation is equal and opposite for two enantiomers of the same compound.

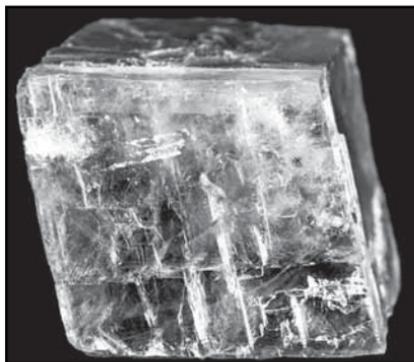
Polarized Light

- Viking sailors as early as the first century B.C. claimed to have discovered a miraculous talisman known as “sunstone.” Narratives about historical figures of that time suggest that this stone could be used to locate the position of the Sun even on the cloudiest of days. Whether or not such navigational techniques were used remains a bit of debate among archaeologists.
- There are those who believe that this apparently fictional and fantastic stone is actually a piece of Icelandic spar, also known as the mineral calcite. Calcite is unusual among common minerals because of a property called birefringence. Calcite has the ability to refract light at two different angles, depending on the orientation of the electromagnetic waves making up the incident light. Those waves oscillating perpendicular to the surface of the stone refract at an angle different than others, creating a second image when one looks through the stone.
- Scientists now know that light from the Sun that penetrates the Earth's atmosphere undergoes a process known as scattering, which happens when light encounters small particles in the air. Some familiar effects of this scattering are the blue color of the sky in

the day and the reddish and orange hues of sunset. A second effect is polarization. The scattering that goes on as the light enters the atmosphere causes light that reaches the surface to have waves that are not randomly oriented, but rather polarized, or preferentially oriented in a direction that points back to the source—in our case, the Sun.

- Human eyes are not capable of detecting the difference between polarized light coming directly from the Sun and diffuse light coming from other directions, but with its strong birefringent properties, calcite is. By scanning the horizon looking through the stone and comparing the intensities of the two images one sees, a skilled navigator can pick out the direction of the Sun even on the most overcast of days.

- In 2002, a block of the mineral calcite was found in the wreckage of an Elizabethan ship called the *Alderney*, which sank in 1592. Perhaps most remarkable about this discovery is the fact that the stone was found just a few feet from other navigational tools.



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Calcite has the ability to refract light at two different angles, making it able to differentiate between sunlight and diffuse light coming from other directions.

- Yet another tantalizing observation was made by physicist Guy Ropars at the University of Rennes in 2013. Ropars was able to demonstrate that, when properly trained in its use, a group of everyday people were able to determine the azimuth of the Sun on a cloudy day to within 1% of its true location.

- By the eve of the Industrial Revolution, some 300 years after the sinking of the *Alderney*, the technique seems to have been lost to the ages. We owe its rediscovery in the early 1800s to French soldier, engineer, and physicist Étienne-Louis Malus.
- In the wake of discoveries by Wilhelm Ritter and Sir William Herschel, Malus was contemplating the optical properties of minerals. One day, he was observing the optical properties of an Icelandic spar crystal outside the palace in Luxembourg. Malus noticed that if he looked at various objects through the crystal, he could see light of the same intensity regardless of how he rotated the crystal.
- But then he turned and faced the palace, and again rotated the crystal, looking at the light reflected by the palace's windows. What he saw was remarkable—that the intensity of the transmitted light changed as he rotated the crystal. Clearly, something about the process of reflecting sunlight was changing more than just the direction of its propagation.
- When non-polarized light strikes a smooth surface like a window at an angle that is specific to that material, some of that light is reflected from the surface, but some is also refracted through the surface. When the reflected beam and the refracted beam are at a 90° angle to one another, the reflected beam will be plane-polarized, with all of its constituent waves parallel to the orientation of that surface.
- What Malus saw through his Icelandic spar sample was simply his crystal either allowing that plane-polarized light through when its edge was properly aligned or blocking it from view when it was not.
- This is the principle on which polarized sunglasses work. Most polarized lenses are made by creating long, carefully oriented polymer molecules that are dyed to produce striations too small for the human eye to detect. These striations give the coating

a polarizing effect. The coating is oriented on lenses so that it preferentially absorbs light that is plane-polarized parallel to the ground. In other words, it reduces the amount of road or ground glare you experience in your car or on the ski slopes.

The Polarimeter

- A modern polarimeter conducts an experiment not terribly different than the one conducted by Malus 200 years ago in France, although the parts are much smaller and the lamp life is less than 5 billion years, like our Sun. Malus used the Sun as a source of light, the windows of the palace as a polarizer, a crystal of Icelandic spar as a second polarizer, and his own eye as a detector.
- A modern polarimeter instead uses a source lamp—usually producing light in the ultraviolet or visible spectrum. An optical filter or monochromator ensures that only one wavelength at a time gets through to the polarizer. The polarizer, much like the windows of the palace, ensures that only one plane of polarization makes it to a sample compartment. So, at this point, we have plane-polarized light of a single wavelength encountering a sample.
- The path of the beam finally passes through a second polarizer on its way to a detector. If there is no change in the orientation of the plane of polarization, the rotational position of the second polarizer will have to be exactly the same as the first to maximize the amount of light reaching the detector. So, if we were to rotate the second polarizer, when this flash of light is observed, we know the plane of polarization of the light exiting the spectrometer.

Optical Rotation

- Small organic molecules in solution aren't aligned like polymer strands in your sunglasses. Instead, they tumble and move randomly, so they do not preferentially absorb plane-polarized light like a pair of sunglasses. They do, however, interact with plane-polarized light in a different way.

- Chiral molecules have the interesting ability to rotate plane-polarized light. As a plane-polarized light beam of a specific wavelength passes through a chiral sample, the plane of polarization rotates, so that when the beam exits the sample, the plane of polarization has a new orientation.
- The polarimeter must rotate the second polarizer to let the exiting light through to reach the detector. So, the instrument rotates the second polarizer until the detector sees the maximum intensity of light. The angle between the initial and final planes of polarization is called alpha. This is the measured rotation in a given experiment.
- This ability of chiral molecules to rotate plane-polarized light is called optical activity, and just as the ability to absorb light is an intrinsic property of a compound, so is its optical activity. In other words, a given chiral compound rotates a certain wavelength of light by a known and constant amount. This is called the specific rotation of a compound, and it is usually labeled as a bracketed alpha.
- Our observations so far lead us to derive an equation that is very similar to Beer's law. Just as absorbance is equal to the extinction coefficient multiplied by path length multiplied by concentration, rotation of an enantiopure sample is equal to its specific rotation multiplied by path length multiplied by concentration.
- But this is where polarimetry deviates from Beer's law. In UV-visible spectroscopy, there are no anti-absorbers that reemit the light absorbed by their counterparts, canceling them out. But in polarimetry, there is such a counterpart—the other enantiomer of the compound.
- We have to include a term in our equation that accounts for the opposing rotation of the minor enantiomer. Both terms of the equation share the same optical rotation and path length, so we can separate these algebraically and arrive at an equation that works for samples of a compound that are not enantiopure.

- So, observed rotation is equal to specific rotation multiplied by path length multiplied by the difference in concentration between (*R*) and (*S*) enantiomers. This difference is also called the enantiomeric excess. Journal articles covering chiral syntheses will always include a measure of the enantiomeric excess of the desired chiral product, reported as a percentage simply calculated by dividing the observed rotation by the calculated rotation and multiplying by 100%.

Polarimetry in Practice

- The technique of polarimetry had early and profound influence on the link between chirality and biological systems. Louis Pasteur famously used this technique in 1848 to analyze tartaric acid salt crystals isolated from wine. Pasteur's experiments showed very clearly that biologically sourced tartaric acid had the ability to rotate plane-polarized light but that tartaric acid synthesized in the laboratory did not.
- This lack of optical activity was a conundrum that led Pasteur to take a very close look at synthetic tartaric acid. When he did, he noticed that carefully crystallized tartaric acid actually forms two different types of crystals. It was only when he painstakingly separated these crystals into two different groups by hand that he could recover the optical activity.
- This may be the very first example of a chiral separation. Fortunately, we have better methods today, but they all are dependent on Pasteur's realization that the same compound can have two equal but opposite optically active forms—enantiomers.
- But polarimetry has contributed even more to our understanding of organic reactions. One classical example of this is the work of Saul Winstein, who used polarimetry to recognize that not all S_N1 reactions proceed with total loss of stereochemistry, although most of them do.

- Winstein was able to show using polarimetry that the same S_N1 solvolysis reaction run in solvents of differing polarity not only proceeds at differing rates, but also with differing degrees of racemization. In other words, a chiral substrate might produce a racemic product when reacted in 50:50 water and alcohol but with 50% enantiomeric excess when run in alcohol alone.
- This led Winstein to theorize the existence of concerted ion pairs, in which positively charged carbocations and negatively charged leaving groups stay close to one another in what he called an intimate ion pair. If a nucleophile attacks before the ion pair fully dissociates, the leaving group (though detached) can still block the face of the carbocation from which it came. This explains the lack of total racemization in a reaction showing S_N1 kinetics, and the theory got its start with a polarimetry experiment.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 6.3–6.4.

Wade, *Organic Chemistry*, 13.1–13.10.

Questions to Consider

1. Can the observed optical rotation of a sample ever exceed the calculated rotation? Explain.
2. Is it possible to synthesize enantiopure materials from achiral starting materials?

Nuclear Magnetic Resonance

Lecture 30

In this lecture, you are going to learn about yet another region of the electromagnetic spectrum. You will go all the way to the long-wavelength end of the spectrum—beyond infrared and past microwaves all the way to the radio portion of the spectrum. But before doing so, you need to better understand a property of atoms that is usually thought of as more within the realm of physics than of organic chemistry: magnetism.

Magnetism

- The magnetic properties of nuclei were not well understood by Sir Isaac Newton, Ritter, and Sir William Herschel and went largely unaddressed during the development of optical spectroscopy techniques in the 1800s. But in the early 1900s this changed, in large part due to the efforts of Isidor Rabi, an American physicist who is credited with having the revelation that atoms have certain magnetic properties that can be used to discern one from another in a given molecule.
- Atomic nuclei have a property that physicists call magnetic “spin”—a term that does not actually refer to the rate of rotation, as one might assume from classical mechanics. Certain atomic nuclei have a spin quantum number of $1/2$, which is just a fancy way of saying that there are two possible magnetic states. Such nuclei contain what is known as a magnetic dipole, or a magnetization that can behave much like an atom-sized bar magnet or compass needle.
- Isotopes, or atoms of the same element with different numbers of neutrons, have different magnetic properties. Nearly every element has at least one isotope that is spin $1/2$, including protons, carbon 13, nitrogen 15, and oxygen 17.

- The magnetic dipole of certain atomic nuclei behaves in much the same way as a compass needle—randomly orienting itself in the absence of an external magnetic field, but as soon as a magnetic field is applied, specific orientations of the nuclear dipole become more stable.
- Unlike a compass needle, however, spin $1/2$ atomic nuclei can align their dipoles either parallel to or antiparallel to a magnetic field in which they reside, leading to a distribution of these two states in the population.
- But the energies of the parallel state (called the alpha spin state) and the antiparallel alignment (called the beta spin state) differ by an amount that can be calculated and is referred to as the Zeeman splitting energy, which is a function of the intensity of the external magnetic field and an intrinsic property of the nucleus called the gyromagnetic ratio. All protons in the universe have the exact same gyromagnetic ratio.
- So, for a nucleus of a given type, the stronger the external magnetic field, the greater the energy difference between alpha and beta spin states will be.

Continuous Wave Nuclear Magnetic Resonance

- Early spectrometers consisted of a powerful electromagnet, a radio frequency transmitter, and a radio frequency receiver. A sample of organic material is placed into the magnetic field and irradiated with a constant wave of a specific radio frequency. This is how “continuous wave” nuclear magnetic resonance (NMR) gets its name.
- The current to the electromagnet is slowly increased as the exiting radio wave is monitored. At one very specific field strength, the radio wave will be absorbed in the spin state transition from alpha to beta, manifesting itself as a reduced radio wave intensity at the receiver. This is the basic design of a continuous wave NMR spectrometer.

Chemical Shift

- If all protons have the exact same gyromagnetic ratio and the field in an NMR experiment is uniform, then how is it that this technology is good for anything other than simply detecting the presence of protons? How can it possibly distinguish one proton from another? The answer to this very important question lies in a different term in the Zeeman splitting equation. It is not the gyromagnetic ratio that differs from one proton to the next but, rather, the exact strength of the external field at each nucleus.
- The key to understanding how NMR gives us information lies in another phenomenon—magnetic shielding by electrons. Electron clouds have this interesting ability to attenuate, or weaken, the external field ever so slightly. We can think of this as a new term in the Zeeman equation in which we account for a small reduction in field strength due to shielding.
- A proton in an alkyl group will have a certain amount of electron density around it, ever so slightly reducing the field strength at its nucleus, whereas a proton closer to an electron-withdrawing atom is expected to have less electron density around itself.
- Reduced shielding means that we need to apply a less-powerful field to bring a given proton into resonance with the applied radio-frequency beam.
- The density of the electron cloud at a particular nucleus can cause its peak to shift within the NMR spectrum. This phenomenon is called chemical shift.
- Because they resonate at higher applied fields, more-shielded protons appearing to the right of the spectrum are called upfield. The converse—protons with little shielding—are said to resonate downfield.

- A final factor that must be considered when predicting chemical shifts is the phenomenon of magnetic anisotropy, which is the tendency of electrons in pi systems to be held less tightly and move through a greater volume of space than their sigma counterparts. This leads to a situation in which the electrons behave almost like a small solenoid, acting like a current moving through a wire, generating a magnetic field of their own.

The Standard Unit of NMR Spectroscopy

- Protons in different chemical environments will resonate at distinct applied fields because of effects like shielding. But what happens when a researcher in a lab across the country or across the globe tries to reproduce your experiment? What happens if the researcher's spectrometer produces a field strength or radio wave frequency that is different than yours?
- All shifts of all of the protons will be different, making comparison somewhat difficult. So, we need a method of reporting data that can be easily translated from one spectrometer to the next. We need to normalize the resonance frequencies to account for different applied field strengths.
- We start this process by agreeing to a reference standard. In the case of proton NMR, we use a compound called tetramethylsilane (TMS). We use this compound because the very low electronegativity of silicon pushes electrons toward the methyl groups, producing a strong, consistent resonance frequency that is so far upfield that it rarely interferes with the signals of interest.
- The difference in field needed to produce resonance in the protons of most organic molecules is just a small fraction of 1% of the total field strength. To make the numbers more manageable, we report chemical shift in parts per million from the absolute resonance frequency of that reference compound TMS. This also allows us to compare data collected on one instrument with data collected

on another instrument using a different magnetic field strength. So, parts per million (ppm) has become the standard unit of NMR spectroscopy.

Magnetic Coupling

- How would we expect a continuous wave NMR spectrum to look for a compound that has more than one kind of proton? Let's consider this using a fairly simple organic compound, ethyl chloride, which has two chemically distinct types of protons: those on the carbon bearing the electron-withdrawing chlorine and those one carbon-carbon bond away.
- We expect the former to be more deshielded than the latter, producing a spectrum with two different absorptions: one at about 3.5 ppm and one at about 1.5 ppm. This is, in fact, what we see. But if we look closer, we see that the peak at 3.5 ppm appears to actually have four distinct lobes and the peak at 1.5 has three.
- This is a phenomenon known as spin-spin coupling, a mechanism through which magnetization from one neighboring proton is encoded on the other. This phenomenon is most obvious when the coupled hydrogens are three bonds away from one another and only takes place when the chemical shifts of the coupled protons are different.
- NMR spectroscopists are familiar with the patterns produced by the interplay of nuclei close to one another in a molecule and look for distinctive patterns that help them identify not only the presence, but also the location of groups within a molecule.

Exchangeable Protons

- More than any other element, hydrogen atoms (or protons) tend to exchange between molecules. For example, the acid proton of a carboxylic acid is very labile, potentially protonating molecules of solvent or even other carboxylic acid molecules in the sample. This

transition between and among different chemical states can occur on the timescale of an NMR experiment, which usually takes a few seconds to complete, leading to a “blurring” of the chemical shift associated with that proton.

- A collection of molecules with protons interchanging very slowly will produce spectra with sharp lines for each type of proton, but as their exchange rate increases, the signals coalesce and blur. This explains why protons bonded to nitrogen and oxygen have a tendency to appear at many different chemical shifts and with broader absorption peaks than usual.
- This sort of behavior is very common for acid, alcohol, and amine protons, and it explains why their approximate chemical shifts are so widely varied in shift tables.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 13.7–13.14.

Wade, *Organic Chemistry*, 12.13–12.15.

Questions to Consider

1. Carbon-13 has a gyromagnetic ratio about 1/4 that of a proton. Will carbon-13 nuclei resonate upfield or downfield of protons?
2. Why is it critical for the magnetic field within an NMR spectrometer to be perfectly uniform across the entire sample during the experiment?
3. Most proton NMR experiments are run using solvents containing deuterium instead of hydrogen. Why?

Advanced Spectroscopic Techniques

Lecture 31

This lecture will take our discussion into the new millennium by analyzing what is known as pulsed, or Fourier-transform, NMR. You will also learn about a few other techniques used to characterize organic molecules—specifically, you will learn about X-ray crystallography, which has been used to validate many of the structural theories that preceded it, and mass spectrometry. In addition, you will discover that we must always remember that these techniques have their limitations.

Pulsed NMR

- Several advances in technology have led to the development of the pulsed, or Fourier-transform, NMR technique. First and foremost is the development of superconductors. All modern high-field spectrometers use a superconducting magnet to generate extremely high applied fields to achieve better resolution.
- Keeping these superconducting magnets cold is critical to their function, so spectrometers contain a series of concentric vacuum-walled compartments called dewars—an exterior dewar filled with liquid nitrogen and an interior dewar containing liquid helium and the superconducting magnet. The liquid helium keeps the magnet at 4 kelvins—colder than the dark side of the Moon—while just inches away from it is the sample at room temperature.
- The second advancement that opened the door to the pulsed NMR method is computing technology. The detector in NMR is more often called a receiver because the response that it creates is not a spectrum but, rather, a raw data set that must be manipulated by the computer before it can be used.
- Recall that in the presence of a magnetic field, protons align their dipoles in the parallel alpha spin state or the antiparallel beta spin state, and the populations of these two states are governed by the

Zeeman splitting, which is the energy difference between the alpha and beta states and can be calculated using the field strength at the nucleus and the gyromagnetic ratio.

- There are two additional principles that help explain the pulsed NMR method. First, when an individual atomic dipole aligns itself with external magnetic field lines, the two are not perfectly parallel. The magnetic dipole of a nucleus precesses slower in a weaker field and faster in a stronger one. The frequency of this precession is called the Larmor frequency, which is exactly the same as the resonance frequency for a given nucleus. So, we can calculate the Larmor frequency for a given proton using the same equation, relating it to the gyromagnetic ratio and effective field.
- Second, in a large collection of similar nuclei, the vector sum of all dipoles within the system will in fact be aligned with the applied field because of the dispersion of the rotating dipoles and the slight excess of the alpha spin state in the group. It is this net magnetization that is the source of the pulsed NMR signal.

X-Ray Crystallography

- In 1895, a new class of electromagnetic radiation was discovered by German physicist Wilhelm Röntgen, who immediately realized the significance of his discovery and published his findings that same year, referring to the uncharacterized radiation as “X-rays.” He was awarded a Nobel Prize in Physics—the first ever—in 1901, just six years after his discovery.
- But it would be a decade after Röntgen’s Nobel Prize that one of the most impactful applications of his X-rays would be developed. English physicist Sir William Lawrence Bragg, working in collaboration with his father, opened up this entirely new part of the electromagnetic spectrum to the art of identifying organic molecules when he developed a technique to elucidate the structure of crystalline materials using X-rays.

- Bragg and his father had recognized that crystalline materials had a peculiar effect on X-rays as they interacted. There is a scattering effect caused by the electron cloud of each atom in the solid substance, producing a spherical, diffracted wave of the same wavelength. In a crystalline material, the atoms or ions are spaced regularly and evenly, creating planes of evenly spaced positions capable of causing these spherical waves to form.



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The discovery of X-rays earned Wilhelm Röntgen the first Nobel Prize in Physics and gave us an invaluable diagnostic tool.

- In 1913, Bragg and his father famously published a paper detailing the crystal structure of diamond by X-ray diffraction. This structure proved for the first time that carbon was in fact a tetrahedral atom in its sp^3 -hybridized state, as chemists had suspected for decades. For their contribution, Bragg and his father shared the Nobel Prize in Physics in 1915.
- X-ray diffraction has since been used to validate many structural theories, including some of those offered by chemists long before its creation. It validated Kekule's benzene ring with Robert Robinson's six evenly spaced carbon atoms about a symmetrical six-membered ring. It also has been used to test Hückel's rule for aromaticity and anti-aromaticity using cyclooctatetraene, which clearly has a ring pucker and also two different carbon-carbon bond lengths within the ring.
- In more recent years, it has helped to produce many amazing protein and DNA models, including the remarkable potassium channel protein structures that won Roderick MacKinnon his Nobel Prize. In short, X-ray crystallography may be the most powerful structural determination tool ever invented.

Mass Spectrometry

- Mass spectrometers were first developed to help us better characterize the structure of atoms, but modern mass spectrometers are used commonly in a variety of applications, including sequencing sophisticated proteins, characterizing DNA, and learning more about complex biomolecular systems.
- The influential analytical technique was first developed by British scientist Sir Joseph John Thompson in the first decade of the 20th century. Thompson won the 1906 Nobel Prize for his discovery of the electron a decade earlier.
- As he continued his research into subatomic particles, he turned his attention to the nucleus of the atom, seeking any clue of the existence of subatomic particles there. He found what he was looking for when he was able to create a beam of ionized neon gas in his lab. He aimed his beam at a piece of photographic paper, passing it through a magnetic field to get there.
- Thompson knew that when a charged particle moves through a magnetic field, it experiences a force that is dependent on its charge and velocity, but not its mass. So, basically, the field pushes all ions moving through it with equal force. Naturally, he expected to see all of his neon ions deflected to the same extent, striking the photographic paper in the same spot.
- What he saw was remarkable: Two different spots formed on the developed paper. Thompson had observed neon atoms behaving as if they had two different masses. He had proven the existence of elemental isotopes—atoms of the same element with different molecular masses. The only logical explanation for his observation was that atomic nuclei are made up of something smaller than themselves.

- But mass spectrometry is useful for much more than the study of atomic structure. In the past half century, it has become a favorite technique of chemical researchers and forensics laboratories because of its amazing ability to identify unknown compounds quickly and efficiently.
- There are three main components to a mass spectrometer: an ionizer, a mass analyzer, and a detector. As the name implies, the ionizer is responsible for creating a beam of gas-phase ions. These ions then pass through a mass analyzer, which modifies their motion using an applied magnetic field. Finally, the ions collide with a detector placed such that only ions taking a specific trajectory will strike it.
- How is it that mass spectrometry is so useful for identification when so many molecules share the same molecular mass? The answer lies in a phenomenon that takes place during the ionization process.
- During the high-energy process of ionization, many of the ionized organic compounds fragment into smaller pieces. Usually, this involves the homolytic cleavage of a bond to form two pieces of the original molecule—one neutral radical and one cation.
- The mass spectrum not only gives us the mass of the molecule by detecting its molecular ion, but also produces a sophisticated fingerprint of the molecule through a process called fragmentation. By measuring the mass difference between the molecular ion and its fragments, we can determine the identity of the fragment that was lost to produce each fragment. Not the molecular mass, but the fragmentation pattern is the key to much of the utility of this technique.

The Limitation of Spectrometry

- We have all probably heard the amusing story of a person making the unfortunate decision to eat a poppy seed bagel before a urinalysis drug screening only to be told afterward that he or she has tested positive for heroin use. This situation has been explored by popular programs like *MythBusters* and has been parodied on popular comedy programs like *Seinfeld*.
- If the mass spectrometry used in the urinalysis is so powerful and accurate, then how can it be defeated by something as simple as a poppy seed? The answer is a perfect illustration of the limitation of spectroscopy and spectrometry in general.
- Morphine and heroin only differ in structure by the presence of two acetyl groups. These acetyl groups are added to the naturally occurring morphine from poppy seeds by esterification with acetic anhydride. The seed from mature flowers is needed.
- Once injected, a fraction of the heroin molecules are slowly hydrolyzed back into morphine by enzymes in the blood. The resulting morphine is modified and further broken down in the liver. Finally, these metabolites are eliminated from the user's system, ending up in their urine.
- Many drug urinalysis techniques use mass spectrometry to search for the metabolic by-products of heroin, which are practically identical to those of morphine, which are present naturally in poppy seeds used in the food industry.



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The metabolic by-products of heroin are practically identical to those of morphine, which are present naturally in poppy seeds.

- This is a fantastic example of how the utility of even the most powerful instruments is not only a function of the technology, but also of the human element. In short, no spectral analysis is ever complete without careful contemplation on the part of the researcher.

Suggested Reading

McMurry, *Fundamentals of Organic Chemistry*, 13.1.

Questions to Consider

1. What are some non-spectroscopic applications of the Fourier transform?
2. How does changing the wavelength of diffracted light change the diffraction pattern for a given crystal?
3. How is the fragmentation pattern of a compound used to identify it in a mass spectrometry experiment?

Purifying by Recrystallization

Lecture 32

It is very rare that any organic synthesis runs cleanly to absolute completion, producing no by-products and leaving no starting materials behind. It is even rarer that we find organic materials in highly purified forms in natural sources. So, how do we sufficiently purify organic material? In this segment of the course, you will investigate a few staple techniques used for isolation of organics in modern laboratory and manufacturing settings. Specifically, in this lecture, you will learn about two very important and widely used techniques—one for purification and the other used to determine purity. Both of these techniques rely on the tendency of organic molecules to form highly ordered crystals.

The First Recrystallization Experiment

- To find one of the first examples of mass-scale organic purification, we go to India in the 5th century B.C. Evidence shows that it was around this time that the people of India began harvesting a wild reed that, when they chewed on it, became sweet tasting and pleasant.
- This commodity quickly caught on in other regions of Asia and Europe. Greek physician Dioscorides wrote of it in the first century A.D., and records from the Tang dynasty confirm that it was being cultivated in China as early as 600 A.D.
- But the real turning point in the global spread of this product took place in the 3rd century A.D. During this time, most of what is now northern India was ruled by the Gupta dynasty, which is famous for its deep and altruistic value of cultural development.
- It was during this golden age of Indian culture that techniques were developed to extract the juice from those reeds, and then allow it to form crystals by drying it slowly in sunlight. These crystals, it turns out, retained the sweet flavor of the reeds, yet spoiled far more slowly in their crystalline form.

- They were creating crystalline sugar—sucrose extracted from sugar cane as a solution and then crystallized. By developing this process, the people of the Gupta kingdom were unwittingly performing what may have been mankind's first recrystallization experiment.



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Crystalline sugar is extracted from sugar cane as a solution and then crystallized to create a more viable product.

Crystals: Stability and Purity

- It is actually not so surprising that crystalline organics might be some of the very first organic compounds isolated by man. The reason for this is hidden in the Gibbs free energy of crystals. Crystals are highly ordered, repeating arrangements of atoms or molecules.
- But organic molecules can also achieve these highly repeating patterns in the solid state. When they do so, the intermolecular attractions between and among molecules become stronger, and the free energy of the system naturally decreases. Because lower-energy states are favored in nature, highly ordered materials can form if the energetic benefit of their interactions exceeds the entropic penalty of assuming that ordered state.
- If we can make crystals grow very slowly, under conditions favoring the most stable crystal formation with all the strongest intermolecular attractions, we can produce a crystal of high purity. This is a good thing, because we rarely find compounds like sucrose all alone in nature.

- In biologically sourced solutions like cane juice, which is up to 20% sucrose, we find smaller concentrations of its subunits glucose and fructose as well as small amounts of many other biological molecules.
- In the days of the Gupta dynasty, this was not likely to be a concern to them. Crude, solidified, or crystallized sugar was enough to get the job done, but today's chemists and chefs find a need for highly purified sucrose so that they can use it under the more controlled conditions demanded by the state of their art.

The Process of Recrystallization

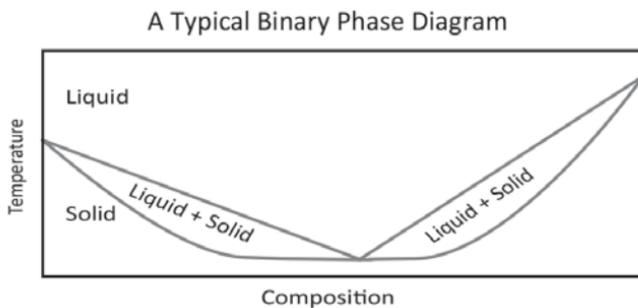
- Early sugar was most likely produced by evaporating water from cane juice as rapidly as possible. If, however, the solution expelled from sugar cane is slowly allowed to concentrate past the point of saturation, the sugars contained therein will be compelled to take on a solid form or precipitate from the solution.
- If we produce a concentrated solution of organic molecules like sucrose and then somehow induce the system to become supersaturated, meaning that it has more dissolved sucrose than it could normally hold, we expect the growing crystals of sucrose to exclude the other contaminant solutes.
- Let's use a compound called phthalic acid to better understand the process of crystallization. We start with a sample of phthalic acid and a beaker of water in which we can dissolve the phthalic acid. Phthalic acid has a solubility of about 18 g/mL in boiling water but of about 0.6 g/mL in cold water.
- If the phthalic acid isn't quite pure, its crystals aren't as stable as they could possibly be. But how are they going to get to that more purified, more stable state? Clearly, the molecules in the crystal are not going to spontaneously rearrange in the solid phase, expelling the contaminants, so we want to speed up the process.

- We need to disassemble the crystals at the molecular level, separating them all in such a way that the phthalic acid molecules get a second chance to order themselves in a more stable state. One way to accomplish this separation is to dissolve the crystals, separating them all with solvent.
- We can create a saturated solution of phthalic acid in boiling water. At the beginning, the phthalic acid has no incentive to precipitate, because it is happy staying dissolved in the hot solution. But then, we turn off the heat source.
- As the solution cools slowly, the solubility of the phthalic acid drops dramatically. Then, the organics have nowhere to go but out of solution. The key here is that we are allowing the process to happen slowly. By cooling slowly, we avoid the trapping of impure molecules in the growing crystals.
- At the completion of the recrystallization, the large, well-formed, pure phthalic acid crystals can simply be removed from solution using filtration. The solution from which they came, sometimes referred to as the mother liquor, contains the impurities still in solution—and, unfortunately, a small amount of the phthalic acid. But it's a small price to pay for such a high-purity product, and in this case, it is about $1/30^{\text{th}}$ of the total amount of phthalic acid in the sample.

Melting: Determining Purity of Crystalline Solids

- Pure crystals tend to be more stable than their impure counterparts. This phenomenon can be used to purify a compound by crystallizing it from a solution, but we can also exploit this phenomenon in a completely different way—by observing the melting behavior of a sample to help us identify it and assess its purity.
- Just as dissolution involves liberating individual molecules from one another by solvation, melting liberates them by heating them until they have sufficient kinetic energy to overcome those forces holding the solid together.

- With this in mind, the logic behind using melting to assess purity becomes clear—that more-purified crystals have greater forces holding them together, meaning that they require more energy to melt. In other words, as purity increases, so does the melting point.
- This concept can be illustrated using a hypothetical phase diagram for a binary system. In order to construct this phase diagram, we take the diagram for a pure substance, which we will call substance A. Its phase diagram includes all of the phase transitions, complete with boundaries for melting and freezing, boiling and condensing, and sublimation and deposition.



- However, the diagram only applies to a pure substance. To create a binary phase diagram, we settle on a constant pressure like 1 atmosphere, and at that pressure, we project the diagram along a third axis of composition. We do this for two hypothetical solids, which we will call A and B, focusing on the melting transition.
- The new x -axis is the mole percentage of one of the two compounds, so the extremes of the axis correspond to pure materials, and the interior corresponds to mixtures of the two in various ratios. The melting process for most mixtures occurs over a range of temperatures rather than a single, distinct temperature.

- The lower temperature barrier for melting is called the solidus. At temperatures below the solidus for a given mixture, no liquid can coexist at equilibrium. The higher temperature barrier is called the liquidus, and it represents the temperature above which only liquid can exist at equilibrium.
- This diagram will allow us to predict the melting behavior of our system as a function of its composition at 1 atmosphere of pressure. The melting points of pure A and B are just that—points of a single temperature at which the solidus and liquidus converge. After all, we learn in general chemistry that the melting of a specific pure substance at 1 atmosphere pressure takes place at one specific temperature.
- But let's consider what happens when we mix a bit of compound B into the solid sample of A—just about 5 mole percent. At this composition, the presence of a few molecules of impurity B are disrupting the crystals of A, reducing its melting point.
- But there is even more going on here. The temperatures at which solid and liquid can coexist are now a range, rather than a single temperature. This is because a process called incongruent melting is taking place.
- Incongruent melting means that the liquid generated first is not of the same composition as the solid. So, the liquid is more concentrated in B than in the solid, meaning that the melting point of the crystal increases as it melts, although it never quite reaches the melting point of the pure solid.
- As we continue to add more and more compound B to the solid and repeat the experiment, we see the trend of melting point depression and broadening continue, until eventually the gap narrows again and comes to a point at a local minimum on the solidus.

- We call this convergence of the solidus and liquidus the eutectic point for the mixture. It is the only temperature at which a mixture of the two components can coexist at one distinct temperature.
- Think of it as the point at which B stops being the impurity in A and the roles are reversed. Adding even more and more B reverses the trend, finally taking us to its own melting point at the far end of the projection.
- This kind of complex phase behavior gives us a very useful tool to confirm the identity and purity of a compound. We use a device called a MelTemp apparatus, which consists of a heating block with a temperature control and a viewing window. If we load a sample of the original crude phthalic acid and one of the recrystallized material, we can confirm that the melting point of the purified material is higher.
- In addition, a third sample consisting of the purified phthalic acid ground thoroughly with a small amount of standard allows us to confirm its identity, because adding anything but the same compound to itself should reduce its melting point. If the sample were anything but phthalic acid, the melting point of the mixture should be depressed.
- We call this simple technique a mixed melting point analysis, and it is a very commonly used quick check for purity and identity when synthesizing compounds in the lab.

Suggested Reading

Wade, *Organic Chemistry*, 3.5B.

Williamson, *Organic Experiments*, Chaps. 3 and 4.

Questions to Consider

1. Is purification by recrystallization driven by enthalpy or entropy?
2. What are some characteristics of a good recrystallization solvent?
3. How does the inclusion of small amounts of impurity lower the melting point of a given compound?

Purifying by Distillation

Lecture 33

Distillation has found many uses through the ages, from producing potable water and alcoholic beverages to refining oil and gasoline. It also finds use frequently in the organic chemistry laboratory as a method for isolating liquids of varying volatility from one another. In this lecture, you will learn about the fundamental laws governing this influential chemical technique, including Raoult's law, Dalton's law, and the ideal gas law. In addition, you will explore some advanced distillation techniques.

Vapor Pressure

- All liquids exist naturally in equilibrium with just a bit of their vapor, even at temperatures well below their boiling points. The exact amount of vapor varies from substance to substance and depends on how well molecules of the same kind stick together through intermolecular attractions.
- We measure the amount of vapor above a liquid in terms of the pressure that it exerts, so this property of liquids has come to be known as vapor pressure. The higher the vapor pressure of a given liquid, the faster and more easily it will convert to the gas phase. We often report vapor pressures in units of torr. One torr is equal to 1 mm of mercury in a barometer.
- Increasing the temperature of a sample means increasing the kinetic energy in the molecules making it up. So, increasing the temperature of a liquid sample gives more of its molecules enough kinetic energy to escape the liquid and become a gas. This increases the vapor pressure of the sample.

- When a liquid is heated to a temperature at which its vapor pressure is equal to the externally applied pressure, such as the 760 torr of pressure exerted by the Earth's atmosphere, the liquid boils. When the pressure we are working against is 1 atmosphere, we refer to this temperature as the normal boiling point.

Raoult's Law, Dalton's Law, and the Ideal Gas Law

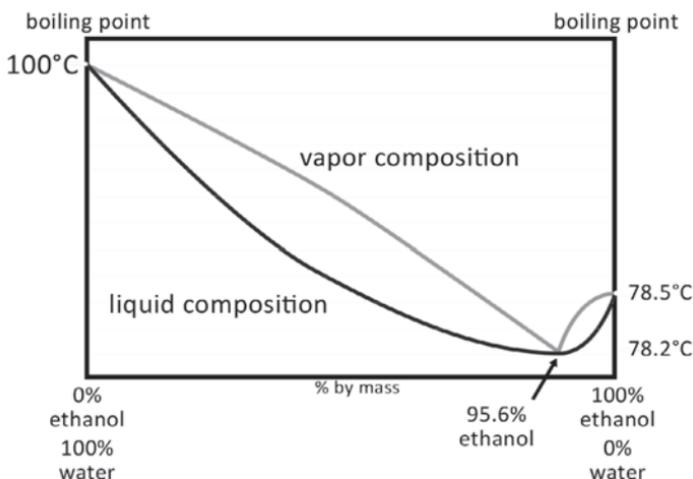
- Raoult's law, named for French chemist François-Marie Raoult, states that the vapor pressure exerted by a component in a mixture of miscible liquids is equal to its vapor pressure when pure multiplied by its mole fraction in the mixture. In other words, the vapor pressure of each component is proportional to the fraction of sample molecules it makes up.
- Dalton's law, named for John Dalton, tells us that the sum of the partial vapor pressures exerted by all of the components of such a system is equal to the total vapor pressure exerted by that system. In other words, vapor pressures are additive. So, varying the amount of each liquid making up the mixture can alter its vapor pressure.
- The ideal gas law is actually a combination of several laws, relating pressure, volume, abundance, and temperature through a constant called the ideal gas constant. The equation for the ideal gas law is $PV = nRT$, where P is pressure, V is the volume occupied by the gas, n is the number of moles of gas, T is the temperature of the vapor, and R is the ideal gas constant. Because R is constant for all systems, we can assert that PV/nT for any gas or collection of gasses should always be equal.
- The ratio of the partial pressure of a gas to the total pressure must be equal to its mole fraction in the sample. The vapor above miscible mixtures of liquids is more enriched in the more volatile component or components.

The Distillation Experiment

- If we could boil the mixture and channel the vapor somewhere else, condensing it in a separate container, we would have a liquid of greater purity than we had started with. It is this process of boiling, transporting, and then condensing a sample that adds up to create the technique of distillation.
- However, this process creates a distillate that is enriched but not purified enough for certain applications. So, how would you get a distillate of higher purity?
- Usually, the first impulse is to simply redistill the distillate, thereby obtaining an even more enriched, higher-purity distillate. The problem with this approach is that it is very labor- and energy-intensive. It requires either a major modification to the still, adding a second condenser and receiving flask, or that we stop, clean the entire apparatus, recharge the boiling flask with the distillate, and run again.
- Neither of these options is particularly attractive, especially when there is an easier way—a technique known as fractional distillation. A fractional still differs from a simple still in just one crucial way: It contains a vertical column between the boiling flask and the still head. It is often packed loosely with inert material like glass or metal, which increases the surface area inside the vertical column.
- The ultimate effect of all this is that a single distillation runs with greater efficiency than a simple still can achieve. If the distillate is as pure as that obtained by two simple distillations, we say that the still runs at two theoretical plates. This is a reference to early fractionating column designs, which actually contained plates along the length of the column, on which one cycle of condensation and vaporization could take place before the vapor moved on to the next-highest plate.

Azeotropes

- As powerful as distillation is as a technique, it does suffer from limitations. For example, grain alcohol is 190 proof—meaning that the mixture is 95% ethanol and 5% water by volume—not 200 proof, or 100% alcohol for a very good reason: Ethanol and water cannot be distilled beyond this proportion.
- Raoult's law, Dalton's law, and the ideal gas law are predictions based on ideal behavior, in which gas molecules do not interact with one another significantly. The truth is often quite different from this. Because these laws are not rigorously accurate models, we often see distortions in the behavior of systems that we are trying to distill.
- The mixture of ethanol and water is actually a rather mild example of this. The liquid-vapor phase diagram for this system has a small local minimum at about 95% ethanol. It looks a lot like the eutectic point, which is the only composition at which the liquid and solid are of the same composition.



- When the analogous feature is seen in a liquid-vapor system, we call the mixture an azeotrope, derived from Greek terms meaning “no change on boiling.” It is a very appropriate name, because the vapor above the liquid is of exactly the same composition as that liquid, making distillation of such a mixture futile.
- A fractionating column that reaches the Moon would not be sufficient to obtain pure ethanol by distillation. We would have to resort to other means to chemically dry the azeotrope and make it 100% ethanol. From the perspective of an alcoholic beverage company, it simply isn’t worth all of the extra effort to remove that last little bit of water from a product that is most likely going to be mixed right back in with another aqueous solution to prepare a drink.

Advanced Distillations

- Since a century or two ago, many additional methods for distillation have been developed to create new spins based on this old technique. While the simple and fractional distillation techniques are designed to carefully coax one volatile organic away from another, there are situations in which we can be a bit more heavy-handed. An example is the rotary evaporator.
- For example, let’s say that we want to recover a nonvolatile solute from solution, such as nonvolatile dye molecules dissolved in a sample of acetone. Essentially, one of our two components has no vapor pressure whatsoever. In this situation, we want to use a system that can quickly and quantitatively distill away all of the volatile material, leaving behind only the nonvolatile dye molecules.
- Another potential sticking point when designing a distillation is how to distill a material that is known to decompose before it reaches its normal boiling point. This can be accomplished in a number of ways, but when the desired compound is immiscible with water, chemists often turn to the technique of steam distillation to get the job done.

- Take the example of eugenol, which is the primary component of the essential oil of cloves and is prized for its anesthetic properties and as a flavoring agent. But it has a very low vapor pressure, giving it a normal boiling point of about 254° Celsius. Such a high boiling point makes eugenol a poor candidate for purification by distillation.
- However, there is one critical property of eugenol that we have not yet considered. It is immiscible with water. This means that Raoult's law does not apply to a mixture of eugenol and water. Instead, water and eugenol will each establish their vapor pressure independently of their mole fraction in a mixture.
- At 100° Celsius, eugenol has a vapor pressure of about 4 torr. This means that in the presence of boiling water, eugenol will only make up about 0.5 mole percent of the molecules in the vapor phase.
- This might seem like a hopeless endeavor, creating a vapor that is only 1 part eugenol and 199 parts water. But keep in mind that this approximation is a mole percentage and not a mass percentage. We can easily convert it into mass percentage, multiplying by the molar mass of eugenol and dividing by the molar mass of water.
- This leads us to the conclusion that the vapor above a mixture of boiling eugenol and water will actually have 4 mass percent eugenol—still a small amount, but not nearly as disappointing as our mole percentage made it seem.
- So, by boiling whole cloves in water, we can generate a vapor that is 4% eugenol in water at a very safe 100° Celsius. Collecting this vapor using a West condenser gives us a mixture of eugenol and water, which are easily separated because they are not miscible.
- What makes steam distillation particularly useful in situations like this is that the steam need not be exactly 100° Celsius. More complex systems can be set up to introduce steam of varying

temperatures, allowing us to maximize the yield of oils without losing product to degradation. This technique is very commonly used to extract oils like that of the clove plant because they tend to be low-volatility, water-immiscible materials.

Suggested Reading

French, *The Art of Distillation*.

Saltzman, M. D., "The Art of Distillation and the Dawn of the Hydrocarbon Society," *Bulletin for the History of Chemistry* 24 (1999): 53–60.

Williamson, *Organic Experiments*, Chap. 5.

Questions to Consider

1. In what situations is simple distillation most likely to be sufficient to separate two miscible liquids from one another?
2. How does packing a fractionating column with solid material serve to improve the efficiency of fractional distillations?

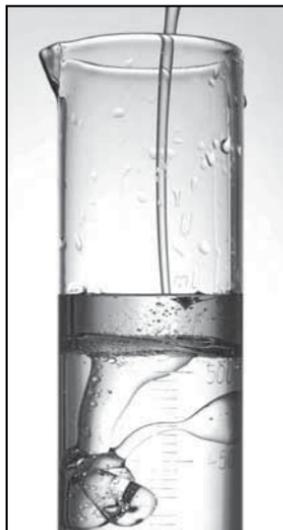
Purifying by Extraction

Lecture 34

When a compound does not have the necessary physical properties for recrystallization, or if it is not the dominant material in a mixture, we can't turn to recrystallization to obtain an effective separation. But there are other ways to isolate organic compounds from one another based on a phenomenon known as partitioning. In this lecture, you will learn about one of the most common classes of techniques based on this principle: extraction. Specifically, you will learn how solubility can be used as a very effective tool for isolation of nonvolatile organic compounds in a process known as liquid-liquid extraction.

Partitioning in the Laboratory

- The contents of a bottle of salad dressing include water and olive oil. We can see these two ingredients because they create two distinct phases. Because the oil and water are immiscible, one simply floats on the other. In this case, it is the oil above the water. Also in the bottle are salt and some herbs. To simplify, the recipe contains just those four components: water and oil as solvents and salt and oregano oil as solutes.
- The water and oil provide two different chemical environments in which the sodium and chloride ions from the salt and the organic carvacrol from the oregano can dissolve. Knowing what we know about intermolecular forces and the role they play in solubility, we expect to find the ions of the salt preferentially dissolved in the high-polarity water, which can orient its



Oil and water create two distinct phases.

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bond dipoles to create favorable interactions with the dissolved ions. The low-polarity carvacrol from the herb oils dissolves in the low-polarity oil layer on top, because the larger oil molecules are more polarizable and can form dispersion forces that solvate the carvacrol.

- It is exactly because of this separation that the proper blend of flavors is only obtained when we vigorously shake the bottle just before use. To pour just the top layer would be to put only the herb oils onto the salad, while to pour just the lower layer would be to only add the salt and acid flavors. When we do not shake the dressing—but, rather, deliberately allow the two phases to stay separate, dispensing each individually—we are doing a very simple form of liquid-liquid extraction.
- In this system, we assumed that all of a particular solute accumulated in one of the two phases available to it. We were able to make this assumption because of how drastically different sodium chloride and carvacrol are, being ionic and organic, respectively.
- But the truth for most organic molecules in a system like this is not so simple. Many of them have an appreciable solubility in both water and a certain organic solvent. When this is the case, we can expect a solute to establish a set of equilibrium concentrations in both solvents based on its solubility in each.
- This effect is called partitioning, and the equilibrium constant that governs it is called a partitioning coefficient. Partitioning coefficients are easily calculated from the maximum solubility of the solute in each of the two solvents. They give a numerical value that allows us to predict how much of each solute will be in each layer at equilibrium.

Effect of pH on Partitioning

- Compounds of varying solubilities can be concentrated or reduced in samples with a well thought-out liquid-liquid extraction. But there is a very powerful trick that we have not yet considered—that many organic compounds are titratable, meaning that they can be ionized by protonation or deprotonation in suitably strong acid or base, respectively.
- Partitioning depends on relative solubility of the solute in each solvent, so if we can change the solubility of the compound in one layer, we can change the partitioning coefficient. The key to understanding acid–base extraction is to recognize that when ionized, organic compounds tend to strongly favor dissolution in aqueous media because of its high polarity.
- Let's think about a simple organic acid with the formula HA. Its acid dissociation reaction is governed by the equilibrium constant K_a for this compound. An expression that relates the ionization state of the compound to the ratio between the dissociation constant K_a and the proton concentration in the water is $K_a = [\text{H}^+][\text{A}^-]/[\text{HA}]$.
- The Henderson-Hasselbach equation relates the ratio of acid and conjugate base through the difference in $\text{p}K_a$ and pH: $\text{pH} = \text{p}K_a + \log_{10}([\text{A}^-]/[\text{HA}])$. Using this relationship, we can generate a plot of the percent ionized in water as a function of pH.
- The logarithmic relationship leads to a situation in which the acid is 99% in its neutral protonated form when the pH is two units lower than its $\text{p}K_a$. Conversely, it is 99% in its charged conjugate base form when the pH is two units higher than its $\text{p}K_a$.
- This means that we can maximize its partitioning into an organic phase by lowering the pH of the aqueous phase using a strong mineral acid, or we can maximize its partitioning into the aqueous phase by raising its pH using a base.

- For example, let's say we have phenol, a weak organic acid with a pK_a of about 10 that can deprotonate to become phenolate. If we were to mix a solution of phenol in ether with an aqueous solution at pH of 7, we create a situation in which the phenol can be neutral in the organic layer or neutral in the aqueous layer. It will prefer the organic layer.
- But if instead we use an aqueous solution at pH 12, the phenol has a choice between being neutral in the organic layer or a being a charged phenolate in the aqueous layer. This time, the aqueous layer competes much better for the solute, and the partitioning behavior of that solute changes.

Acid–Base Extractions

- The effect of altering the pH in an extraction can be significant and is fairly predictable, allowing us to tune an extraction to our liking in many cases. Let's again take the example of phenol, but this time let's assume that we need to separate a sample of phenol from a physical mixture containing benzoic acid. Both are similar aromatic compounds with similar polarities.
- If we were to dissolve the mixture in ether and then attempt an extraction with an aqueous solution at pH 2, because we are below the pK_a of both compounds, we expect them each to preferentially accumulate in the ether layer. The separation is not optimized.
- But say that we instead buffer the aqueous layer to a pH of 7. This time, we are three units above the pK_a of benzoic acid but three units below that of phenol. We are in a range of the Henderson-Hasselbach plot, which shows that benzoic acid will dissolve in the aqueous as benzoate, but the phenol will have to be neutral. So, the benzoic acid is expected to partition into the aqueous layer to a much greater extent.

- Finally, let's consider what would happen if the aqueous layer were pH 12. We are now well above the pK_a of both compounds, meaning that not only can benzoic acid dissolve in the aqueous layer as its charged conjugate base, but so can phenol. Both compounds prefer the aqueous layer, and the separation will again suffer.
- So, the selection of an aqueous layer pH must be carefully considered when attempting to isolate titratable organic compounds from one another.
- Yet another consideration comes up when dealing with organic bases, such as aniline. Aniline is an aromatic amine, which is in fact basic. As a base, its conjugate acid is anilinium ion, which has a pK_a of about 5.
- But because aniline is a base, its conjugate acid will be charged, meaning that its Henderson-Hasselbach plot will be inverted on the y -axis, reflecting its high water solubility in more acidic solutions. If we were to instead need to separate this base from phenol, the effect of this on pH selection is dramatic.
- We now must use an aqueous layer with a pH less than 3 or higher than 12 to reach a position in which one of the two components ionizes well in water. So, the drawback to separating acids from bases is that we must use extreme pH conditions, but the benefit is that we now get to choose which compound accumulates in the aqueous layer and which accumulates in the organic layer.

Extraction from Solids

- Partitioning can take place between any two distinct phases, not just two immiscible liquid phases. Some other examples are solid-liquid or liquid-gas systems. So, naturally, it should be possible to conduct extractions using such systems as well.

- Probably the most obvious example of an extraction using solid-liquid partitioning is the process of brewing a cup of tea. As we add hot water to a tea leaf, certain compounds dissolve into the water better than others. The large and insoluble material making up the tea leaves can interact with the caffeine, polyphenols, and other compounds that would otherwise be soluble in cold water.
- However, steeping tea in cold water leads to a very weak solution. So, just as we can manipulate the partitioning coefficient of a liquid-liquid extraction with pH, we can manipulate the partitioning coefficient of a compound in a solid-liquid system using temperature.
- Green tea is famous for its delicate flavors and aromas, but it also contains particularly high levels of tannins, a polyphenolic compound with a bitter taste and dry mouthfeel. So, the goal when preparing this delightful beverage is temperature control.
- Fine green teas require careful attention to brewing temperature, because water just below boiling partitions the pleasant and aroma-giving compounds into the water effectively—but water too close to boiling will separate the polyphenolic compounds that have a more bitter taste, ruining the otherwise enjoyable experience of a well-crafted green tea.



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We can manipulate the partitioning coefficients of compounds in solid-liquid systems using temperature; tea connoisseurs will understand this well.

Suggested Reading

Williamson, *Organic Experiments*, Chap. 8.

Questions to Consider

1. For a given amount of extraction solvent, is it better to conduct one large extraction or several smaller extractions, pooling the extract at the end?
2. How does one determine the best-possible aqueous layer pH to separate two compounds by liquid-liquid extraction?

Purifying by Chromatography

Lecture 35

This lecture will explore the last topic on the science of separations. Instead of focusing on partitioning between two phases that are at rest, in this lecture, one of these phases will be set in motion, opening up the discussion to one of the most powerful separation techniques ever invented: chromatography. When properly applied, chromatography allows us to isolate almost anything we can imagine. From recrystallization, to distillation, to liquid extractions, to chromatography, there is a solution for nearly any separation problem that can come up in the lab.

Chromatography

- Mikhail Tsvet, the inventor of chromatography, was educated in Switzerland, where he received his Ph.D. in 1896. Shortly after this, however, he found himself in Russia, where his foreign credential nearly marginalized him. Tsvet's non-Russian credential was not recognized by the national establishment, prompting him to undertake a second Ph.D. program to become a functional scientist in the Russian system. It was the topic of this second Ph.D. that earned him immortality in the science of separation.
- Tsvet became interested in cell physiology during his first Ph.D. program and wanted to continue working with natural plant products, trying to understand the chemistry that drives their unique biology. It was during experiments with the ubiquitous plant pigment chlorophyll that he made the observation that would forever change his life and the science of separations.
- Tsvet knew that isolated chlorophyll could be easily dissolved in an organic solvent known as petroleum ether. However, when he attempted to extract the pigments from the leaves of plants, he noted that it was very difficult to dissolve. Even after grinding and tearing the leaves to expose more surface area and break open cells, the distinctive, dark green pigment simply wouldn't cooperate.

- His conclusion was that the chlorophyll pigment must be adhered to the solid plant matter through intermolecular forces, reducing its solubility in the solvent. Using this idea as a springboard for his research, Tsvet tried adhering chlorophyll to different solid surfaces, then washing it away with various solvents by allowing those solvents to flow through the solid matrix.
- He found that not only did chlorophyll migrate at different rates in different systems, but also that mixtures of pigments would many times separate in space because of the differing attractive forces at work between them and the two phases. This created an array of colors on Tsvet's column, prompting him to call his new technique chromatography, from the Greek words meaning "color" and "writing."
- Where Tsvet's creation really differed from simple liquid-liquid or solid-liquid extraction is that he added motion to the equation. By allowing one of the phases to move across the other, the partitioning of a solute between heterogeneous phases can be used to move compounds across the stationary phase at varying rates. The more time a particular compound spends partitioned into the mobile phase, the faster it moves.

Thin-Layer Chromatography and Paper Chromatography

- Chromatography has advanced considerably over the past century. Stationary phases like calcium carbonate and sugar from Tsvet's experiments have been replaced by a number of superior options. The first of these was actually paper.
- Paper consists of cellulose, a long polymer consisting mostly of interconnected glucose units. We already know that these glucose units have many hydroxyls that are available to interact with polar or hydrogen bonding compounds.
- English chemists Archer J. P. Martin and Richard L. M. Synge developed a method of chromatography using paper and organic solvents as stationary and mobile phases, respectively. In 1942, they

published a paper outlining their technique but, more importantly, discussing the fundamentals of partitioning as it applied to chromatographic systems.

- This technique proved extremely useful in the identification of small organic molecules, including amino acids like glycine and alanine. This method was so influential that Martin and Synge received the 1952 Nobel Prize in Chemistry for this concept. A year later, young Stanley Miller used this method to verify the presence of those amino acids in his now-famous primitive Earth experiment.
- More recently, advances in material manufacturing have made quick identifications like Miller's even easier and more accurate. For example, microporous silica can now be manufactured. Silica is a fantastic stationary phase, because even though its formula is SiO_2 , at its surface are an array of silanol groups, or SiOH . These groups interact well with anything of high polarity or hydrogen-bonding ability. Because silica can be manufactured with tremendous surface-area-to-volume ratios, more compounds can be separated with greater efficacy or on larger scales.
- For example, instead of the everyday paper used by Martin and Miller, modern organic chemistry researchers often use a thin-layer chromatography plate with a plastic backing with just a 200-micron-thick layer of silica bound to it. That is just about the width of a human hair, but that small amount of silica has a surface area of hundreds of square meters because of the extremely small size and porosity of the silica particles.
- In the technique of thin-layer chromatography, a small amount of the compound to be analyzed is spotted onto the plate and allowed to dry. Once the spot is dried, it is placed into a developing chamber containing a thin pool of the selected mobile phase.
- As the mobile phase wicks up through the plate by capillary action, the different compounds in the sample move at different rates. Compounds that interact more strongly with the polar silica move

a shorter distance, while those that interact better with the lower-polarity mobile phase move a greater distance.

- At the completion of the experiment, we measure the distance traveled by the sample spot as a fraction of the distance traveled by the mobile phase and report this number as the retention factor (R_f) value for that sample in that particular system. This value gives us a semiquantitative way to describe simple chromatographic mobility.

Column Chromatography

- Thin-layer chromatography may be a versatile, quick, low-cost way to observe the chromatographic mobility of a compound, but working with such small quantities makes collection of a meaningful sample of the compound difficult.
- In order to collect a sample that can be used as a raw material, drug, analytical sample, or synthetic intermediate, we need to increase the scale of the experiment.
- This is frequently done in the lab using a technique known as column chromatography. In column chromatography, we abandon the thin layer of stationary phase on a backing for a column. Bringing the third dimension into play means that a 2-centimeter-wide column can separate about 8000 times as much sample as a TLC lane 200 microns thick.
- In this rather simple technique, we use a glass column with a Teflon stopcock at the base. The neck of the column is plugged with a piece of glass wool and filled with sand to provide a level layer onto which we can build a column of silica that is then saturated with the mobile phase.
- Then, we drain the mobile phase through the stopcock to expose the top of the column and gently add a narrow, concentrated band of the compound we want to analyze. We then drain that to get it in contact with the silica gel before topping it off with more mobile phase.

- After loading the column, we can open the stopcock and let it run. As the mobile phase moves downward under the force of gravity, the compounds again separate, but this time in large enough quantity that we can collect a band consisting of just one component. This fraction is now ready to be worked with. We can recover the solute by rotary evaporation, liquid extraction, or another technique, and then we are ready to work with the purified dye material.

Advanced Chromatography: HPLC

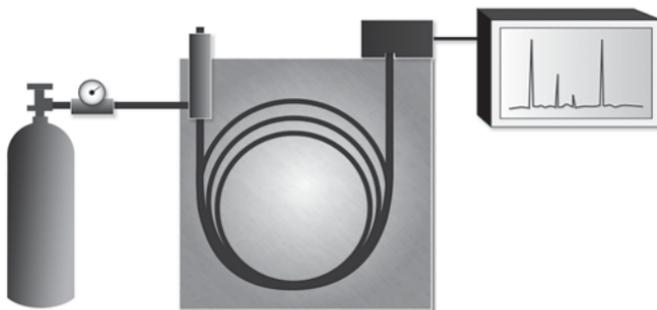
- In recent decades, chromatography has undergone a virtual explosion of advancements, leading to techniques involving ultramicroscopic silica particles with such small pores that powerful pumps must be used to push solvent through them at high pressure in a technique called high-performance liquid chromatography (HPLC).
- The extremely high surface area of the HPLC column packing allows very precise separations, but it also requires a closed system consisting of a steel column to be used so that it can resist the pressure applied by the pumps. So, it is impossible to load compounds in the same way as traditional chromatography, because the system is sealed. Similarly, it is impossible to see even colored compounds as they move through the system.
- The loading problem is solved with a device called an injection loop, which consists of a manifold with two separate loops made of a pressure-resistant tubing. When the valve handle is rotated, one loop is in line with the flowing mobile phase and the other is in line with a special injection septum.
- The sample is pushed into the open loop using a syringe, and then the handle is turned, placing the injection loop in line with the mobile phase, thereby introducing the sample into the chromatographic system without ever opening it and losing pressure.

- Because columns need to be packed into stainless steel cases, it becomes impossible to monitor a run with our eyes, even if our compounds are visible. So, HPLC systems also have a detecting system that is usually something like a simple spectrophotometer flow cell. The simplest example of this is a UV-visible detection system, in which a specific wavelength of light is aimed so that it passes through the eluting solvent, striking a detector.
- As the sample molecules move out of the column and through the detector cell, they absorb the light, leading to a reduced intensity at the detector. If we plot the observed absorbance as a function of time, starting with the injection of the sample at zero minutes, we can create what is called a chromatogram, or a graphical representation of the separation taking place.

Gas Chromatography

- There are many more chromatographic methods available to the modern chemist, including gas chromatography (GC). Archer J. P. Martin is the name most commonly associated with the invention of GC. Martin is actually most famous for his invention of paper chromatography, the technique used by Stanley Miller to detect the amino acids in his primordial concoction in Harold Urey's lab.
- Martin explored ways in which partitioning could be exploited to separate organic compounds faster and more effectively. It was around the time of his Nobel Prize that he hit on another great concept. Partitioning involves the motion of molecules from one phase to another, so why confine this methodology to transitions between adhered solid states and dissolved liquid states? After all, molecules move faster in gasses and slowest of all in solids. It stands to reason that molecules could switch from phase to phase more quickly if the gas phase were somehow included in the experiment.

Gas Chromatography



- Martin wondered whether a form of chromatography could be developed using liquid as the stationary phase and gas as the mobile phase. His idea proved viable. He demonstrated that separation could be accomplished with extreme speed and precision using a dense liquid phase and a gas like helium as the mobile phase. By slowly heating a column filled with the liquid stationary phase, through which a carrier gas like helium or nitrogen is flowing, compounds are driven off one by one in order of decreasing volatility.
- His new method allowed faster separation with far less material and has become a staple technique in forensic and analytical labs all around the world. Using various detection methods, GC can be used to analyze practically anything that will vaporize.

Suggested Reading

Scott, *Techniques and Practice of Chromatography*.

Wade, *Organic Chemistry*, 5.6.

Williamson, *Organic Experiments*, Chaps. 9 and 10.

Questions to Consider

1. What distinguishes chromatography systems from the liquid-liquid extraction systems discussed in the previous lecture?
2. If a mobile phase contains an aqueous component, how is the pH of that component expected to affect the mobility of basic or acidic compounds?
3. How will the chromatography of compounds change when a very low-polarity stationary phase is used in place of the very polar silica?

The Future of Organic Chemistry

Lecture 36

From atomic and molecular structure, to the synthesis of organic compounds, to a host of identification techniques and methods used for purification, in the last 35 lectures you have gained an understanding of some of the most basic tenets of organic chemistry. In this final lecture, you will experience the joy of taking some of what you have learned throughout this course, adding a dash of imagination, and trying to gaze into the future—through the eyes of an organic chemist.

The Origins of Life

- Our understanding of the origins of life continues to evolve. Even as the scientific community begins to get a handle on just how complex biological systems can be—such as those driving DNA translation or protein structure and function—we still struggle with the simplest question of all: How did it all get started? Even now, evidence of exactly how the first carbon-containing compounds blinked into existence on Earth is scarce.
- Stanley Miller gave us some insight into how certain biological materials might form under the conditions of the primitive Earth's atmosphere 3 billion years ago, but there are those who believe that these molecules did not form on Earth at all—that life may have fallen to Earth from outer space.
- In 1969, a huge fireball rocketed across the Australian sky before separating into several pieces and finally crashing to Earth near the town of Murchison, Victoria. This meteorite strike is unusual because it was witnessed, so there is no debating its extraterrestrial origins; it was rather large, delivering more than 100 kilograms of material; and it appears to have carried with it a buffet of organic compounds.
- In 2010, careful chromatographic separation of the extracts analyzed by mass spectrometry and NMR spectroscopy revealed

that the meteorite contained thousands or even tens of thousands of different small organic molecules encased within. The implication is that just like the meteorite, which is unquestionably an authentic space rock, those molecules that were trapped within its matrix must have fallen from space.

- Even more tantalizing evidence of extraterrestrial organics has been collected in recent decades as organizations like NASA launch sophisticated probes and telescopes like the Spitzer Space Telescope, which operated in the middle of the first decade of the 21st century. Spitzer found not only evidence of carbon, but specifically of *sp*³-hybridized carbon.

Chirality

- Another curiosity that scientists are still trying to address is that all life on Earth that we know of uses l-amino acids, or left-handed amino acids, as the principle constituent of the proteins of life. That means that even though we may think of ourselves as being achiral at the macroscopic level, we are in fact not symmetrical when we look at ourselves through molecular eyes. At the molecular level, we are chiral.
- However, every reliable source of data on abiologically synthesized organics suggests that racemic mixtures of these compounds are created in natural processes. This leads us to two important questions. First, why l-amino acids? The molecular machinery that our bodies use to create the proteins and enzymes we need to live are chiral themselves, so it makes sense that we should use all of one handed amino acid or the other. So, clearly, nature had to make a choice early on: left-handed biochemistry or right-handed biochemistry?
- But is there any real difference between our biochemical world and its mirror image? Is there some quantum mechanical effect that we do not understand perfectly that dictated that choice, or was it just a cosmic coin toss that led us to be composed of l-amino acids instead of d-amino acids?

- This question was answered in the early 1990s, when the labs of Stephen Kent at The Scripps Research Institute used modified techniques pioneered by Bruce Merrifield to create a perfect mirror image of the protein HIV protease. He then tested it for activity against mirror images of its normal substrates, finding that the chemical activity of the right-handed protein was identical in every way to its left-handed version.
- This closed the book on the question of handedness in the chemistry of life. Racemic sources of material that led to our left-handed biochemistry should be equally capable of seeding right-handed biochemistry. So, if we ever do make contact with extraterrestrial, carbon-based life-forms, it would appear that there is a 50% chance that their biochemistry will be a perfect reflection of ours.
- Kent's research opened up a whole new vein of inquiry. Now that we know that d-amino acids can be used to create enzymes with every bit as much power to promote highly specialized chemistry, researchers are trying to develop new therapeutics made from d-amino acids.

Biomimetic Chemistry

- When humans sought to take to the air and fly, birds and their wings were an obvious inspiration for the design of early aircraft. Scientists call this kind of design strategy—one of observing the properties of natural systems and applying them to engineering—biomimicry.
- Similarly, as we learn more and more about the biomolecular world, scientists more often turn to the biological for inspiration in their designs of useful compounds. This practice of imitating the function of biological



Biomimicry is evident in the designs for early aircraft wings.

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molecules is called biomimetic chemistry, and it may provide the springboard that we need to create small molecules with the exact chemical properties that we need to accomplish a number of tasks.

- Researchers at the University of Leeds have successfully synthesized what they call porphyrin cored hyperbranched polymers, which have oxygen-binding properties similar to hemoglobin but can be easily created in a lab. Someday, compounds like this one might offer a non-biological oxygen carrier for use in medical applications like surgery. An artificial blood like this would all but eliminate concerns over disease transmission or incompatible antibodies associated with human blood transfusions.

Synthetic Life

- Our ability to imitate life goes far beyond creating small, mimetic molecules. In 2010, scientists at the J. Craig Venter Institute reported that they had chemically synthesized a genome of over a million base pairs and then substituted that DNA for the native DNA in bacteria.
- In this proof-of-concept experiment, the researchers made just a few small changes between the natural DNA of the bacteria and their synthetic form, targeting regions of the genome that were known to act as structural support rather than those coding for specific proteins. Such a simple change was enough that it could be detected in the cells that had accepted the transplant without compromising the viability of the cells.
- So, the genetic deck was stacked in favor of success in this experiment. Still, this achievement will no doubt take us to the next level of biomolecular engineering, as it demonstrates clearly and effectively that the molecular machinery of life is modular and can be transplanted from one cell to another.
- This experiment shows that with enough understanding and cautious, dedicated effort, genetic material and the cellular machinery that uses it can be mixed, matched, and altered to

produce any biochemistry we desire. Someday, we may even create entire cells from chemicals on a lab bench using organic reactions that are available to us today.

Carbon Sequestration

- Carbon-containing compounds contain a great deal of chemical energy, and whether we are burning fuels or using foods for respiration, a large amount of the organic material in the world is destined to become carbon dioxide. In addition, when humans and other creatures are done with their biomass for good, decomposition naturally releases much of their carbon as CO_2 .
- Carbon dioxide acts as a greenhouse gas, absorbing radiated heat from the Earth's surface, leading to climate change when it is not properly balanced. This has led to a global movement to devise ways to store and use carbon dioxide in ways that prevent its release into the atmosphere.
- For example, the U.S. Department of Energy has estimated that 2.4 billion metric tons of industrially produced CO_2 could be stored by injecting it into subsurface structures like un-minable coal seams, where it can become adsorbed to the surface of the underground carbon.
- The concern is that there are other gasses already bound to the coal in seams like these, most notably methane. Those who advocate this method are betting on irreversible binding of carbon dioxide to subsurface structures like the carbon-rich coal deposits of coal seams—binding so strong that it can displace methane.
- There's a good chance that such an idea would work, but it depends on how well each environmental gas adsorbs to the stationary coal phase relative to its tendency to vaporize. In complex geological systems like these, the overall composition and chemical behavior of formations can be tricky to predict, so we won't know the best method for sequestering CO_2 until we try and see the results.

Molecular Engineering

- When we have completely exhausted the ability of our planet to provide for us, even with some assistance from science, the natural next step is that we look beyond the Earth for places to live, continue to expand our knowledge, and carry our species into the reaches of the solar system—and eventually the cosmos.
- To do so, at least to get started, will require that we take with us everything and everyone that a colony might need to get to and survive on a new celestial body. But that leads to a number of logistical questions, including how to get that much material off of the Earth and into space. With current rocket technology, it costs thousands or even tens of thousands of dollars to get just one pound of material into orbit around the Earth.
- There are many possible approaches to the challenge of finding a cost-effective way to escape the gravity of Earth. One very interesting proposal is the construction of a so-called space elevator, which would consist of a line that reaches from the equator of the Earth to an altitude of about 36,000 kilometers, the altitude at which a geostationary orbit is obtained.
- It is unlikely that any such structure could support its own weight. One proposed solution to this problem is to use a structure that is supported not by compression, but by tension—constructing a cable with a counterweight reaching so far into space that its center of mass is above 36,000 kilometers and whose overall length is 100,000 kilometers so that it is held taut under its own momentum as it turns with the Earth.
- Using a cable like this, a mechanical climber could simply move up the cable, taking its payload of people and supplies to the necessary altitude to escape Earth's gravity and reach outer space. Estimates are that a device like this, though profoundly expensive to build, once operating could lower the cost of delivering material into space by more than tenfold.

- In order to construct this modern marvel, a cable about 100,000 kilometers in length—more than twice the circumference of the Earth—would be produced. But to build a cable that long that can withstand the tension produced by its orbiting counterweight, we have to find the lightest, most durable material with the greatest tensile-strength-to-weight ratio ever developed. And the front-runner is carbon nanotubes.
- Under one proposal, nanotubes several meters in length could be woven together into a rope, creating the longest man-made object in human history and providing us with the cable needed to make the space elevator a reality.
- Researchers have reported that they have managed to create single nanotubes with lengths approaching the necessary mark needed to form the proposed cable. So, it would seem that soon the only thing standing in the way of a space elevator will be our own imagination—and about \$20 billion.

Suggested Reading

Deamer and Szostak, *The Origins of Life*.

Edwards and Westling, *The Space Elevator*.

Questions to Consider

1. How might the small organic compounds found within the Murchison meteorite have formed?
2. Are there any other materials that rival the strength of carbon nanotubes that might be used in the construction of a so-called space elevator? Even once a cable material has been successfully developed, what other engineering challenges remain to be addressed?

Glossary

acetal: The product formed from the reaction between an aldehyde and an alcohol under acidic conditions.

acid: A substance yielding hydrogen ions (H^+) when dissolved in water.

addition reaction: A reaction in which two molecules combine to form one product molecule.

aglycone: The newly added group on a glycoside.

alcohol: Organic compounds containing a hydroxyl (OH) group.

aldehyde: A compound of the type $R(C=O)H$.

aldose: A carbohydrate in which the carbonyl is placed at the end of the chain.

aliphatic: A compound that is nonaromatic.

alkane: A hydrocarbon in which all carbons are sp^3 hybridized.

alkene: An unsaturated hydrocarbon containing a double bond.

alkyl halide: A compound of the type RX , where X is a halogen substituent.

alkyl shift: The movement of an alkyl substituent from one atom to another.

alkyne: An unsaturated hydrocarbon containing a triple bond.

allotropes: Two or more forms of the same element, differing significantly in chemical/physical properties.

alpha helix: A secondary structure of proteins coiled like a spring.

amide bond: Also referred to as a peptide bond; a covalent chemical bond formed between two molecules when the carboxyl group of one molecule reacts with the amino group of another.

amine: A compound with nitrogen taking an sp^3 hybridization state, forming three single bonds to distinct partners: ($-NH_2$), ($-NHR$), or (NR_2).

amino acid: A molecule containing a carboxylic acid motif connected to an amine group via at least one intervening carbon.

amphiprotic: A molecule/substance that can donate or accept a proton.

amphoterlic: A species that can act as both an acid and a base.

anabolism: The building up of complex organs and tissues in the body.

angle strain: Strain associated with the distortion of bond angles.

anion: An ion in which electrons outnumber protons to afford a net negative charge.

annulene: Cyclic molecules with alternating double bonds.

aprotic solvent: Any type of solvent lacking acidic hydrogens.

aromaticity: Special stability related with aromatic compounds.

base: A substance yielding hydroxide ions (OH^-) when dissolved in water.

Beer's law: $A = \epsilon bc$, where A is the absorbance, ϵ is the sample extinction coefficient, b is the path length, and c is the sample concentration.

benzene ring: A ring of six carbons sharing double bonds.

bicyclic alkane: Two hydrocarbon rings sharing one or more atoms.

biomimetic chemistry: The practice of imitating biological molecules.

birefringence: The ability to refract light at two different angles, depending on the orientation of the electromagnetic waves making up the incident light.

carbocation: A positively charged hydrocarbon species.

carbonyl group: A group consisting of a carbon double bonded to an oxygen (C=O).

cation: An ion in which protons outnumber electrons to afford a net positive charge.

chirality: The existence of handedness of molecules.

cholesterol: The most abundant steroid in animals and a common starting material in biological synthesis.

chromatography: A technique in which organic compounds may be separated from one another based on one or more properties.

coding DNA: The portions of DNA that code for proteins.

conjugation: A phenomenon in which multiple pi bonds are in resonance with one another, lending extra stability to a compound or an ion.

continuous wave NMR: The most basic form/technique of NMR spectroscopy.

copolymer: Polymers constructed from multiple monomers.

covalent bonding: The sharing of electrons between two or more atoms.

crystal: Highly ordered, repeating arrangements of atoms or molecules.

cuvette: A cell, often made of quartz, used to hold liquid samples.

cyclic alkane: A cyclic chain of hydrocarbons.

Dalton's law: The sum of all partial pressures in a system is equal to the total pressure of the system.

deprotonation: The removal of a proton.

dewar: A vacuum-walled storage vessel used to hold liquids below ambient temperature.

diastereomer: One of two compounds that are non-superimposable non-mirror images.

Diels-Alder reaction: A reaction to make a six-membered ring by a [4+2] cycloaddition.

diene: A hydrocarbon containing two carbon-carbon double bonds.

dihedral angle: The angle between two substituent bonds on adjacent carbons.

dimer: A molecule formed by combining two identical molecules.

dipole: An intermittent charge buildup.

double bond: A chemical bond involving the sharing of four electrons between two atoms.

E1 reaction: An elimination reaction in which a weak base deprotonates a carbocation to give an alkene.

E2 reaction: An elimination reaction in which a strong base abstracts a proton on a carbon adjacent to the leaving group and the leaving group leaves, producing an alkene.

electrophile: An electron-deficient nucleus capable of receiving electrons from a nucleophile.

elimination reaction: A reaction in which a halide ion leaves another atom/ion.

enantiomer: One of two compounds that are non-superimposable mirror images.

enantiopure: A sample having all of its molecules having the same chirality sense.

enthalpy: The heat content of a substance, denoted by H .

entropy: Randomness; disorder.

equilibrium: A dynamic process in which the forward and reverse reaction rates are equal.

equilibrium constant: A constant (K) expressing the concentrations of both reactants and products at equilibrium.

ester: A compound of the type $\text{RO}(\text{C}=\text{O})\text{R}'$.

ether: Organic compounds composed of two alkyl groups bonded to an oxygen ($\text{R}-\text{O}-\text{R}'$).

eutectic point: The only point/temperature at which a mixture of the two components can coexist at one distinct temperature.

fingerprint region: The lower-frequency region of the infrared spectrum containing a complex set of vibrations within the skeleton of a molecule.

Fischer esterification: A process of producing esters from an organic acid and an alcohol.

Fischer projection: A method of projection useful for conveying the arrangements of larger chains of atoms.

frontier molecular orbital: Orbitals that are involved in a chemical reaction, generally involving the HOMO of one reactant and the LUMO of the other reactant.

Frost circle: A method giving the Hückel pi molecular orbitals for cyclic conjugated molecules.

functional group: An atom or group of atoms in a molecule responsible for its reactivity under a given set of reaction conditions.

functional group region: The higher-frequency region of the infrared spectrum used to catalog the presence or absence of functional groups.

Gabriel synthesis: A reaction transforming primary alkyl halides into primary amines.

glycoside: A carbohydrate derivative in which the anomeric C1 group has been replaced by another group.

Grignard reaction: An organometallic reaction in which an alkyl/aryl halide adds to a carbonyl group of an aldehyde or a ketone, forming a C-C bond.

Haber-Bosch process: A process of converting nitrogen gas to ammonia.

halogen: Elements (fluorine, chlorine, bromine, iodine, astatine) found in group 17 of the periodic table.

halogenation: The replacement of a hydrogen with a halogen.

Hayworth projection: A representation of sugars in their cyclic forms with a three-dimensional perspective.

heteroatom: Any atom other than carbon and hydrogen.

HOMO: Highest occupied molecular orbital.

homopolymer: A polymer formed from one monomer.

hybrid orbital: A mixture of atomic orbitals (e.g. orbitals with both *s* and *p* character).

hydride shift: The movement of a hydride (hydrogen with a pair of electrons) from one atom to another.

hydrocarbon: An organic compound consisting solely of hydrogen and carbon.

hydrohalogenation: Reactions that produce alkyl halides from alkenes.

hydroxyl group: Also known as an OH group.

hyperconjugation: The delocalization of electrons in a sigma bond through a system of overlapping orbitals.

ideal gas law: $PV = nRT$; can be rearranged to demonstrate that partial pressures of gasses in a mixture are proportional to the number of moles of each compound present.

imine: A compound with nitrogen taking an sp^2 hybridization state, forming a double bond and a single bond: $R_2C=NR'$.

immiscible liquids: Liquids incapable of mixing together to form one homogenous substance.

internal alkene/alkyne: An alkene/alkyne having a localized pi system in the middle of a carbon chain.

ion: A charged species in which the number of electrons does not equal the number of protons.

ionic bonding: A type of bonding in which atoms of significantly different electronegativities come together.

isotope: Atoms that have the same number of protons but different numbers of neutrons.

junk DNA: The structural support regions of DNA that hold the coding pieces of the DNA sequence in place.

ketal: The product formed from the reaction between a ketone and an alcohol under acidic conditions.

ketone: A compound of the type $R(C=O)R'$.

ketose: A carbohydrate in which the carbonyl is placed in the middle/interior of the chain.

l-amino acid: An amino acid with the amino group (NH_2) on the left in the Fischer projection.

Larmor frequency: The frequency of precession of the nucleus in question.

ligand: An atom or group attached to another atom (in this case, a metal).

London dispersion forces: Attractive forces arising as a result of temporary dipoles induced in the atoms or molecules.

lone-pair electrons: Electron pairs not involved in bonding.

LUMO: Lowest unfilled molecular orbital.

magnetic anisotropy: The tendency of electrons in pi systems to be held less tightly and move through a greater volume of space than their sigma counterparts, creating a magnetic field of their own.

magnetic coupling: Synonymous with spin-spin coupling; a mechanism through which magnetization from one neighboring proton is encoded on another.

Markovnikov's rule: The addition of hydrogen halides to alkenes will occur with the halide to the more-substituted carbon.

mass spectrometry: A technique used to measure the molecular weights of atoms and molecules.

Merrifield synthesis: Also known as solid phase peptide synthesis; a method for synthesizing peptides and proteins with exotic side chains.

meso compound: Achiral compounds possessing chirality centers.

miscible liquids: Liquids capable of mixing together to form one homogenous substance.

mole: A quantity used to count atoms/molecules.

monochromator: A device used to disperse different wavelengths of light to the sample.

Newman projection: A method of projection useful for depicting dihedral bond angles.

nitrate: A polyatomic ion with the formula NO_3^- .

nitrile: Compounds containing a terminal nitrogen triple-bonded to a carbon.

nuclear magnetic resonance (NMR): In chemistry, a technique used for the structure determination of organic molecules.

nucleic acid: A substance found in living cells consisting of many nucleotides in the nuclei of cells.

nucleophile: A species that easily donates an electron pair to form a new chemical bond with another nucleus.

octet rule: An atom (other than hydrogen) tends to form bonds until surrounded by eight valence electrons.

optical activity: The ability of chiral molecules to rotate plane-polarized light.

orbital hybridization: The combination of atomic orbitals to produce hybrid orbitals.

organic acid: An organic compound having acidic properties.

organic chemistry: The study of carbon-based molecules.

organometallic chemistry: The study of compounds containing carbon-metal bonds.

***p* orbital:** A dumbbell-shaped orbital.

partitioning coefficient: The ratio of concentrations of a solute that is distributed between two immiscible solvents at equilibrium.

peptide bond: An amide bond formed between two molecules.

photon: A particle of light.

π bond: A class of covalent bonds involving the overlap of *p* atomic orbitals in a side-to-side fashion, forming electron density above and below the bonded atoms.

π system: Long, interconnected systems of *p* orbitals.

π -to- π^* transition: The process in which electrons move from the highest occupied π molecular orbital to the lowest unfilled π molecular orbital.

$\text{p}K_a$ value: A measure of an acid's strength.

plane-polarized light: Light that is composed of waves vibrating in one plane.

polarimeter: An instrument used to measure optical activity.

polymer: Very large molecules consisting of repeating units of monomers.

polymerase chain reaction (PCR): A process used to induce a DNA sample to replicate.

prodrug: A modified active compound that is later chemically converted into its active form by the patient's own biochemistry.

protein: A compound containing two or more amino acids linked together by amide bonds.

protic solvent: Any type of solvent containing acidic hydrogens.

proton transfer: The transferring of a proton from one species to another.

protonation: The addition of a proton.

pulsed NMR: Also known as Fourier transform (FT) NMR; often used as a more efficient NMR technique to acquire spectra simultaneously.

purine base: A nine-membered double ring with four nitrogens and five carbons.

pyrimidine base: A six-membered ring containing two nitrogens and four carbons.

quanta: A packet of energy that can only be absorbed in a transition of equal energy.

racemic mixture: A mixture containing both enantiomers in equal amounts.

radical: A species with unpaired electrons.

Raoult's law: A component in a mixture of miscible liquids will exert a vapor pressure equal to that of the pure solvent times its mole fraction in the mixture.

rate-determining step: The slowest step of a multistep mechanism.

regioisomer: Isomers that have the same molecular formula but differ in connectivity.

regiospecificity: A reaction that tends to occur at one particular position among other similar positions.

resonance hybrid: An average structure of all resonance contributors.

resonance structures: A collection of Lewis structures that can be drawn and differ only by the placement of valence electrons.

restriction enzyme: An enzyme that cuts the amplified DNA at very specific points.

retrosynthetic analysis: A technique used in which the synthetic problem is worked backward to minimize the number of reactions considered.

ring strain: The overall measure of the instability of a ring.

s orbital: A spherically symmetrical orbital.

saturated hydrocarbon: A hydrocarbon containing only sigma-bonded hydrogen and carbon atoms.

sigma bond: A class of covalent bonds involving the overlap of orbitals along the internuclear axis.

S_N1 reaction: A type of substitution reaction in which one molecule is involved in the transition state of the rate-limiting step.

S_N2 reaction: A type of substitution reaction in which the rate-limiting step involves the collision of two molecules.

spectroscopy: The observation of the interaction of light with matter.

spin: Also known as spin quantum number; usually refers to atomic nuclei having two possible magnetic states.

spin-spin coupling: Synonymous with magnetic coupling; a mechanism through which magnetization from one neighboring proton is encoded on another.

stereochemistry: The study of the three-dimensional structure and arrangement of molecules.

stereoisomer: Isomers having the same connectivity but different arrangements in space.

substituent: A different or more complex group in place that would otherwise be bonded to a hydrogen.

substitution reaction: A reaction in which an atom is replaced by another atom.

substrate: The entire molecule undergoing substitution.

tetrahedral: A molecular geometry consisting of an atom at the center connected with four other atoms, creating a tetrahedron with bond angles of 109.5° .

torsional strain: Strain associated with the resistance to bond twisting.

triple bond: A chemical bond involving the sharing of six electrons between two atoms.

unsaturated hydrocarbon: A hydrocarbon containing pi bonds.

valence shell: The outermost shell of an atom that is comprised of valence electrons.

Williamson ether synthesis: An organic reaction used to form an ether from an alkyl halide and an alcohol.

X-ray crystallography: A very powerful tool used for structure determination of crystals.

Zaitsev's rule: The major product of an elimination reaction will be the most-substituted alkene possible.

Zeeman splitting energy: The energy difference between the alpha and beta states.

zwitterion: A molecule/species containing a positive and negative charge in separate regions.

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