1
Introduction

Chemistry is an old science that influences every aspect of life on earth (from toothpaste to life-saving medicines) because just about everything that we can touch and feel is made of chemicals, which is why it is known as the *mother science* or *central science*. The chemical cornucopia (a hollow basket filled with various kinds of festive materials) is truly impressive. While chemistry is, indeed, an old subject (~1000 BC), modern chemistry (Antoine-Laurent de Lavoisier (1743–1794), the ''Father of modern chemistry'') is ~230 years old, while organic synthesis is only about 150 years old. The essential feature of this central science is synthesis. The chemist who designs and completes an original and aesthetically pleasing synthesis is like the composer, artist, or poet, who with great individuality fashions new forms of beauty from the interplay of mind and spirit.

Chemistry occupies a unique middle position between physics and mathematics on the one side and biology, ecology, sociology, and economics on the other. It is said that chemistry is reducible into physics and finally mathematics. On the one hand, it deals with biology and provides explanations for how molecules determine the processes of life. On the other hand, it mingles with physics as well as mathematics, and finds explanations for chemical phenomena in the fundamental processes and particles of the universe:

> ''The greatest scientific advance of the last 50 years is the way biology is becoming a molecular science (chemistry) . . . .''

Chemistry is playing a vital role in every area of our increasingly technological society that links the familiar with the fundamental.

Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. It is the science of molecules, but organic chemistry is something more, that is, a tentative attempt to understand the chemistry of life. The task of the organic chemist is to make tools (molecules), that is, the art and science of constructing the molecules of nature available for various uses. Essentially all chemical reactions that take place in living systems, including in our own bodies, are organic reactions because the molecules of life – proteins, enzymes, vitamins, lipids, carbohydrates, and nucleic acids – all are organic compounds. All

things originating from living things are organic but anything containing carbon is also organic. The food we eat, the wood to make our homes, the clothing we wear (whether natural cotton or polyester), gasoline, rubber, plastics, medicines, pesticides, herbicides, all are made from organic compounds. We can thank organic chemistry for making our life easier in the modern age, and furthermore a responsibility lies on the shoulders of synthetic organic chemists to make life even better.

Chemistry is a vibrant subject filled with light, colors, fragrance, flavors, action, and excitement; a subject that begs to be taught by the points of inquiry method. When you picked up this book, your muscles were performing chemical reactions on sugars to give you the energy you required. As you go through this book, your eyes are using an organic compound (11-*cis*-retinal) to switch visible light into nerve impulses. Gaps between your brain cells are being bridged by simple organic molecules (neurotransmitter amines) so that nerve impulses can be passed around your brain. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus to understand structure and mechanism. Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties.

To understand organic chemistry one must be familiar with two languages. One is the structure and representation of molecules. The second is the description of the reaction mechanism in terms of curly arrows. The first is static and the second dynamic. Synthesis is considered difficult because you need to have a grasp of lots of reactions. Well, if you have an understanding of simple basic organic chemistry plus a few special ''tools'' you can do a surprising amount and enjoy the challenge. A detailed understanding of reactive intermediates is at the heart of chemical transformations, and thus of modern synthetic chemistry. The term reactive further implies a certain degree of instability of the species. Reactive intermediates are typically isolable only under special conditions, and most of the information regarding the structure and properties of reactive intermediates comes from indirect experimental evidence. Reaction mechanisms are a fundamental and most important part of organic chemistry, telling us about the interaction between electron-deficient and electron-rich species. The functional group is the site of reactivity in a molecule. By looking at the structure of the functional group, it is possible to predict the kind of reactions it will undergo.

A chemical reaction at the molecular level is an event in which two molecules collide in such a way as to break one or more of their bonds and make one or more new bonds, and hence new molecules. The sequence and timing of the bond-breaking and bond-making processes will be important to our understandings of the reactions. To find out how molecules react with each other and how to predict their reactions we need to know the *reaction mechanism*. Organic chemistry encompasses a very large number of compounds (many millions). To recognize these actors (compounds), we turn to the roles they are inclined to play in the

scientific drama staged by the multitude of chemical reactions that define organic chemistry. We begin by defining some basic terms that will be used very frequently as this subject is elaborated:

Chemical reaction: A chemical reaction is a process that leads to the transformation of one set of chemical substances into another. Classically, chemical reactions encompass changes that strictly involve the motion of electrons in the forming and breaking of chemical bonds between atoms, and can often be described by a chemical equation. A transformation results in the change of composition, constitution, and/or configuration of a compound (referred to as the *reactant* or *substrate*) by making or breaking of carbon–carbon (C–C), carbon–hydrogen (C–H), and/or carbon–heteroatom (C–X) bond(s). Chemical reactions are described with chemical equations, which graphically present the starting materials, end products, and sometimes intermediate products and reaction conditions.

Reactant or substrate: The starting material undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.

Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic, small or large, or gas, liquid, or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.

Product(s): In a chemical reaction, substances (elements and/or compounds) called *reactants* are changed into other substances (compounds and/or elements) called *products*, the final form taken by the major reactant(s) of a reaction. Product(s) are formed during chemical reactions as reagents are consumed. Products have lower energy than the reagents and are produced during the reaction according to the second law of thermodynamics.

Reaction conditions: Reaction conditions summarize the experimental details relating to how transformations are carried out in laboratory settings; the optimum environmental conditions are needed, such as temperature, pressure, time, catalysts, and solvent under which a reaction progresses smoothly.

Catalysts: Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions. A catalyst may participate in multiple chemical transformations. Catalysts that speed up the reaction are called *positive catalysts*. Substances that slow a catalyst's effect in a chemical reaction are called *inhibitors*. Substances that increase the activity of catalysts are called *promoters*, and substances that deactivate catalysts are called *catalytic poisons*. Catalytic reactions have a lower rate-limiting free energy of activation than the corresponding uncatalyzed reaction, resulting in higher reaction rate at the same temperature.

Electrophile: An electron-deficient atom, ion, or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile. In general, electrophiles (literally *electron-lover*) are positively charged or neutral species that participate in a chemical reaction by accepting an electron pair in order to bond to a nucleophile. Because electrophiles accept electrons, they are Lewis acids.

Nucleophile: An atom, ion, or molecule that has an electron pair that may be donated in bonding to an electrophile or Lewis acid; all nucleophiles are Lewis bases. **Nucleophilicity**, sometimes referred to as *nucleophile strength*, refers to a substance's nucleophilic character and is often used to compare the affinity of atoms.

The terms *nucleophile* and *electrophile* were introduced by Christopher Kelk Ingold in 1929, replacing the terms *cationoid* and *anionoid* proposed earlier by A.J. Lapworth in 1925.

1.1
Reaction Mechanism and Reaction Arrows

Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course. This is best accomplished by perceiving the reaction pathway or mechanism of a reaction. A detailed description of the changes in structure and bonding that take place during a reaction and the sequence of such events are called the *reaction mechanism*. Here, you will meet mechanisms, the dynamic language used by chemists to talk about reactions. A reaction mechanism should include a representation of plausible electron reorganization as well as the identification of any intermediate species that may be formed as the reaction progresses. Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and nonbonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a *mechanism*. In general, two kinds of curved arrows are used in drawing mechanisms. A curly arrow represents the actual movement of a pair of electrons from a filled orbital into an empty orbital, in either an intermolecular or intramolecular fashion. The tail of the arrow shows the source of the electron pair (highest occupied molecular orbital, HOMO) such as a lone pair or a pi (π) bond or a sigma (σ) bond. The head of the arrow indicates the ultimate destination of the electron-pair, which will either be an electronegative atom that can support a negative charge (a leaving group) or an empty orbital (LUMO, lowest unoccupied molecular orbital) when a new bond will be formed or an antibonding orbital (π^* or σ^*) when that bond will break.

A full head on the arrow indicates the movement or shift of an electron pair:
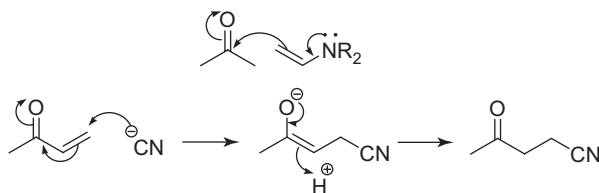
A partial head (fishhook) on the arrow indicates the shift of a single electron:

$$R_3Sn\cdot \quad Br\!-\!CR_3 \quad \longrightarrow \quad R_3SnBr \ + \ \cdot CR_3$$

Chemists also use *other arrow symbols* for other purposes, and it is essential to use them correctly. These arrows include the reaction arrow: ⟶ ; the equilibrium arrow: ⇌ ; and the resonance arrow: ⟷ .

Charge is conserved in each step of a reaction. If we start with neutral molecules and make a cation, we must make an anion too. Charge cannot be created or destroyed. If our starting materials have an overall charge plus (+) or minus (−) then the same charge must appear in the products.

It is a prerequisite for any mechanistic investigation that the reactants, all products, and the stoichiometry of the reaction are known. Many cases can be found in the literature where false mechanistic conclusions were drawn because this principle was neglected. Side products, even if very minor, can give useful hints concerning the mechanism as they are often derived from a common intermediate in a parallel reaction. Long-lived intermediates can be distinguished from products by analyzing the reaction mixture not only at the end but also as a function of the reaction time. Reactions where intermediates can be isolated in a normal workup are rather rare. More often, intermediates might be observable by spectroscopic techniques. The existence of short-lived intermediates or of intermediates occurring after the rate-determining step (RDS) can still be demonstrated by trapping reactions or by special techniques such as matrix isolation.

1.2
Properties and Characteristics of a Reaction

In an effort to understand how and why reactions of functional groups take place in the way they do, chemists try to discover just how different molecules and ions interact with each other as they come together. To this end, it is important to consider the various properties and characteristics of a reaction that may be

observed and/or measured as the reaction proceeds. The most common and useful of these are covered below.

1.2.1
Reactants and Reagents

Variations in the structure of the reactant and reagent may have a marked influence on the course of a reaction.

1.2.2
Product Selectivity

1) **Regioselectivity:** Regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions. It is often the case that addition and elimination reactions may proceed to more than one product. If one possible product out of two or more is formed preferentially, the reaction is said to be regioselective.

2) **Stereoselectivity:** Stereoselectivity is the property of a chemical reaction in which a single reactant forms an unequal mixture of stereoisomers during the non-stereospecific creation of a new stereocenter or during the non-stereospecific transformation of a preexisting one. The selectivity arises from differences in steric effects and electronic effects in the mechanistic pathways leading to the different products. Stereoselectivity can vary in degree but it can never be total since the activation energy difference between the two pathways is finite. If the reaction products are such that stereoisomers may be formed, a reaction that yields one stereoisomer preferentially is said to be stereoselective.

An **enantioselective** reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme, or a chiral reagent. The degree of relative selectivity is measured by the enantiomeric excess (ee).

A **diastereoselective** reaction is one in which one diastereomer is formed in preference to another (or in which a subset of all possible diastereomers dominates the product mixture), establishing a preferred relative stereochemistry. In this case, either two or more chiral centers are formed at once such that one relative stereochemistry is favored or a preexisting chiral center (which need not be optically pure) biases the stereochemical outcome during the creation of another. The degree of relative selectivity is measured by the diastereomeric excess (de).

Stereoconvergence can be considered an opposite of stereoselectivity, when the reaction of two different stereoisomers yields a single product stereoisomer.

3) **Stereospecificity:** In chemistry, stereospecificity is the property of a reaction mechanism that leads to different stereoisomeric reaction products from different stereoisomeric reactants, or which operates on only one (or a subset) of the stereoisomers. This term is applied to cases in which stereoisomeric

reactants behave differently in a given reaction. The quality of stereospecificity is focused on the reactants and their stereochemistry; it is concerned with the products too, but only as they provide evidence of a difference in behavior between reactants.

4) **Chemoselectivity** is the ability of a reagent to react selectively with one functional group in the presence of another similar functional group. An example of a chemoselective reagent is a reducing agent that can reduce an aldehyde and not a ketone. In cases where chemoselectivity cannot be achieved, the functional group that needs to be prevented from participating in the reaction can be protected by converting it into a derivative that is unreactive to the reagent involved. The usual strategy employed to allow for such selective differentiation of the same or similar groups is to convert each group into a masked (protected) form, which is not reactive, but can be unmasked (deprotected) to yield the group when necessary.

1.2.3
Reaction Characteristics

1) **Reaction rates:** Some reactions proceed very rapidly, and some so slowly that they are not normally observed. Among the variables that influence reaction rates are temperature (reactions are usually faster at a higher temperature), solvent, and reactant/reagent concentrations. Useful information about reaction mechanisms may be obtained by studying the manner in which the rate of a reaction changes as the concentrations of the reactant and reagents are varied. This field of study is called *kinetics*.

2) **Intermediates:** Many reactions proceed in a stepwise fashion. This can be convincingly demonstrated if an intermediate species can be isolated and shown to proceed to the same products under the reaction conditions. Some intermediates are stable compounds in their own right; however, some are so reactive that isolation is not possible. Nevertheless, evidence for their existence may be obtained by other means, including spectroscopic observation or inference from kinetic results.

1.2.4
Factors that Influence Reactions

It is helpful to identify some general features of a reaction that have a significant influence on its facility. Some of the most important of these are:

1) **Energetics:** The potential energy of a reacting system changes as the reaction progresses. The overall change may be **exothermic** (energy is released) or **endothermic** (energy must be added), and there is usually an **activation energy** requirement as well. Tables of standard bond energies are widely used by chemists for estimating the energy change in a proposed reaction. As a

rule, compounds constructed of strong covalent bonds are more stable than compounds incorporating one or more relatively weak bonds.

2) **Electronic effects:** The distribution of electrons at sites of reaction (functional groups) is a particularly important factor. Electron-deficient species or groups, which may or may not be positively charged, are attracted to electron-rich species or groups, which may or may not be negatively charged. We refer to these species as electrophiles and nucleophiles, respectively. In general, *opposites attract and like repel.*

The charge distribution in a molecule is usually discussed with respect to two interacting effects: an **inductive effect**, which is a function of the electronegativity differences that exist between atoms (and groups), and a **resonance effect**, in which electrons move in a discontinuous fashion between parts of a molecule. Other factors that influence a reaction include:
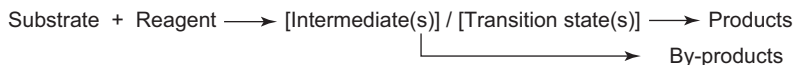
1) **Steric effects:** Steric effects arise from the fact that each atom within a molecule occupies a certain amount of space. If atoms are brought too close together there is an associated cost in energy due to overlapping electron clouds and this may affect the molecule's preferred shape (conformation) and reactivity. When they are crowded together, van der Waals repulsions produce an unfavorable **steric hindrance**. Steric hindrance occurs when the large size of groups within a molecule prevents chemical reactions that are observed in related molecules with smaller groups. Steric hindrance may influence conformational equilibria, as well as destabilizing transition states of reactions. When a Lewis acid and Lewis base cannot combine due to steric hindrance, they are said to form a frustrated Lewis pair.

   The structure, properties, and reactivity of a molecule depend on straightforward bonding interactions including covalent bonds, ionic bonds, hydrogen bonds, and lesser forms of bonding. This bonding supplies a basic molecular skeleton that is modified by repulsive forces. These repulsive forces include the steric interactions described above. Basic bonding and steric factor are at times insufficient to explain many structures, properties, and reactivity. Thus steric effects are often contrasted and complemented by electronic effects implying the influence of effects such as induction, conjunction, orbital symmetry, electrostatic interactions, and spin state. There are more esoteric electronic effects but these are among the most important when considering structure and chemical reactivity.

2) **Stereoelectronic effects:** Stereoelectronic effects are simply the chemical and kinetic consequences of orbital overlap. In many reactions atomic or molecular orbitals interact in a manner that has an optimal configurational or geometrical alignment. Departure from this alignment inhibits the reaction. Stereoelectronic effects guide the geometry and reactivity pattern of most functional groups.

3) **Solvent effects:** The nature of the solvent used in reactions often has a profound effect on how the reaction proceeds. Solvent effects are the group of effects that a solvent has on chemical reactivity. Solvents can have an effect on solubility,

stability, and reaction rates. Thus, choosing the appropriate solvent allows for thermodynamic and kinetic control over a chemical reaction. Most reactions are conducted in solution and the solvent selected for a given reaction may exert a strong influence on its course. A solute dissolves in a solvent when it forms favorable interactions with the solvent. This dissolving process depends upon the free energy change of both solute and solvent. The free energy of solvation is a combination of several factors. Different solvents can affect the equilibrium constant of a reaction by differential stabilization of the reactant or product. The ionization equilibrium of an acid or a base is affected by a solvent change. The effect of the solvent is not only due its acidity or basicity but also because of its dielectric constant and its ability to preferentially solvate and thus stabilizes certain species in acid–base equilibria. A change in the solvating ability or dielectric constant can thus influence the acidity or basicity.
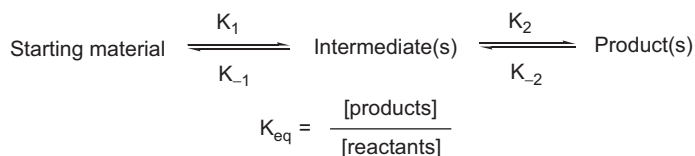
Many organic reactions seem at first glance to be highly complex, taking place in several stages involving formation of one or more transient intermediates, which undergo further reaction until the final product is reached. Such reactions are termed *multistep reactions*. A description of the step-by-step process, that is, its sequence of steps and the details of electron movement, bond breaking and making, and the timing by which reactants are changed into products is called the *mechanism of the reaction*. The mechanism will be clearer if ''curved arrows'' are used to show the movement of the electrons from an electron-rich center to an electron-deficient center. The organic starting material, in which a change of functional group is involved, is called the *substrate* or *reactant*, which is attacked by the **reagent**. The reagent is very commonly an inorganic or very simple organic substance and is used to create the desired transformation in the substrate:

$$\text{Substrate } + \text{ Reagent } \longrightarrow \text{ [Intermediate(s)] / [Transition state(s)] } \longrightarrow \text{ Products}$$
$$\longrightarrow \text{ By-products}$$

For chemists it is very important to understand in detail what is going on when the molecules in the starting materials react with each other and create the molecules characteristic of the product. This is the process of determining the mechanism of the reaction. Knowledge about mechanisms makes it possible to develop better and less expensive methods to prepare products of technical importance.

Reactive intermediates are short lived and their importance lies in the assignment of reaction mechanisms on the pathway from the starting substrate to stable products. The lifetimes of these intermediates range from 10^{-12} s upwards. These intermediates may be formed by attack of various reagents on substrates, by dissociation of organic compounds, or by promotion of molecules to excited states by absorption of light or interaction with high-energy radiation. These reactive intermediates are, in general, not isolated but are detected by spectroscopic methods or trapped chemically or their presence is confirmed by indirect evidence. These intermediates may be formed by attack of various reagents on substrates, by

dissociation of organic compounds, or by promotion of molecules to excited states by absorption of light. Many of the reactions of organic chemistry proceed by way of reactive intermediates according to the following schematic equation:

$$\text{Starting material} \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} \text{Intermediate(s)} \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} \text{Product(s)}$$

$$K_{eq} = \frac{[\text{products}]}{[\text{reactants}]}$$

where K_{eq} is equal to the relative concentrations of products and reactants at equilibrium. If the products are more stable (have lower free energy) than the reactants, there will be a higher concentration of products than reactants at equilibrium ($K_{eq} > 1$). In contrast, if the reactants are more stable than the products, there will be a higher concentration of reactants than products at equilibrium ($K_{eq} < 1$). In most of the cases of interest to us in this book $k_2 > k_1$ otherwise the intermediate would represent an isolable compound or a species in rapid equilibrium with reactants. In general, reactive intermediates correspond to a relatively shallow dip in a free energy versus reaction coordinate diagram and they can either proceed to products faster than returning to starting material, that is, $k_2 > k_{-1}$, or vice versa, $k_{-1} > k_2$.

Much effort has been expended in certain famous test cases such as with ''nonclassical'' carbocations in deciding whether an intermediate actually exists. It is usually considered that a reactive intermediate is significant if the depth of the free energy well containing it is sufficient to prevent every molecular vibration along the reaction coordinate proceeding back to reactants or forward to products. Generally, the rate of a multistep reaction depends on the slowest step (i.e., highest energy step) in a multistep chemical reaction and is called the *rate-limiting step* or *rate-determining step* of the reaction that controls the overall rate of the reaction. The rate of a reaction is dependent on the following three factors:

1) The number of effective collisions taking place between the reacting molecules in a given period of time. The greater the number of collisions, the faster the reaction.
2) The fraction of collisions that occur with sufficient energy to get the reacting molecules over the energy barrier (not all collisions between molecules lead to chemical change).
3) The fraction of collisions that occur with the proper orientation.

There are two ways of speeding reactions up: (i) we can heat the reactants so that a higher proportion of them have the activation energy on collision; (ii) we can add a suitable catalyst to the reaction mixture. The rate of a reaction in solution is almost always dependent on the nature of the solvent. Two characteristics of the solvent play a part in determining the relative free energies of reactant and transition state, and therefore the rate of the reaction. First, energy is needed to separate the unlike charges and the amount of energy decreases as the dielectric

constant of the solvent increases. Second, the solvating power of the solvent is important. The transition state can be stabilized by solvation of both the developing positive and the developing negative ions with protic solvents.

Whenever a reaction can give more than one possible products, two or more reactions are in competition. One reaction predominates when it occurs more rapidly than the competing reactions. The rate of a chemical reaction can be defined as the number of reactant molecules converted into products in a given time. As the reactants change into products, they pass through an unstable state of maximum free energy, called the *transition state* or *activated complex* that is not stable, having transient existence, and cannot be isolated. The transition state is a molecular complex in which reactants have been forced together in such a way that they are ready to collapse into products. The structure of the transition state is between the structure of the reactants and the structure of the products. The transition state represents an energy maximum on passing from reactants to products; it is not a real molecule, having partially formed/broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules. *Intermediates* are molecule or ion that represent a localized energy minimum having fully formed bonds and existing for some finite length of time with some stability. The transition state has a higher energy than either the reactants or products. The energy required to reach the transition state from the reactant energy minimum is defined as the *activation energy*. This activation energy, also called the *energy barrier* for a reaction, is the minimum energy molecules must have if they are to react. A reaction coordinate diagram describes the energy changes that take place in each of the steps (Figure 1.1).

The field of chemistry that describes the properties of a system at equilibrium is called *thermodynamics*. It is helpful to look at the driving forces that cause a given reaction to occur such as the changes in energy content of products versus reactants (thermodynamics) and the pathway, and rate by which the molecules
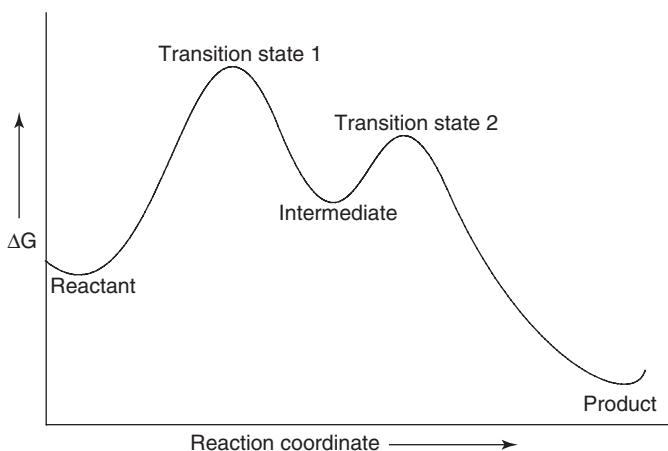

Figure 1.1 Reaction profile showing the reaction intermediate where $k_2 > k_{-1}$.

become transformed from reactants into products (kinetics). Thermodynamics and kinetics are important features in describing how various energy contents affect reactions. Free energy has both enthalpy (bond energy) and entropy (disorder) components. Enthalpy changes are almost always important in chemical reactions, but entropy changes are usually significant in organic reactions only when the number of product molecules differs from the number of reactant molecules. The product that is forms fastest is called the *kinetic product* and the most stable product is called the *thermodynamic product*. Thus, the nitration of methylbenzene is found to be *kinetically controlled*, whereas the Friedel–Crafts alkylation of the same species is often *thermodynamically controlled*. The form of control that operates may also be influenced by the reaction condition; thus the sulfonation of naphthalene with concentrated H_2SO_4 at $80\,°C$ is essentially *kinetically controlled*, whereas at $160\,°C$ it is *thermodynamically controlled*.

Selectivity means that one of several reaction products is formed preferentially or exclusively, for example, reaction product **A** is formed at the expense of reaction product **B**. Selectivities of this type are usually the result of a *kinetically controlled reaction process*, or ''**kinetic control**.'' This means that they are usually not the consequence of an equilibrium being established under the reaction conditions between the alternative reaction products **A** and **B**. In this latter case one would have a *thermodynamically controlled reaction process*, or ''**thermodynamic control**.'' If the reactions leading to the alternative reaction products are one step, the most stable product is produced most rapidly, that is, more or less selectively. This type of selectivity is called *product-development control*.

From the value of K_{eq} we can calculate the change in free energy. The difference between the free energy content of the products and the free energy content of the reactants at equilibrium under standard conditions is called the *Gibbs standard free energy change* ($\Delta G°$). If $\Delta G°$ is negative, that is, less than zero, the reaction will be an **exergonic reaction** (the transition state is similar to the *starting material* with respect to energy and structure) and if $\Delta G°$ is positive, that is, greater than zero, the reaction will be an **endergonic reaction** (the transition state is similar to the *product* with respect to energy and structure). The Gibbs standard free energy change ($\Delta G°$) has an enthalpy ($\Delta H°$) component and an entropy ($\Delta S°$) component:

$$\Delta G° = \Delta H° - T\Delta S°$$

The enthalpy term ($\Delta H°$) is the heat given off or the heat absorbed during the course of the reaction, usually given in kilocalories (or kilojoules) per mole, and T is the absolute temperature. Heat is given off when bonds are formed, and heat is consumed when bonds are broken. A reaction with a negative $\Delta H°$ is called an *exothermic reaction* (weaker bonds are broken and stronger bonds are formed) and a reaction with a positive $\Delta H°$ is called an *endothermic reaction* (stronger bonds are broken and weaker bonds are formed). Reactions tend to favor products with the lowest enthalpy (those with the stronger bonds). Entropy ($\Delta S°$) is defined as the degree of disorder, which is a measure of the freedom of motion or randomness in a system. Restricting the freedom of motion of a molecule causes a decrease in entropy. For example, in a reaction in which two molecules come together to

form a single molecule, the entropy in the product will be less than the entropy in the reactants, because two individual molecules can move in ways that are not possible when the two are bound together in a single molecule. In such a reaction, the $\Delta S°$ will be negative. For a reaction in which a single molecule is cleaved into two separate molecules the products will have greater freedom of motion than the reactants, and $\Delta S°$ will be positive. A reaction with a negative $\Delta G°$ is said to have a favorable driving force. Negative values of $\Delta H°$ and positive value of $\Delta S°$ contribute to make $\Delta G°$ negative, that is, the formation of products with stronger bonds and with greater freedom of motion causes $\Delta G°$ to be negative.

For a spontaneous reaction, there must be an increase in entropy overall (i.e., the entropy change of the universe must be positive). The universe to a chemist consists of the reaction (system) that we are studying and its surroundings. It is comparatively easy to measure entropy changes of the reaction, but those of the surroundings are more difficult to determine directly. Fortunately, the change in entropy of the surroundings usually results from the heat released to, or absorbed from, the reaction. Heat released to the surroundings (an exothermic reaction) will increase the entropy of the surroundings while absorption of heat (an endothermic reaction) will lead to a decrease in entropy of the surroundings. Thus we can determine whether a reaction is spontaneous from the entropy and enthalpy changes of the reaction (Table 1.1).

The sign of $\Delta G°$ for a reaction tells us whether the starting materials or products are favored at equilibrium, but it tells us nothing about how long it will take before equilibrium is reached. If $\Delta G°$ for a reaction is *negative*, the products will be favored at equilibrium. If $\Delta G°$ for a reaction is *positive*, the reactants will be favored at equilibrium. If $\Delta G°$ for a reaction is 0, the equilibrium constant for the reaction will be 1. A small change in $\Delta G°$ makes a big difference in equilibrium constant K.

The functional groups determine the way the molecule works both chemically and biologically. Understanding chemical reactions in greater detail requires numerous different pieces of information, such as structural parameters, orbital interactions, energetic details, effect of media, and other external perturbations. One of my basic goals is to answer questions on stereoselectivity, catalysis, stability and reactivity of reactive intermediates, kinetic and thermodynamic aspects of chemical transformation, and so on. Many of the reactive intermediates of organic chemistry are charged species, such as **carbocations** (carbenium and carbonium ions) and **carbanions**, but there is an important subgroup of formally neutral

Table 1.1   Factors affecting the spontaneity of a reaction.

ΔH	ΔS	ΔG	Result
Negative	Positive	Always negative	Spontaneous
Positive	Negative	Always positive	Non-spontaneous
Positive	Positive	Negative at high T	Spontaneous at high T
Negative	Negative	Negative at low T	Spontaneous at low T

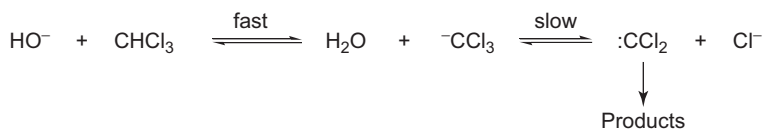**Table 1.2** Common reactive intermediates and their relationships.

Type	C	N	O
-Onium ion	R_5C^+ carbonium ion	R_4N^+ ammonium ion	R_3O^+ oxonium ion
Neutral molecule	R_4C	R_3N	R_2O
Anion	R_3C^- carbanion	R_2N^- amide anion	RO^- alkoxide
Radical	$R_3C^{\bullet}$ carbon radical	$R_2N^{\bullet}$ aminyl radical	$RO^{\bullet}$ oxyl radical
-Enium ion	R_3C^+ carbenium ion	R_2N^+ nitrenium ion	RO^+ oxenium ion
-Ene	R_2C : carbene	RN : nitrene	: O : oxene

electron-deficient reactive intermediates. For example, a carbon-containing reactive center can be either trivalent, with a single nonbonding electron, that is, a carbon centered **radical**, or divalent with two nonbonding electrons, that is, a **carbene**. Neutral reactive intermediates such as radicals, carbenes, nitrenes, and arynes occupy a fascinating place in the history of organic chemistry. First regarded as mere curiosities, neutral reactive intermediates ultimately came under the intense scrutiny of physical organic chemists from a mechanistic point of view. This concise text concentrates on how these electron-deficient species now play a key role in synthetic chemistry research. Important reactions are clearly and simply laid out with carefully chosen examples that illustrate their use in organic synthesis. Table 1.2 gives a comparison of various neutral reactive intermediates and their relationship to corresponding cations and anions.

There are many other kinds of reactive intermediates, which do not fit into the previous classifications. Some are simply compounds that are unstable for various possible reasons, such as structural strain or an unusual oxidation state, and are discussed in Chapter 7. This book is concerned with the chemistry of carbocations, carbanions, radicals, carbenes, nitrenes (the nitrogen analogs of carbenes), and miscellaneous intermediates such as arynes, *ortho*-quinone methides, zwitterions and dipoles, anti-aromatic systems, and tetrahedral intermediates. This is not the place to describe in detail the experimental basis on which the involvement of reactive intermediates in specific reactions has been established but it is appropriate to mention briefly the sort of evidence that has been found useful in this respect. Transition states have no real lifetime, and there are no physical techniques by which they can be directly characterized. Probably one of the most direct ways in which reactive intermediates can be inferred in a particular reaction is by a kinetic study. Trapping the intermediate with an appropriate reagent can also be very valuable, particularly if it can be shown that the same products are produced in the same ratios when the same postulated intermediate is formed from different precursors.

A classic example of the combined uses of kinetic and product-trapping studies is that of Hine and coworkers in their work on the hydrolysis of chloroform under basic conditions. The observation that chloroform undergoes deuterium for hydrogen exchange (in D_2O) faster than hydrolysis and further that the rate

of hydrolysis is retarded by addition of chloride ion is strong evidence in favor of the mechanism shown. Further circumstantial evidence for dichlorocarbene formation is provided by trapping experiments, for example, with alkenes, giving 1,1-dichlorocyclopropanes as products (Scheme 1.1).

$$HO^- + CHCl_3 \underset{}{\overset{fast}{\rightleftharpoons}} H_2O + {}^-CCl_3 \underset{}{\overset{slow}{\rightleftharpoons}} :CCl_2 + Cl^-$$

$$\downarrow$$

$$Products$$

Scheme 1.1

Organic structures can be determined accurately and quickly by spectroscopic methods. Mass spectrometry determines mass of a molecule and its atomic composition. NMR spectroscopy reveals the carbon skeleton of the molecule, whereas IR spectroscopy determines functional groups in the molecules. UV-visible spectroscopy tells us about the conjugation present in a molecule. Spectroscopic methods have also provided valuable evidence for the intermediacy of transient species. Most of the common spectroscopic techniques are not appropriate for examining reactive intermediates. The exceptions are visible and ultraviolet spectroscopy, whose inherent sensitivity allows them to be used to detect very low concentrations; for example, particularly where combined with flash photolysis when high concentrations of the intermediate can be built up for UV detection, or by using matrix isolation techniques when species such as *ortho*-benzyne can be detected and their IR spectra obtained. Unfortunately, UV and visible spectroscopy do not provide the rich structural detail afforded by IR and especially ^{1}H and ^{13}C NMR spectroscopy. Current mechanistic studies use mostly stable isotopes such as ^{2}H, ^{13}C, ^{15}N, ^{17}O, and ^{18}O. Their presence and position in a molecule can be determined by NMR. Mass spectroscopy, although much more sensitive than NMR, usually allows us to determine the degree of labeling but the position of the label can be identified only in favorable cases (via fragmentation).

In the case of transient species with unpaired electrons such as free radicals, and the triplet states of carbenes or nitrenes, electron spin resonance (ESR) spectroscopy can provide unique evidence about the structure of the intermediate. Useful information about intermediates in reactions involving radical pair coupling can also be obtained by a technique known as chemically-induced dynamic nuclear polarization (CIDNP). However, detailed discussions of ESR and CIDNP are outside the scope of this book and for further information suitable text books on physical organic chemistry or the references given in the Further Reading section should be consulted.

Besides the kinetics of a reaction there are several other ways of studying reactions. The final mechanism deduced for a reaction must explain the following:

  products and side products;
  intermediates observable where possible;

kinetics;
stereochemical results;
isotope studies;
relative reactivity of different reagents;
relative reactivity of different substrates;
effect of different solvents.

So far, we have looked at the following aspects: why molecules generally do not react with each other; why sometimes molecules do react with each other; how in chemical reactions electrons move from full to empty orbitals, which is the key to reactivity; molecular shape and structure determine reactivity; charge attraction and orbital overlap bring molecules together; the right orientation to use any attraction; charge is conserved in each step of a reaction and representing the movement of electrons in chemical reactions by curly arrows, which are vital for learning reaction mechanism.

You cannot learn the whole subject of reactive intermediates, there is just too much of it. You can learn trivial things like the name of intermediates but that does not help you to understand the principles behind the subject. You have to understand the principles and fundamentals because the only way to tackle organic reaction mechanisms is to learn to work it out. That is why I have provided end-of chapter problems. The end-of chapter problems should set you on your way but they are not the end of the journey to understanding. They are to help you discover if you have understood the material presented in each chapter. You are probably reading this text as part of a university/college course and you should find out what kind of examination problems your university/college uses and practice them, too. This first chapter gives a general introduction, illustrating material that will subsequently be covered in detail. The remaining six chapters with their special topics take up specific classes of reactions and discuss their mechanisms and applications. The criteria used to select these classes of reactions are (i) the reactions are highly important in synthetic organic chemistry and (ii) a fair amount is known about their mechanisms. It is hoped that the choice of topics made will indicate both the scope and the depth of current mechanistic theories.

1.3
Summary

- The electrons in any atom are grouped in energy levels whose energies are universally proportional to the inverse square of a very important number n. This number is called the *principal quantum number* and it can have only a few integral values ($n = 1, 2, 3 \ldots$). The energy levels also depend on the type of atom. Electrons in atoms are best described as waves.
- The 1s orbital is spherically symmetrical and has no nodes. The 2s orbital has one radial node and the 3s orbital two radial nodes. They are both spherically symmetrical.

- The bonding MO (molecular orbital) is lower in energy than the AOs (atomic orbitals) and the antibonding MO is higher in energy than the AOs.
- All normal compounds of carbon have eight electrons in the outer shell ($n = 2$) of the carbon atom, all shared in bonds. It does not matter where these electrons come from; just fit them into the right MOs on sp, sp², or sp³ atoms.
- All normal compounds of nitrogen have eight electrons in the outer shell ($n = 2$) of the nitrogen atom, six shared in bonds and two in a lone pair. Similarly, all compounds of oxygen have eight electrons in the outer shell ($n = 2$) of the oxygen atom, four shared in bonds and four in lone pairs.
- The *activation energy*, also called the *energy barrier* for a reaction, is the minimum energy molecules must have if they are to react.
- Nucleophiles do not really react with the nucleus but with empty electronic orbitals. In a reaction mechanism, nucleophiles donate electrons and electrophiles accept electrons.
- For any reaction molecules must approach each other so that they have enough energy to overcome the repulsion and have the right orientation and suitable symmetry to use any attraction.
- Curly arrows are used to represent the reaction mechanisms, which show the movement of electrons within molecules. A curly arrow shows the movement of a pair of electrons.
- If you make a new bond to uncharged H, C, N, or O you must also break one of the existing bonds in the same step. Make sure that overall charge is conserved in your mechanism.
- Conjugation focuses on the sequence of alternating double and single bonds, while delocalization focuses on the molecular orbitals covering the whole system. Electrons are delocalized over the whole of a conjugated system.
- The stronger the acid HA, the weaker is its conjugate base, A⁻ (the more stable the conjugate base, the stronger the acid) and the stronger the base A⁻, the weaker its conjugate acid AH.
- A transition state is a structure that represents an energy maximum on passing from reactant to products, which cannot be isolated. It is not a real molecule in that it may have partially formed or broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules.
- An intermediate is a molecule or ion that represents a localized energy minimum – an energy barrier must be overcome before the intermediate forms something more stable.
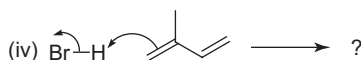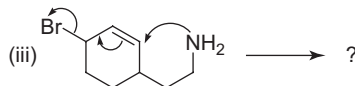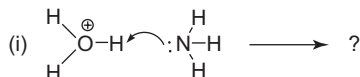
Problems

1. Draw a reaction diagram profile for a one-step exothermic reaction. Label the parts that represent the reactants, products, transition state, activation energy, and heat of reaction.

2. Draw a reaction energy diagram for a two-step endothermic reaction with a rate-limiting second step.
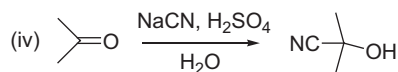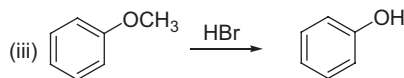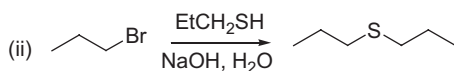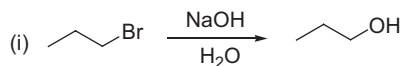
3. Consider the following reaction:

$$CH_4 + Cl^{\bullet} \rightarrow {}^{\bullet}CH_3 + HCl$$
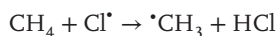
This reaction has activation energy (E_a) of $+4$ kcal mol^{-1}($+17$ kJ mol^{-1}) and a $\Delta H°$ of $+1$ kcal mol^{-1}($+4$ kJ mol^{-1}). Draw a reaction energy diagram for this reaction.

4. Complete the following mechanisms by drawing the structure of the products in each case.

(i)

(ii)

(iii)

(iv)

5. Draw mechanisms for the following reactions.

(i) Br $\xrightarrow[\text{H}_2\text{O}]{\text{NaOH}}$ OH

(ii) Br $\xrightarrow[\text{NaOH, H}_2\text{O}]{\text{EtCH}_2\text{SH}}$ S

(iii) OCH$_3$ $\xrightarrow{\text{HBr}}$ OH

(iv) O $\xrightarrow[\text{H}_2\text{O}]{\text{NaCN, H}_2\text{SO}_4}$ NC OH

6. Explain the following terms with appropriate examples: regioselectivity, chemoselectivity, stereoselectivity, transition state, intermediate, and activation energy.

7. Draw transition states and intermediates for the following reactions and fit each on an energy profile diagram.
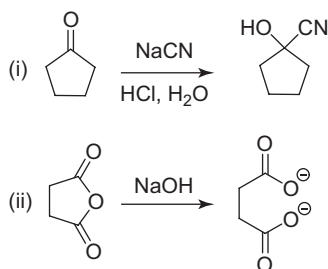
8. The equilibrium between a carbonyl compound and its hydrate usually favors the aldehyde or ketone. Explain why and draw an energy profile to express this.

9. Hemiacetal formation is catalyzed by acid or base, but acetal formation is possible only with an acid. Explain why with suitable examples.

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