Structure and Bonding

An atom consists of a positively charged nucleus surrounded by one or more negatively charged electrons. The electronic structure of an atom can be described by a quantum mechanical wave equation, in which electrons are considered to occupy **orbitals** around the nucleus. Different orbitals have different energy levels and different shapes. For example, s orbitals are spherical and p orbitals are dumbbell-shaped. The **ground-state electron configuration** of an atom can be found by assigning electrons to the proper orbitals, beginning with the lowest-energy ones.

A **covalent bond** is formed when an electron pair is shared between atoms. According to **valence bond (VB) theory**, electron sharing occurs by the overlap of two atomic orbitals. According to **molecular orbital (MO) theory**, bonds result from the mathematical combination of atomic orbitals to give molecular orbitals, which belong to the entire molecule. Bonds that have a circular cross-section and are formed by head-on interaction are called **sigma (σ) bonds**; bonds formed by sideways interaction of p orbitals are called **pi (π) bonds**.

In the valence bond description, carbon uses hybrid orbitals to form bonds in organic molecules. When forming only single bonds with tetrahedral geometry, carbon uses four equivalent **sp3 hybrid orbitals**. When forming a double bond with planar geometry, carbon uses three equivalent **sp2 hybrid orbitals** and one unhybridized p orbital. When forming a triple bond with linear geometry, carbon uses two equivalent **sp hybrid** orbitals and two unhybridized p orbitals. Other atoms such as nitrogen, phosphorus, oxygen, and sulfur also use hybrid orbitals to form strong, oriented bonds.

Organic molecules are usually drawn using either condensed structures or skeletal structures. In **condensed structures**, carbon–carbon and carbon–hydrogen bonds aren’t shown. In **skeletal structures**, only the bonds and not the atoms are shown. A carbon atom is assumed to be at the ends and at the junctions of lines (bonds), and the correct number of hydrogens is supplied mentally.

Polar Bonds

Organic molecules often have **polar covalent bonds** as a result of unsymmetrical electron sharing caused by differences in the **electronegativity** of atoms. A carbon–oxygen bond is polar, for example, because oxygen attracts the shared electrons more strongly than carbon does. Carbon–hydrogen bonds are relatively nonpolar. Many molecules as a whole are also polar, owing to the presence of individual polar bonds and electron lone pairs. The polarity of a molecule is measured by its **dipole moment**, **μ**.

Plus (+) and minus (–) signs are often used to indicate the presence of **formal charges** on atoms in molecules. Assigning formal charges to specific atoms is a bookkeeping technique that makes it possible to keep track of the valence electrons around an atom and offers some clues about chemical reactivity.

Some substances, such as acetate ion and benzene, can’t be represented by a single line-bond structure and must be considered as a **resonance hybrid** of two or more structures, none of which would be correct by themselves. The only difference between two **resonance forms** is in the location of their π and nonbonding electrons. The nuclei remain in the same places in both structures, and the hybridization of the atoms remains the same.

Acidity and basicity are closely related to the ideas of polarity and electronegativity. A **Brønsted–Lowry acid** is a compound that can donate a proton (hydrogen ion, H+), and a **Brønsted–Lowry base** is a compound that can accept a proton. The strength of a Brønsted–Lowry acid or base is expressed by its **acidity constant, Ka**, or by the negative logarithm of the acidity constant, **pKa**. The larger the pKa, the weaker the acid. More useful is the Lewis definition of acids and bases. A **Lewis acid** is a compound that has a low-energy empty orbital that can accept an electron pair; Mg2**+**, BF3, AlCl3, and H+ are examples. A **Lewis base** is a compound that can donate an unshared electron pair; NH3 and H2O are examples. Most organic molecules that contain oxygen and nitrogen can act as Lewis bases toward sufficiently strong acids.

A variety of **noncovalent interactions** have a significant effect on the properties of large biomolecules. **Hydrogen bonding**—the attractive interaction between a positively polarized hydrogen atom bonded to an oxygen or nitrogen atom with an unshared electron pair on another O or N atom, is particularly important in giving proteins and nucleic acids their shapes.

Organic Compounds

Alkanes are relatively unreactive and rarely involved in chemical reactions, but they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we’ve used alkanes to introduce the basic approach to naming organic compounds and to take an initial look at some of the three-dimensional aspects of molecules.

A **functional group** is a group of atoms within a larger molecule that has a characteristic chemical reactivity. Because functional groups behave in approximately the same way in all molecules where they occur, the chemical reactions of an organic molecule are largely determined by its functional groups.

**Alkanes** are a class of **saturated hydrocarbons** with the general formula CnH2n+2. They contain no functional groups, are relatively inert, and can be either **straight-chain** (normal) or **branched**. Alkanes are named by a series of IUPAC rules of nomenclature. Compounds that have the same chemical formula but different structures are called **isomers**. More specifically, compounds such as butane and isobutane, which differ in their connections between atoms, are called **constitutional isomers**.

Carbon–carbon single bonds in alkanes are formed by σ overlap of carbon sp3 hybrid orbitals. Rotation is possible around σ bonds because of their cylindrical symmetry, and alkanes therefore exist in a large number of rapidly interconverting **conformations**. **Newman projections** make it possible to visualize the spatial consequences of bond rotation by sighting directly along a carbon–carbon bond axis. Not all alkane conformations are equally stable. The **staggered conformation** of ethane is 12 kJ/mol (2.9 kcal/mol) more stable than the **eclipsed conformation** because of **torsional strain**. In general, any alkane is most stable when all its bonds are staggered.

**Cycloalkanes** are saturated cyclic hydrocarbons with the general formula CnH2n. In contrast to open-chain alkanes, where nearly free rotation occurs around C−C bonds, rotation is greatly reduced in cycloalkanes. Disubstituted cycloalkanes can therefore exist as **cis–trans isomers**. The cis isomer has both substituents on the same side of the ring; the trans isomer has substituents on opposite sides. Cis–trans isomers are just one kind of **stereoisomer**—compounds that have the same connections between atoms but different three-dimensional arrangements.

Not all cycloalkanes are equally stable. Three kinds of strain contribute to the overall energy of a cycloalkane: (1) **angle strain** is the resistance of a bond angle to compression or expansion from the normal 109° tetrahedral value, (2) torsional strain is the energy cost of having neighboring C−H bonds eclipsed rather than staggered, and (3) steric strain is the repulsive interaction that arises when two groups attempt to occupy the same space.

Cyclopropane (115 kJ/mol strain) and cyclobutane (110.4 kJ/mol strain) have both angle strain and torsional strain. Cyclopentane is free of angle strain but has a substantial torsional strain due to its large number of eclipsing interactions. Both cyclobutane and cyclopentane pucker slightly away from planarity to relieve torsional strain.

Cyclohexane is strain-free because it adopts a puckered **chair conformation**, in which all bond angles are near 109° and all neighboring C–H bonds are staggered. Chair cyclohexane has two kinds of positions: **axial** and **equatorial**. Axial positions are oriented up and down, parallel to the ring axis, while equatorial positions lie in a belt around the equator of the ring. Each carbon atom has one axial and one equatorial position.

Chair cyclohexanes are conformationally mobile and can undergo a **ring-flip**, which interconverts axial and equatorial positions. Substituents on the ring are more stable in the equatorial position because axial substituents cause **1,3-diaxial interactions**. The amount of 1,3-diaxial steric strain caused by an axial substituent depends on its size.

An object or molecule that is not superimposable on its mirror image is said to be **chiral**, meaning “handed.” A chiral molecule is one that does not have a plane of symmetry cutting through it so that one half is a mirror image of the other half. The most common cause of chirality in organic molecules is the presence of a tetrahedral, sp3-hybridized carbon atom bonded to four different groups—a so-called **chirality center**. Chiral compounds can exist as a pair of nonsuperimposable mirror-image stereoisomers called **enantiomers**. Enantiomers are identical in all physical properties except for the direction in which they rotate plane-polarized light.

The stereochemical **configuration** of a chirality center can be specified as either **R** (rectus) or **S** (sinister) by using the **Cahn–Ingold–Prelog rules**. First rank the four substituents on the chiral carbon atom, and then orient the molecule so that the lowest-ranked group points directly back. If a curved arrow drawn in the direction of decreasing rank (1 → 2 → 3) for the remaining three groups is clockwise, the chirality center has the R configuration. If the direction is counterclockwise, the chirality center has the S configuration.

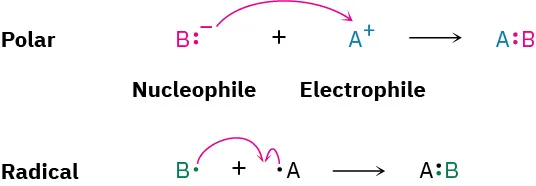
Some molecules have more than one chirality center. **Enantiomers** have opposite configuration at all chirality centers, whereas **diastereomers** have the same configuration in at least one center but opposite configurations at the others. **Epimers** are diastereomers that differ in configuration at only one chirality center. A compound with n chirality centers can have a maximum of 2n stereoisomers.

A **meso compound** contains a chirality center but is achiral overall because it has a plane of symmetry. Racemic mixtures, or **racemates**, are 50 : 50 mixtures of (+) and (−) enantiomers. Racemates and individual diastereomers differ in their physical properties, such as solubility, melting point, and boiling point.

A molecule is **prochiral** if it can be converted from achiral to chiral in a single chemical step. A prochiral sp2-hybridized atom has two faces, described as either **Re** or **Si**. An sp3-hybridized atom is a **prochirality center** if, by changing one of its attached atoms, a chirality center results. The atom whose replacement leads to an R chirality center is **pro-R,** and the atom whose replacement leads to an S chirality center is **pro-S.**

There are four common kinds of reactions: **addition reactions** take place when two reactants add together to give a single product; **elimination reactions** take place when one reactant splits apart to give two products; **substitution reactions** take place when two reactants exchange parts to give two new products; and **rearrangement reactions** take place when one reactant undergoes a reorganization of bonds and atoms to give an isomeric product.

A full description of how a reaction occurs is called its **mechanism**. There are two general kinds of mechanisms by which most reactions take place: **radical** mechanisms and **polar** mechanisms. Polar reactions, the more common type, occur because of an attractive interaction between a **nucleophilic** (electron-rich) site in one molecule and an **electrophilic** (electron-poor) site in another molecule. A bond is formed in a polar reaction when the nucleophile donates an electron pair to the electrophile. This transfer of electrons is indicated by a curved arrow showing the direction of electron travel from the nucleophile to the electrophile. Radical reactions involve species that have an odd number of electrons. A bond is formed when each reactant donates one electron.



The energy changes that take place during reactions can be described by considering both rates (how fast the reactions occur) and equilibria (how much the reactions occur). The position of a chemical equilibrium is determined by the value of the **free-energy change (Δ*G*)** for the reaction, where Δ*G* = Δ*H* − *T*Δ*S*. The **enthalpy** term (Δ*H*) corresponds to the net change in strength of chemical bonds broken and formed during the reaction; the **entropy** term (Δ*S*) corresponds to the change in the amount of molecular randomness during the reaction. Reactions that have negative values of Δ*G* release energy, are said to be **exergonic**, and have favorable equilibria. Reactions that have positive values of Δ*G* absorb energy, are said to be **endergonic**, and have unfavorable equilibria.

A reaction can be described pictorially using an energy diagram that follows the reaction course from reactants through transition state to product. The **transition state** is an activated complex occurring at the highest-energy point of a reaction. The amount of energy needed by reactants to reach this high point is the **activation energy, Δ*G*‡**. The higher the activation energy, the slower the reaction.

Many reactions take place in more than one step and involve the formation of a **reaction intermediate**. An intermediate is a species that lies at an energy minimum between steps on the reaction curve and is formed briefly during the course of a reaction.

An **alkene** is a hydrocarbon that contains a carbon–carbon double bond. Because they contain fewer hydrogens than alkanes with the same number of carbons, alkenes are said to be **unsaturated**.

Because rotation around the double bond can’t occur, substituted alkenes can exist as cis–trans stereoisomers. The configuration of a double bond can be specified by applying the Cahn–Ingold–Prelog sequence rules, which rank the substituents on each double-bond carbon. If the higher-ranking groups on each carbon are on the same side of the double bond, the configuration is **Z** (zusammen, “together”); if the higher-ranking groups on each carbon are on opposite sides of the double bond, the configuration is **E** (entgegen, “apart”).

Alkene chemistry is dominated by **electrophilic addition reactions**. When HX reacts with an unsymmetrically substituted alkene, **Markovnikov’s rule** predicts that the H will add to the carbon having fewer alkyl substituents and the X group will add to the carbon having more alkyl substituents. Electrophilic additions to alkenes take place through carbocation intermediates formed by reaction of the nucleophilic alkene π bond with electrophilic H+. Carbocation stability follows the order

Tertiary (3°) > Secondary (2°) > Primary (1°) > Methyl

R3C+ > R2CH+ > RCH2+ > CH3+

Markovnikov’s rule can be restated by saying that, in the addition of HX to an alkene, a more stable carbocation intermediate is formed. This result is explained by the **Hammond postulate**, which says that the transition state of an exergonic reaction step structurally resembles the reactant, whereas the transition state of an endergonic reaction step structurally resembles the product. Since an alkene protonation step is endergonic, the stability of the more highly substituted carbocation is reflected in the stability of the transition state leading to its formation.

Evidence in support of a carbocation mechanism for electrophilic additions comes from the observation that structural rearrangements often take place during reaction. Rearrangements occur by shift of either a hydride ion, **:**H− (a **hydride shift**), or an alkyl anion, **:**R−, from a carbon atom to the neighboring positively charged carbon. This results in isomerization of a less stable carbocation to a more stable one.

HCl, HBr, and HI add to alkenes by a two-step electrophilic addition mechanism. Initial reaction of the nucleophilic double bond with H+ gives a carbocation intermediate, which then reacts with halide ion. Bromine and chlorine add to alkenes via three-membered-ring **bromonium ion** or chloronium ion intermediates to give addition products having **anti stereochemistry**. If water is present during the halogen addition reaction, a **halohydrin** is formed.

Hydration of an alkene—the addition of water—is carried out by either of two procedures, depending on the product desired. **Oxymercuration–demercuration** involves electrophilic addition of Hg2+ to an alkene, followed by trapping of the cation intermediate with water and subsequent treatment with NaBH4. **Hydroboration** involves addition of borane (BH3) followed by oxidation of the intermediate organoborane with alkaline H2O2. The two hydration methods are complementary: oxymercuration–demercuration gives the product of Markovnikov addition, whereas hydroboration–oxidation gives the product with non-Markovnikov **syn stereochemistry**.

Alkenes are **reduced** by addition of H2 in the presence of a catalyst such as platinum or palladium to yield alkanes, a process called catalytic **hydrogenation**. Alkenes are also **oxidized** by reaction with a peroxyacid to give **epoxides**, which can be converted into trans-1,2-diols by acid-catalyzed hydrolysis. The corresponding cis-1,2-diols can be made directly from alkenes by **hydroxylation** with OsO4. Alkenes can also be cleaved to produce carbonyl compounds by reaction with ozone, followed by reduction with zinc metal. In addition, alkenes react with divalent substances called **carbenes,** **R2C:**, to give cyclopropanes. Nonhalogenated cyclopropanes are best prepared by treatment of the alkene with CH2I2 and zinc–copper, a process called the **Simmons–Smith reaction**.

Alkene **polymers**—large molecules resulting from repetitive bonding of many hundreds or thousands of small **monomer** units—are formed by chain-reaction polymerization of simple alkenes. Polyethylene, polypropylene, and polystyrene are examples. As a general rule, radical addition reactions are not common in the laboratory but occur frequently in biological pathways.

Many reactions give chiral products. If the reactants are optically inactive, the products are also optically inactive. If one or both of the reactants is optically active, the products can also be optically active.

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Alkyne carbon atoms are sp-hybridized, and the triple bond consists of one sp–sp σ bond and two p–p π bonds. There are relatively few general methods of alkyne synthesis. Two favorable ones are the alkylation of an acetylide anion with a primary alkyl halide and the twofold elimination of HX from a vicinal dihalide.

The chemistry of alkynes is dominated by electrophilic addition reactions, similar to those of alkenes. Alkynes react with HBr and HCl to yield vinylic halides and with Br2 and Cl2 to yield 1,2-dihalides (vicinal dihalides). Alkynes can be hydrated by reaction with aqueous sulfuric acid in the presence of mercury(II) catalyst. The reaction leads to an intermediate **enol** that immediately **tautomerizes** to yield a ketone. Because the addition reaction occurs with Markovnikov regiochemistry, a methyl ketone is produced from a terminal alkyne. Alternatively, hydroboration–oxidation of a terminal alkyne yields an aldehyde.

Alkynes can be reduced to yield alkenes and alkanes. Complete reduction of the triple bond over a palladium hydrogenation catalyst yields an alkane; partial reduction by catalytic hydrogenation over a **Lindlar catalyst** yields a cis alkene. Reduction of the alkyne with lithium in ammonia yields a trans alkene.

Terminal alkynes are weakly acidic. The alkyne hydrogen can be removed by a strong base such as Na+ −NH2 to yield an **acetylide anion**. An acetylide anion acts as a nucleophile and can displace a halide ion from a primary alkyl halide in an **alkylation** reaction. Acetylide anions are more stable than either alkyl anions or vinylic anions because their negative charge is in a hybrid orbital with 50% s character, allowing the charge to be closer to the nucleus.

**Alkyl halides** are not often found in terrestrial organisms, but the kinds of reactions they undergo are among the most important and well-studied reaction types in organic chemistry. In this chapter, we saw how to name and prepare alkyl halides, and we’ll soon make a detailed study of their substitution and elimination reactions.

Simple alkyl halides can be prepared by radical halogenation of alkanes, but mixtures of products usually result. The reactivity order of alkanes toward halogenation is identical to the stability order of radicals: R3C**·** > R2CH**·** > RCH2**·**. Alkyl halides can also be prepared from alkenes by reaction with N-bromosuccinimide (NBS) to give the product of **allylic** bromination. The NBS bromination of alkenes takes place through an intermediate allylic radical, which is stabilized by resonance.

Alcohols react with HX to form alkyl halides, but the reaction works well only for tertiary alcohols, R3COH. Primary and secondary alkyl halides are normally prepared from alcohols using either SOCl2, PBr3, or HF in pyridine. Alkyl halides react with magnesium in ether solution to form organomagnesium halides, called **Grignard reagents (RMgX)**, which are both nucleophilic and strongly basic.

Alkyl halides also react with lithium metal to form organolithium reagents, RLi. In the presence of CuI, these form diorganocoppers, or **Gilman reagents (LiR2Cu)**. Gilman reagents react with organohalides to yield coupled hydrocarbon products.

Nucleophilic substitutions are of two types: **SN2 reactions** and **SN1 reactions**. In the SN2 reaction, the entering nucleophile approaches the halide from a direction 180° away from the leaving group, resulting in an umbrella-like inversion of configuration at the carbon atom. The reaction is kinetically **second-order** and is strongly inhibited by increasing steric bulk of the reactants. Thus, SN2 reactions are favored for primary and secondary substrates.

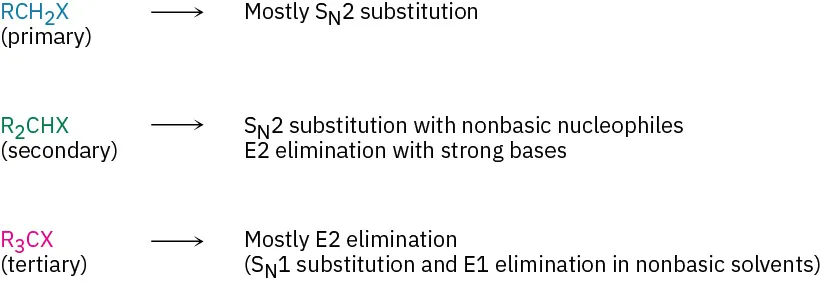
In the SN1 reaction, the substrate spontaneously dissociates to a carbocation in a slow **rate-limiting step**, followed by a rapid reaction with the nucleophile. As a result, SN1 reactions are kinetically **first-order** and take place with substantial racemization of configuration at the carbon atom. They are most favored for tertiary substrates. Both SN1 and SN2 reactions occur in biological pathways, although the leaving group is typically a diphosphate ion rather than a halide.

Eliminations of alkyl halides to yield alkenes occur by three mechanisms: **E2 reactions**, **E1 reactions**, and **E1cB reactions**, which differ in the timing of C–H and C–X bond-breaking. In the E2 reaction, C–H and C–X bond-breaking occur simultaneously when a base abstracts H+ from one carbon while the leaving group departs from the neighboring carbon. The reaction takes place preferentially through an **anti periplanar** transition state in which the four reacting atoms—hydrogen, two carbons, and leaving group—are in the same plane. The reaction shows **second-order kinetics** and a **deuterium isotope effect**, and occurs when a secondary or tertiary substrate is treated with a strong base. These elimination reactions usually give a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev’s rule**).

In the E1 reaction, C–X bond-breaking occurs first. The substrate dissociates to yield a carbocation in the slow rate-limiting step before losing H+ from an adjacent carbon in a second step. The reaction shows **first-order kinetics** and no deuterium isotope effect and occurs when a tertiary substrate reacts in polar, nonbasic solution.

In the E1cB reaction, C–H bond-breaking occurs first. A base abstracts a proton to give a carbanion, followed by loss of the leaving group from the adjacent carbon in a second step. The reaction is favored when the leaving group is two carbons removed from a carbonyl, which stabilizes the intermediate anion by resonance. Biological elimination reactions typically occur by this E1cB mechanism.

In general, substrates react in the following way:



Spectrometry

Finding the structure of a new molecule, whether a small one synthesized in the laboratory or a large protein found in living organisms, is central to the progression of chemistry and biochemistry. The structure of an organic molecule is usually determined using spectroscopic methods, including mass spectrometry and infrared spectroscopy. **Mass spectrometry (MS)** tells the molecular weight and formula of a molecule; **infrared (IR) spectroscopy** identifies the functional groups present in the molecule.

In small-molecule mass spectrometry, molecules are first ionized by collision with a high-energy electron beam. The ions then fragment into smaller pieces, which are magnetically sorted according to their mass-to-charge ratio (m/z). The ionized sample molecule is called the molecular ion, M+, and measurement of its mass gives the molecular weight of the sample. Structural clues about unknown samples can be obtained by interpreting the fragmentation pattern of the molecular ion. Mass-spectral fragmentations are usually complex, however, and interpretation is often difficult. In biological mass spectrometry, molecules are protonated using either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), and the protonated molecules are separated by time-of-flight (TOF) mass analysis.

Infrared spectroscopy involves the interaction of a molecule with **electromagnetic radiation**. When an organic molecule is irradiated with infrared energy, certain **frequencies** are absorbed by the molecule. The frequencies absorbed correspond to the amounts of energy needed to increase the amplitude of specific molecular vibrations such as bond stretching and bending. Since every functional group has a characteristic combination of bonds, every functional group has a characteristic set of infrared absorptions. For example, the terminal alkyne ≡C–H bond absorbs IR radiation of 3300 cm–1, and the alkene C═C bond absorbs in the range 1640 to 1680 cm–1. By observing which frequencies of infrared radiation are absorbed by a molecule and which are not, it’s possible to determine the functional groups a molecule contains.

**Nuclear magnetic resonance spectroscopy**, or **NMR**, is the most valuable of the numerous spectroscopic techniques used for structure determination. Although we focused in this chapter on NMR applications with small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

When magnetic nuclei, such as 1H and 13C, are placed in a strong magnetic field, their spins orient either with or against the field. On irradiation with radiofrequency (rf) waves, energy is absorbed and the nuclei “spin-flip” from the lower energy state to the higher energy state. This absorption of rf energy is detected, amplified, and displayed as an NMR spectrum.

Each electronically distinct 1H or 13C nucleus in a molecule comes into resonance at a slightly different value of the applied field, thereby producing a unique absorption signal. The exact position of each peak is called the **chemical shift**. Chemical shifts are caused by electrons setting up tiny local magnetic fields that **shield** a nearby nucleus from the applied field.

The NMR chart is calibrated in **delta units (δ)**, where 1 δ = 1 ppm of spectrometer frequency. Tetramethylsilane (TMS) is used as a reference point because it shows both 1H and 13C absorptions at unusually high values of applied magnetic field. The TMS absorption occurs on the right-hand (**upfield**) side of the chart and is arbitrarily assigned a value of 0 δ.

13C spectra are run on Fourier-transform NMR (**FT–NMR**) spectrometers using broadband decoupling of proton spins so that each chemically distinct carbon shows a single unsplit resonance line. As with 1H NMR, the chemical shift of each 13C signal provides information about a carbon’s chemical environment in the sample. In addition, the number of protons attached to each carbon can be determined using the DEPT–NMR technique.

In 1H NMR spectra, the area under each absorption peak can be electronically **integrated** to determine the relative number of hydrogens responsible for each peak. In addition, neighboring nuclear spins can **couple**, causing the **spin–spin splitting** of NMR peaks into **multiplets**. The NMR signal of a hydrogen neighbored by n equivalent adjacent hydrogens splits into n + 1 peaks (the **n + 1 rule**) with **coupling constant J**.

The unsaturated compounds we’ve looked at previously have had only one double bond, but many compounds have numerous sites of unsaturation, which gives them some distinctive properties. Many such compounds are common in nature, including pigments and hormones.

A **conjugated** diene or other compound is one that contains alternating double and single bonds. One characteristic of conjugated dienes is that they are more stable than their nonconjugated counterparts. This stability can be explained by a molecular orbital description in which four p atomic orbitals combine to form four π molecular orbitals. Only the two bonding orbitals are occupied; the two antibonding orbitals are unoccupied. A π bonding interaction in the lowest-energy MO introduces some partial double-bond character between carbons 2 and 3, thereby strengthening the C2–C3 bond and stabilizing the molecule.

Conjugated dienes undergo several reactions not observed for nonconjugated dienes. One is the 1,4-addition of electrophiles. When a conjugated diene is treated with an electrophile such as HCl, **1,2-** and **1,4-addition** products are formed. Both result from the same resonance-stabilized allylic carbocation intermediate and are produced in varying amounts depending on the reaction conditions. The 1,2 adduct is usually formed faster and is said to be the product of **kinetic control**. The 1,4 adduct is usually more stable and is said to be the product of **thermodynamic control**.

Another reaction unique to conjugated dienes is **Diels–Alder cycloaddition**. Conjugated dienes react with electron-poor alkenes (**dienophiles**) in a single step through a cyclic transition state to yield a cyclohexene product. The reaction is stereospecific, meaning that only a single product stereoisomer is formed, and can occur only if the diene is able to adopt an s-cis conformation.

**Ultraviolet (UV) spectroscopy** is a method of structure determination applicable specifically to conjugated π-electron systems. When a conjugated molecule is irradiated with ultraviolet light, energy absorption occurs and a π electron is promoted from the **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**. For 1,3-butadiene, radiation of λmax = 217 nm is required. The greater the extent of conjugation, the less the energy needed and the longer the wavelength of radiation required.

Aromatic rings are a common part of many biological structures and are particularly important in nucleic acid chemistry and in the chemistry of several amino acids. In this chapter, we’ve seen how and why aromatic compounds are different from such apparently related compounds as cycloalkenes.

The word **aromatic** is used for historical reasons to refer to the class of compounds related structurally to benzene. Aromatic compounds are systematically named according to IUPAC rules, but many common names are also used. Disubstituted benzenes are referred to as **ortho** (1,2 disubstituted), **meta** (1,3 disubstituted), or **para** (1,4 disubstituted) derivatives. The C6H5– unit itself is referred to as a **phenyl** group, and the C6H5CH2– unit is a **benzyl** group.

Benzene is described by valence-bond theory as a resonance hybrid of two equivalent structures and is described by molecular orbital theory as a planar, cyclic, conjugated molecule with six *π* electrons. According to the **Hückel rule**, a molecule must have **4*n*** + **2 *π* electrons**, where *n* = 0, 1, 2, 3, and so on, to be aromatic. Planar, cyclic, conjugated molecules with other numbers of *π* electrons are **antiaromatic**.

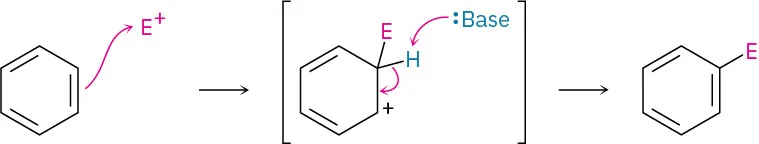
Other substances besides benzene-like compounds are also aromatic. The cyclopentadienyl anion and the cycloheptatrienyl cation, for instance, are aromatic ions. Pyridine and pyrimidine are six-membered, nitrogen-containing, aromatic **heterocycles**. Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles. Naphthalene, quinoline, indole, and many others are polycyclic aromatic compounds.

Aromatic compounds have the following characteristics:

* Aromatic compounds are cyclic, planar, and conjugated.
* Aromatic compounds are unusually stable. Benzene, for instance, has a heat of hydrogenation 150 kJ/mol less than we might expect for a cyclic triene.
* Aromatic compounds react with electrophiles to give substitution products, in which cyclic conjugation is retained, rather than addition products, in which conjugation is destroyed.
* Aromatic compounds have 4*n* + 2 *π* electrons, which are delocalized over the ring.

We’ve continued the coverage of aromatic molecules in this chapter, shifting focus to concentrate on reactions. In particular, we’ve looked at the relationship between aromatic structure and reactivity, a relationship critical to understanding how numerous biological molecules and pharmaceutical agents are synthesized and why they behave as they do.

An **electrophilic aromatic substitution reaction** takes place in two steps—initial reaction of an electrophile, **E+**, with the aromatic ring, followed by loss of H+ from the resonance-stabilized carbocation intermediate to regenerate the aromatic ring.



Many variations of the reaction can be carried out, including halogenation, nitration, and sulfonation. **Friedel–Crafts alkylation** and **acylation** reactions, which involve reaction of an aromatic ring with carbocation electrophiles, are particularly useful. They are limited, however, by the fact that the aromatic ring must be at least as reactive as a halobenzene. In addition, polyalkylation and carbocation rearrangements often occur in Friedel–Crafts alkylation.

Substituents on the benzene ring affect both the reactivity of the ring toward further substitution and the orientation of that substitution. Groups can be classified as ortho- and para-directing activators, ortho- and para-directing deactivators, or meta-directing deactivators. Substituents influence aromatic rings by a combination of resonance and inductive effects. **Resonance effects** are transmitted through *π* bonds; **inductive effects** are transmitted through *σ* bonds.

Halobenzenes undergo **nucleophilic aromatic substitution** through either of two mechanisms. If the halobenzene has a strongly electron-withdrawing substituent in the ortho or para position, substitution occurs by addition of a nucleophile to the ring, followed by elimination of halide from the intermediate anion. If the halobenzene is not activated by an electron-withdrawing substituent, substitution can occur by elimination of HX to give a **benzyne**, followed by addition of a nucleophile.

The benzylic position of an alkylbenzene can be brominated by reaction with *N*-bromosuccinimide, and the entire side chain can be degraded to a carboxyl group by oxidation with aqueous KMnO4. Aromatic rings can also be reduced to cyclohexanes by hydrogenation over a platinum or rhodium catalyst, and aryl alkyl ketones are reduced to alkylbenzenes by hydrogenation over a platinum catalyst.

**Alcohols** are among the most versatile of all organic compounds. They occur widely in nature, are important industrially, and have an unusually rich chemistry. The most widely used methods of alcohol synthesis start with carbonyl compounds. Aldehydes, esters, and carboxylic acids are reduced by reaction with LiAlH4 to give primary alcohols (RCH2OH); ketones are reduced to yield secondary alcohols (R2CHOH).

Alcohols are also prepared by reaction of carbonyl compounds with Grignard reagents, RMgX. Addition of a Grignard reagent to formaldehyde yields a primary alcohol, addition to an aldehyde yields a secondary alcohol, and addition to a ketone or an ester yields a tertiary alcohol. The Grignard reaction is limited by the fact that Grignard reagents can’t be prepared from alkyl halides that contain reactive functional groups in the same molecule. This problem can sometimes be avoided by **protecting** the interfering functional group. Alcohols are often protected by formation of trialkylsilyl ethers.

Alcohols undergo many reactions and can be converted into many other functional groups. They can be dehydrated to give alkenes by treatment with POCl3 and can be transformed into alkyl halides by treatment with PBr3 or SOCl2. Furthermore, alcohols are weakly acidic (pKa ≈ 16–18) and react with strong bases and with alkali metals to form **alkoxide anions**, which are used frequently in organic synthesis. Perhaps the most important reaction of alcohols is their oxidation to carbonyl compounds. Primary alcohols yield either aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols are not normally oxidized.

**Phenols** are aromatic counterparts of alcohols but are more acidic (pKa ≈ 10) because their corresponding **phenoxide anions** are resonance stabilized by delocalization of the negative charge into the aromatic ring. Substitution of the aromatic ring by an electron-withdrawing group increases phenol acidity, and substitution by an electron-donating group decreases acidity. Phenols can be oxidized to **quinones**, and quinones can be reduced back to **hydroquinones**.

This chapter has finished the coverage of functional groups with C–O and C–S single bonds, focusing primarily on ethers, epoxides, thiols, and sulfides. **Ethers** are compounds that have two organic groups bonded to the same oxygen atom, ROR′. The organic groups can be alkyl, vinylic, or aryl, and the oxygen atom can be in a ring or in an open chain. Ethers are prepared by either Williamson ether synthesis, which involves SN2 reaction of an alkoxide ion with a primary alkyl halide, or the **alkoxymercuration** reaction, which involves Markovnikov addition of an alcohol to an alkene.

Ethers are inert to most reagents but react with strong acids to give cleavage products. Both HI and HBr are often used. The cleavage reaction takes place by an SN2 mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen, but by an SN1 or E1 mechanism if one of the alkyl groups bonded to oxygen is tertiary.

Epoxides are cyclic ethers with a three-membered, oxygen-containing ring. Because of the strain in the ring, epoxides undergo a cleavage reaction with both acids and bases. Acid-catalyzed ring-opening occurs with a regiochemistry that depends on the structure of the epoxide. Cleavage of the C–O bond at the less highly substituted site occurs if both epoxide carbons are primary or secondary, but cleavage of the C–O bond to the more highly substituted site occurs if one of the epoxide carbons is tertiary. Base-catalyzed epoxide ring-opening occurs by SN2 reaction of a nucleophile at the less hindered epoxide carbon.

**Thiols**, the sulfur analogs of alcohols, are usually prepared by SN2 reaction of an alkyl halide with thiourea. Mild oxidation of a thiol yields a **disulfide**, and mild reduction of a disulfide returns the thiol. **Sulfides**, the sulfur analogs of ethers, are prepared by an SN2 reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are more nucleophilic than ethers and can be alkylated by reaction with a primary alkyl halide to yield a **sulfonium ion**. Sulfides can also be oxidized to **sulfoxides** and to **sulfones**.

Aldehydes and ketones are among the most important of all functional groups, both in the chemical industry and in biological pathways. In this chapter, we’ve looked at some of their typical reactions. Aldehydes are normally prepared in the laboratory by oxidation of primary alcohols or by partial reduction of esters. Ketones are similarly prepared by oxidation of secondary alcohols.

The **nucleophilic addition reaction** is the most common general reaction type for aldehydes and ketones. Many different kinds of products can be prepared by nucleophilic additions. Aldehydes and ketones are reduced by NaBH4 or LiAlH4 to yield primary and secondary alcohols, respectively. Addition of Grignard reagents to aldehydes and ketones also gives alcohols (secondary and tertiary, respectively), and addition of HCN yields **cyanohydrins**. Primary amines add to carbonyl compounds yielding **imines**, or **Schiff bases**, and secondary amines yield **enamines**. Reaction of an aldehyde or ketone with hydrazine and base gives an alkane (the **Wolff–Kishner reaction**). Alcohols add to carbonyl groups to yield **acetals**, which are valuable as protecting groups. Phosphorus **ylides** add to aldehydes and ketones in the **Wittig reaction** to give alkenes.

α,β-Unsaturated aldehydes and ketones often react with nucleophiles to give the product of **conjugate addition**, or **1,4-addition**. Particularly useful are the conjugate addition of an amine and the conjugate addition of an organic group by reaction with a diorganocopper reagent.

IR spectroscopy is helpful for identifying aldehydes and ketones. Carbonyl groups absorb in the IR range 1660 to 1770 cm–1, with the exact position highly diagnostic of the kind of carbonyl group present in the molecule. 13C NMR spectroscopy is also useful for aldehydes and ketones because their carbonyl carbons show resonances in the 190 to 215 δ range. 1H NMR is useful for aldehyde –CHO protons, which absorb near 10 δ. Aldehydes and ketones undergo two characteristic kinds of fragmentation in the mass spectrometer: α cleavage and McLafferty rearrangement.

**Carboxylic acids** are among the most useful building blocks for synthesizing other molecules, both in nature and in the laboratory. Thus, an understanding of their properties and reactions is fundamental to understanding biological chemistry. In this chapter, we’ve looked both at acids and at their close relatives, **nitriles (𝐑𝐂≡𝐍)**.

Carboxylic acids are named systematically by replacing the terminal -e of the corresponding alkane name with -oic acid. Like aldehydes and ketones, the carbonyl carbon atom is sp2-hybridized; like alcohols, carboxylic acids are associated through hydrogen-bonding and therefore have high boiling points.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids such as HCl, carboxylic acids dissociate much more readily than alcohols because the resultant carboxylate ions are stabilized by resonance between two equivalent forms.

Most carboxylic acids have pKa values near 5, but the exact pKa of a given acid depends on structure. Carboxylic acids substituted by electron-withdrawing groups are more acidic (have a lower pKa) because their carboxylate ions are stabilized. Carboxylic acids substituted by electron-donating groups are less acidic (have a higher pKa) because their carboxylate ions are destabilized. The extent of dissociation of a carboxylic acid in a buffered solution of a given pH can be calculated with the Henderson–Hasselbalch equation. Inside living cells, where the physiological pH = 7.3, carboxylic acids are entirely dissociated and exist as their carboxylate anions.

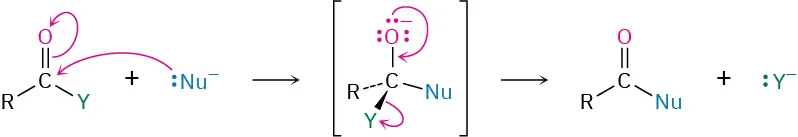
Methods of synthesis for carboxylic acids include (**1**) oxidation of alkylbenzenes, (**2**) oxidation of primary alcohols or aldehydes, (**3**) reaction of Grignard reagents with CO2 **(carboxylation)**, and (**4**) hydrolysis of nitriles. General reactions of carboxylic acids include (**1**) loss of the acidic proton, (**2**) nucleophilic acyl substitution at the carbonyl group, (**3**) substitution on the α carbon, and (**4**) reduction.

Nitriles are similar in some respects to carboxylic acids and are prepared either by SN2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar C≡N bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with Grignard reagents to yield ketones.

Carboxylic acids and nitriles are easily distinguished spectroscopically. Acids show a characteristic IR absorption at 2500 to 3300 cm–1 due to the O−H bond and another at 1710 to 1760 cm–1 due to the C═O bond; nitriles have an absorption at 2250 cm–1. Acids also show 13C NMR absorptions at 165 to 185 δ and 1H NMR absorptions near 12 δ. Nitriles have a 13C NMR absorption in the range 115 to 130 δ.

**Carboxylic acid derivatives**—compounds in which the –OH group of a carboxylic acid has been replaced by another substituent—are among the most widely occurring of all molecules and are involved in almost all biological pathways. In this chapter, we covered the chemistry necessary for understanding them and thus also necessary for understanding living organisms. **Acid halides, acid anhydrides, esters,** and **amides** are the most common such derivatives in the laboratory; **thioesters** and **acyl phosphates** are common in biological molecules.

The chemistry of carboxylic acid derivatives is dominated by the **nucleophilic acyl substitution reaction**. Mechanistically, these substitutions take place by addition of a nucleophile to the polar carbonyl group of the acid derivative to give a tetrahedral intermediate, followed by expulsion of a leaving group.



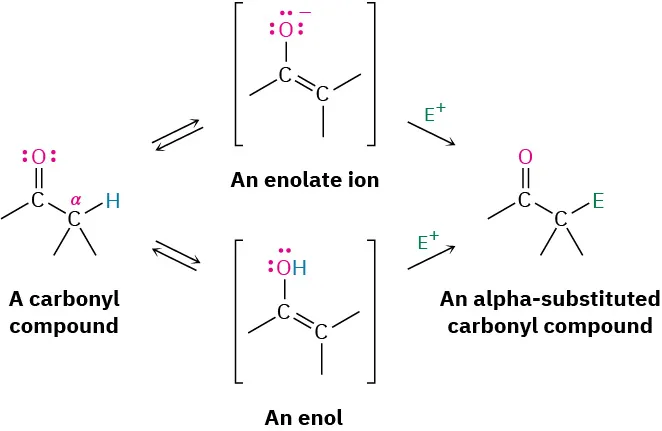
The reactivity of an acid derivative toward substitution depends both on the steric environment near the carbonyl group and on the electronic nature of the substituent, Y. The reactivity order is acid halide > acid anhydride > thioester > ester > amide.

The most common reactions of carboxylic acid derivatives are substitution by water to yield an acid (hydrolysis), by an alcohol to yield an ester (alcoholysis), by an amine to yield an amide (aminolysis), by hydride ion to yield an alcohol (reduction), and by an organomagnesium halide to yield an alcohol (Grignard reaction).

**Step-growth polymers**, such as polyamides and polyesters, are prepared by reactions between difunctional molecules. Polyamides (nylons) are formed by reaction between a diacid and a diamine; polyesters are formed from a diacid and a diol.

IR spectroscopy is a valuable tool for the structural analysis of acid derivatives. Acid chlorides, anhydrides, esters, and amides all show characteristic IR absorptions that can be used to identify these functional groups.

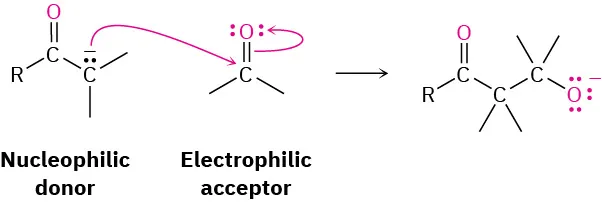
The *α*-substitution reaction of a carbonyl compound through either an **enol** or **enolate ion** intermediate is one of the four fundamental reaction types in carbonyl-group chemistry.



Carbonyl compounds are in an equilibrium with their enols, a process called keto–enol tautomerism. Although enol **tautomers** are normally present to only a small extent at equilibrium and can’t usually be isolated in pure form, they nevertheless contain a highly nucleophilic double bond and react with electrophiles in an ***α*-substitution reaction**. An example is the *α* halogenation of ketones on treatment with Cl2, Br2, or I2 in acid solution. Alpha bromination of carboxylic acids can be similarly accomplished by the Hell–Volhard–Zelinskii (HVZ) reaction, in which an acid is treated with Br2 and PBr3. The *α*-halogenated products can then undergo base-induced E2 elimination to yield *α*,*β*-unsaturated carbonyl compounds.

Alpha hydrogen atoms of carbonyl compounds are weakly acidic and can be removed by strong bases, such as lithium diisopropylamide (LDA), to yield nucleophilic enolate ions. The most useful reaction of enolate ions is their SN2 alkylation with alkyl halides. The **Malonic ester synthesis** converts an alkyl halide into a carboxylic acid with the addition of two carbon atoms (RX → RCH2CO2H). Similarly, the **acetoacetic ester synthesis** converts an alkyl halide into a methyl ketone with the addition of three carbon atoms (RX → RCH2COCH3). In addition, many carbonyl compounds, including ketones, esters, and nitriles, can be directly alkylated by treatment with LDA and an alkyl halide.

In this chapter, we’ve discussed the fourth and last of the common carbonyl-group reactions—the carbonyl condensation. A **carbonyl condensation reaction** takes place between two carbonyl partners and involves both nucleophilic addition and *α*-substitution processes. One carbonyl partner is converted by base into a nucleophilic enolate ion, which then adds to the electrophilic carbonyl group of the second partner. The first partner thus undergoes an *α* substitution, while the second undergoes a nucleophilic addition.



The **aldol reaction** is a carbonyl condensation that occurs between two aldehyde or ketone molecules. Aldol reactions are reversible, leading first to *β*-hydroxy aldehydes/ketones and then to *α*,*β*-unsaturated products after dehydration. Mixed aldol condensations between two different aldehydes or ketones generally give a mixture of all four possible products. A mixed reaction can be successful, however, if one of the two partners is an unusually good donor (ethyl acetoacetate, for instance) or if it can act only as an acceptor (formaldehyde and benzaldehyde, for instance). Intramolecular aldol condensations of 1,4- and 1,5-diketones are also successful and provide a good way to make five- and six-membered rings.

The **Claisen condensation reaction** is a carbonyl condensation that occurs between two ester components and gives a *β*-keto ester product. Mixed Claisen condensations between two different esters are successful only when one of the two partners has no acidic *α* hydrogens (ethyl benzoate and ethyl formate, for instance) and thus can function only as the acceptor partner. Intramolecular Claisen condensations, called **Dieckmann cyclization reactions**, yield five- and six-membered cyclic *β*-keto esters starting from 1,6- and 1,7-diesters.

The conjugate addition of a carbon nucleophile to an *α*,*β*-unsaturated acceptor is known as the **Michael reaction**. The best Michael reactions take place between relatively acidic donors (*β*-keto esters or *β*-diketones) and unhindered *α*,*β*-unsaturated acceptors. Enamines, prepared by reaction of a ketone with a disubstituted amine, are also good Michael donors in the Stork enamine reaction.

Carbonyl condensation reactions are widely used in synthesis. One example of their versatility is the **Robinson annulation reaction**, which leads to the formation of a substituted cyclohexenone. Treatment of a *β*-diketone or *β*-keto ester with an *α*,*β*-unsaturated ketone leads first to a Michael addition, which is followed by intramolecular aldol cyclization. Condensation reactions are also used widely in nature for the biosynthesis of such molecules as fats and steroids.

We’ve now seen all the common functional groups that occur in organic and biological chemistry. Of those groups, amines are among the most abundant and have among the richest chemistry. In addition to proteins and nucleic acids, the majority of pharmaceutical agents contain amine functional groups and many of the common coenzymes necessary for biological reactions are amines.

**Amines** are organic derivatives of ammonia. They are named in the IUPAC system either by adding the suffix -amine to the name of the alkyl substituent or by considering the amino group as a substituent on a more complex parent molecule.

The chemistry of amines is dominated by the lone-pair electrons on nitrogen, which makes amines both basic and nucleophilic. The basicity of **arylamines** is generally lower than that of **alkylamines** because the nitrogen lone-pair electrons are delocalized by interaction with the aromatic π system. Electron-withdrawing substituents on the aromatic ring further weaken the basicity of a substituted aniline, while electron-donating substituents increase basicity. Alkylamines are sufficiently basic that they exist almost entirely in their protonated form at the physiological pH of 7.3.

**Heterocyclic amines** are compounds that contain one or more nitrogen atoms as part of a ring. Saturated heterocyclic amines usually have the same chemistry as their open-chain analogs, but unsaturated heterocycles such as pyrrole, imidazole, pyridine, and pyrimidine are aromatic. All four are unusually stable, and all undergo aromatic substitution on reaction with electrophiles. Pyrrole is nonbasic because its nitrogen lone-pair electrons are part of the aromatic π system. Fused-ring heterocycles such as quinoline, isoquinoline, indole, and purine are also commonly found in biological molecules.

Arylamines are prepared by nitration of an aromatic ring followed by reduction. Alkylamines are prepared by SN2 reaction of ammonia or an amine with an alkyl halide or by the **Gabriel amine synthesis**. Amines can also be prepared by a number of reductive methods, including LiAlH4 reduction of amides, nitriles, and azides. Also important is the **reductive amination** reaction in which a ketone or an aldehyde is treated with an amine in the presence of a reducing agent such as NaBH4. In addition, amines result from **Hofmann** and **Curtius rearrangements** of carboxylic acid derivatives. Both methods involve migration of the –R group bonded to the carbonyl carbon and yield a product that has one less carbon atom than the starting material.

Many of the reactions of amines are familiar from past chapters. Thus, amines react with alkyl halides in SN2 reactions and with acid chlorides in nucleophilic acyl substitution reactions. Amines also undergo E2 elimination to yield alkenes if they are first quaternized by treatment with iodomethane and then heated with silver oxide, a process called the **Hofmann elimination**.

Arylamines are converted by diazotization with nitrous acid into **arenediazonium salts**, ArN2+ X–. The diazonio group can then be replaced by many other substituents by the **Sandmeyer reaction** to give a wide variety of substituted aromatic compounds. Aryl chlorides, bromides, iodides, and nitriles can be prepared from arenediazonium salts, as can arenes and phenols. In addition to their reactivity toward substitution reactions, diazonium salts undergo coupling with phenols and arylamines to give brightly colored **azo compounds**.

Now that we’ve now seen all the common functional groups and reaction types, our focus has changed to looking at the major classes of biological molecules. **Carbohydrates** are polyhydroxy aldehydes and ketones. They are classified according to the number of carbon atoms and the kind of carbonyl group they contain. Glucose, for example, is an aldohexose, a six-carbon aldehydo sugar. **Monosaccharides** are further classified as either **D sugars** or **L sugars**, depending on the stereochemistry of the chirality center farthest from the carbonyl group. Carbohydrate stereochemistry is frequently depicted using **Fischer projections**, which represent a chirality center as the intersection of two crossed lines.

Monosaccharides normally exist as cyclic hemiacetals rather than as open-chain aldehydes or ketones. The hemiacetal linkage results from reaction of the carbonyl group with an –OH group three or four carbon atoms away. A five-membered cyclic hemiacetal is called a **furanose**, and a six-membered cyclic hemiacetal is called a **pyranose**. Cyclization leads to the formation of a new chirality center called the **anomeric center** and the production of two diastereomeric hemiacetals called **alpha (α) and beta (β) anomers**.

Much of the chemistry of monosaccharides is the familiar chemistry of alcohols and aldehydes/ketones. Thus, the hydroxyl groups of carbohydrates form esters and ethers. The carbonyl group of a monosaccharide can be reduced with NaBH4 to form an **alditol**, oxidized with aqueous Br2 to form an **aldonic acid**, oxidized with HNO3 to form an **aldaric acid**, oxidized enzymatically to form a **uronic acid**, or treated with an alcohol in the presence of acid to form a **glycoside**. Monosaccharides can also be chain-lengthened by the multistep **Kiliani–Fischer synthesis** and can be chain-shortened by **Wohl degradation**.

**Disaccharides** are complex carbohydrates in which simple sugars are linked by a glycoside bond between the **anomeric center** of one unit and a hydroxyl of the second unit. The sugars can be the same, as in maltose and cellobiose, or different, as in lactose and sucrose. The glycosidic bond can be either α (maltose) or β (cellobiose, lactose) and can involve any hydroxyl of the second sugar. A 1→4 link is most common (cellobiose, maltose), but others such as 1→2 (sucrose) are also known. **Polysaccharides**, such as cellulose, starch, and glycogen, are used in nature as structural materials, as a means of long-term energy storage, and as cell-surface markers.

**Proteins** and **peptides** are large biomolecules made of **α-amino acid residues** linked together by amide, or peptide, bonds. Twenty amino acids are commonly found in proteins, and all except glycine have stereochemistry similar to that of L sugars. In neutral solution, amino acids exist as dipolar **zwitterions**.

Amino acids can be synthesized in racemic form by several methods, including ammonolysis of an α-bromo acid, alkylation of diethyl acetamidomalonate, and reductive amination of an α-keto acid. Alternatively, an enantioselective synthesis of amino acids can be carried out using a chiral hydrogenation catalyst.

Determining the structure of a peptide or protein begins with amino acid analysis. The peptide is hydrolyzed to its constituent α-amino acids, which are separated and identified. Next, the peptide is sequenced. **Edman degradation** by treatment with phenyl isothiocyanate (PITC) cleaves one residue from the N terminus of the peptide and forms an easily identifiable phenylthiohydantoin (PTH) derivative of the **N-terminal amino acid**. An automated series of Edman degradations can sequence peptide chains up to 50 residues in length.

Peptide synthesis involves the use of protecting groups. An N-protected amino acid with a free –CO2H group is coupled using DCC or EDC to an O-protected amino acid with a free –NH2 group. Amide formation occurs, the protecting groups are removed, and the sequence is repeated. Amines are usually protected as their tert-butyloxycarbonyl (Boc) or fluorenylmethyloxycarbonyl (Fmoc) derivatives; acids are usually protected as esters. The synthesis is often carried out by the Merrifield solid-phase method, in which the peptide is bonded to insoluble polymer beads.

Proteins have four levels of structure. **Primary structure** describes a protein’s amino acid sequence; **secondary structure** describes how segments of the protein chain orient into regular patterns—either **α helix** or **β-pleated sheet**; **tertiary structure** describes how the entire protein molecule coils into an overall three-dimensional shape; and **quaternary structure** describes how individual protein molecules aggregate into larger structures.

Proteins are classified as either globular or fibrous. **Fibrous proteins** such as α-keratin are tough, rigid, and water-insoluble; **globular proteins** such as myoglobin are water-soluble and roughly spherical in shape. Many globular proteins are **enzymes**—substances that act as catalysts for biological reactions. Enzymes are grouped into six classes according to the kind of reaction they catalyze. In addition to their protein part, many enzymes contain **cofactors**, which can be either metal ions or small organic molecules called **coenzymes**.

**Lipids** are the naturally occurring materials isolated from plants and animals by extraction with a nonpolar organic solvent. Animal fats and vegetable oils are the most widely occurring lipids. Both are **triacylglycerols**—triesters of glycerol with long-chain **fatty acids**. Animal fats are usually saturated, whereas vegetable oils usually have unsaturated fatty acid residues.

**Phospholipids** are important constituents of cell membranes and are of two kinds. Glycerophospholipids, such as phosphatidylcholine and phosphatidylethanolamine, are closely related to fats in that they have a glycerol backbone esterified to two fatty acids (one saturated and one unsaturated) and to one phosphate ester. Sphingomyelins have the amino alcohol sphingosine for their backbone.

**Eicosanoids** and **terpenoids** are still other classes of lipids. Eicosanoids, of which prostaglandins are the most abundant kind, are derived biosynthetically from arachidonic acid, are found in all body tissues, and have a wide range of physiological activity. Terpenoids are often isolated from the essential oils of plants, have an immense diversity of structure, and are produced biosynthetically from the five-carbon precursor isopentenyl diphosphate (IPP). Isopentenyl diphosphate is itself biosynthesized from 3 equivalents of acetate in the mevalonate pathway.

**Steroids** are plant and animal lipids with a characteristic tetracyclic carbon skeleton. Like the eicosanoids, steroids occur widely in body tissues and have a large variety of physiological activities. Steroids are closely related to terpenoids and arise biosynthetically from the triterpenoid lanosterol. Lanosterol, in turn, arises from cationic cyclization of the acyclic hydrocarbon squalene.

**DNA (deoxyribonucleic acid)** and **RNA (ribonucleic acid)** are biological polymers that act as chemical carriers of an organism’s genetic information. Enzyme-catalyzed hydrolysis of nucleic acids yields **nucleotides**, the monomer units from which RNA and DNA are constructed. Further enzyme-catalyzed hydrolysis of the nucleotides yields **nucleosides** plus phosphate. Nucleosides, in turn, consist of a purine or pyrimidine base linked to the C1 of an aldopentose sugar—ribose in RNA and 2-deoxyribose in DNA. The nucleotides are joined by phosphate links between the 5′ phosphate of one nucleotide and the 3′ hydroxyl on the sugar of another nucleotide.

Molecules of DNA consist of two complementary polynucleotide strands held together by hydrogen bonds between heterocyclic bases on the different strands and coiled into a **double helix**. Adenine and thymine form hydrogen bonds to each other, as do cytosine and guanine.

Three processes take place in deciphering the genetic information of DNA:

* **Replication** of DNA is the process by which identical DNA copies are made. The DNA double helix unwinds, complementary deoxyribonucleotides line up in order, and two new DNA molecules are produced.
* **Transcription** is the process by which RNA is produced to carry genetic information from the nucleus to the ribosomes. A short segment of the DNA double helix unwinds, and complementary ribonucleotides line up to produce **messenger RNA (mRNA)**.
* **Translation** is the process by which mRNA directs protein synthesis. Each mRNA is divided into **codons**, ribonucleotide triplets that are recognized by small amino acid–carrying molecules of **transfer RNA (tRNA)**, which deliver the appropriate amino acids needed for protein synthesis.

Sequencing of DNA is carried out by the **Sanger dideoxy method**, and small DNA segments can be synthesized in the laboratory by automated instruments. Small amounts of DNA can be amplified by factors of 106 using the **polymerase chain reaction (PCR)**.

**Metabolism** is the sum of all chemical reactions in the body. Reactions that break down large molecules into smaller fragments are called **catabolism**, and those that build up large molecules from small pieces are called **anabolism**. Although the details of specific biochemical pathways are sometimes complex, all the reactions that occur follow the normal rules of organic chemical reactivity.

The catabolism of fats begins with digestion, in which ester bonds are hydrolyzed to give glycerol and fatty acids. The fatty acids are degraded in the four-step ***β*-oxidation pathway** by removal of two carbons at a time, yielding acetyl CoA. Catabolism of carbohydrates begins with the hydrolysis of glycoside bonds to give glucose, which is degraded in the ten-step **glycolysis** pathway. Pyruvate, the initial product of glycolysis, is then converted into acetyl CoA. Acetyl CoA next enters the eight-step **citric acid cycle**, where it is further degraded into CO2. The cycle is a closed loop of reactions in which the product of the final step (oxaloacetate) is a reactant in the first step.

Catabolism of proteins is more complex than that of fats or carbohydrates because each of the 20 different amino acids is degraded by its own unique pathway. In general, though, the amino nitrogen atoms are removed and the substances that remain are converted into compounds that enter the citric acid cycle. Most amino acids lose their nitrogen atom by **transamination**, a reaction in which the  –NH2 group of the amino acid trades places with the keto group of an *α*-keto acid such as *α*-ketoglutarate. The products are a new *α*-keto acid and glutamate.

The energy released in catabolic pathways is used in the *electron-transport chain* to make molecules of adenosine triphosphate, ATP. ATP, the final result of food catabolism, couples to and drives many otherwise unfavorable reactions.

Biomolecules are synthesized as well as degraded, but the pathways for anabolism and catabolism are not the exact reverse of one another. Fatty acids are biosynthesized from acetate by an 8-step pathway, and carbohydrates are made from pyruvate by the 11-step **gluconeogenesis** pathway.

A **pericyclic reaction** takes place in a single step through a cyclic transition state without intermediates. There are three major classes of pericyclic processes: electrocyclic reactions, cycloaddition reactions, and sigmatropic rearrangements. The stereochemistry of these reactions is controlled by the symmetry of the orbitals involved in bond reorganization.

**Electrocyclic reactions** involve the cyclization of conjugated acyclic polyenes. For example, 1,3,5-hexatriene cyclizes to 1,3-cyclohexadiene on heating. Electrocyclic reactions can occur by either **conrotatory** or **disrotatory** pathways, depending on the symmetry of the terminal lobes of the *π* system. Conrotatory cyclization requires that both lobes rotate in the same direction, whereas disrotatory cyclization requires that the lobes rotate in opposite directions. The reaction course in a specific case can be found by looking at the symmetry of the **highest occupied molecular orbital (HOMO)**.

**Cycloaddition reactions** are those in which two unsaturated molecules add together to yield a cyclic product. For example, Diels–Alder reaction between a diene (four *π* electrons) and a dienophile (two *π* electrons) yields a cyclohexene. Cycloadditions can take place either by **suprafacial** or **antarafacial** pathways. Suprafacial cycloaddition involves interaction between lobes on the same face of one component and on the same face of the second component. Antarafacial cycloaddition involves interaction between lobes on the same face of one component and on opposite faces of the other component. The reaction course in a specific case can be found by looking at the symmetry of the HOMO of one component and the **lowest unoccupied molecular orbital (LUMO)** of the other.

**Sigmatropic rearrangements** involve the migration of a *σ*-bonded group across a *π* electron system. For example, Claisen rearrangement of an allylic vinylic ether yields an unsaturated carbonyl compound, and Cope rearrangement of a 1,5-hexadiene yields an isomeric 1,5-hexadiene. Sigmatropic rearrangements can occur with either suprafacial or antarafacial stereochemistry; the selection rules for a given case are the same as those for cycloaddition reactions.

The stereochemistry of any pericyclic reaction can be predicted by counting the total number of electron pairs (bonds) involved in bond reorganization and then applying the mnemonic “**T**he **E**lectrons **C**ircle **A**round.” That is, **thermal** (ground-state) reactions involving an even number of electron pairs occur with either conrotatory or antarafacial stereochemistry. Exactly the opposite rules apply to **photochemical** (excited-state) reactions.

Synthetic polymers can be classified as either chain-growth or step-growth. Chain-growth polymers are prepared by chain-reaction polymerization of vinyl monomers in the presence of a radical, an anion, or a cation initiator. Radical polymerization is sometimes used, but alkenes such as 2-methylpropene that have electron-donating substituents on the double bond polymerize easily by a cationic route through carbocation intermediates. Similarly, monomers such as methyl *α*-cyanoacrylate that have electron-withdrawing substituents on the double bond polymerize by an anionic, conjugate addition pathway.

Copolymerization of two monomers gives a product with properties different from those of either homopolymer. **Graft copolymers** and **block copolymers** are two examples.

Alkene polymerization can be carried out in a controlled manner using a **Ziegler–Natta catalyst**. Ziegler–Natta polymerization minimizes the amount of chain branching in the polymer and leads to stereoregular chains—either **isotactic** (substituents on the same side of the chain) or **syndiotactic** (substituents on alternate sides of the chain), rather than **atactic** (substituents randomly disposed).

Step-growth polymers, the second major class of polymers, are prepared by reactions between difunctional molecules, with individual bonds in the polymer formed independently of one another. **Polycarbonates** are formed from a diester and a diol, and **polyurethanes** are formed from a diisocyanate and a diol.

The chemistry of synthetic polymers is similar to the chemistry of small molecules with the same functional groups, but the physical properties of polymers are greatly affected by size. Polymers can be classified by physical property into four groups: **thermoplastics**, **fibers**, **elastomers**, and **thermosetting resins**. The properties of each group can be accounted for by the structure, the degree of crystallinity, and the amount of cross-linking they contain.