6

MECHANISMS AND
METHODS OF
DETERMINING THEM

A mechanism is the actual process by which a reaction takes place—which bonds are broken, in what order, how many steps are involved, the relative rate of each step, etc. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details which is still puzzling, and for some reactions even the gross mechanism is not yet clear. The problems involved are difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In some cases there are several proposed mechanisms, each of which completely explains all the data.

Types of Mechanism

In most reactions of organic compounds one or more covalent bonds are broken. We can divide organic mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *heterolytic*. Such reactions do not necessarily involve ionic intermediates, though they usually do. The important thing is that the electrons are never unpaired. For most reactions it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book we shall always designate as the substrate that molecule that supplies carbon to the new bond. When carbon–carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which the attacking reagent. In heterolytic reactions the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent that brings an electron pair is called a *nucleophile* and the reaction is *nucleophilic*. A reagent that takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group that carries away an electron pair is called a *nucleofuge*. If it comes away without the electron pair, it is called an *electrofuge*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *homolytic* or *free-radical mechanisms*.

3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*.[1]

Examples of all three types of mechanisms are given in the next section.

Types of Reaction

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types that follows, the immediate products are shown, though in many cases they then react with something else. All the species are shown without charges, since differently charged reactants can undergo analogous changes. The descriptions given here are purely formal and are for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

1. *Substitutions.*   If heterolytic, these can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).
   a. Nucleophilic substitution (Chapters 10, 13).

$$A{-}X + \overline{Y} \longrightarrow A{-}Y + \overline{X}$$
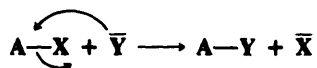
   b. Electrophilic substitution (Chapters 11, 12).

$$A{-}X + Y \longrightarrow A{-}Y + X$$
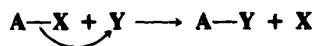
   c. Free-radical substitution (Chapter 14).
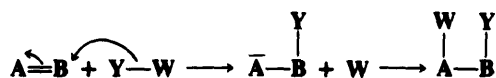
$$A{-}X + Y{\cdot} \longrightarrow A{-}Y + X{\cdot}$$

In free-radical substitution, Y• is usually produced by a previous free-radical cleavage, and X• goes on to react further.
   2. *Additions to double or triple bonds* (Chapters 15, 16).   These reactions can take place by all three of the mechanistic possibilities.
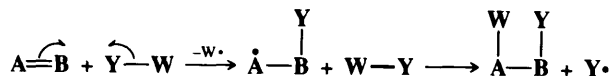   **a.** Electrophilic addition (heterolytic).

$$A{=}B + Y{-}W \longrightarrow A{-}\overset{\displaystyle Y}{B} + \overline{W} \longrightarrow A{-}\overset{\displaystyle W\ Y}{B}$$
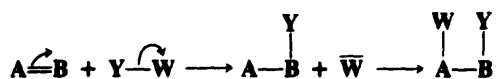
   b. Nucleophilic addition (heterolytic).

$$A{=}B + Y{-}W \longrightarrow \overline{A}{-}\overset{\displaystyle Y}{B} + W \longrightarrow A{-}\overset{\displaystyle W\ Y}{B}$$
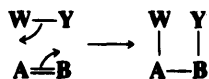
[1]For a classification of pericyclic reactions, see Hendrickson *Angew. Chem. Int. Ed. Engl.* **1974,** *13,* 47-76 [*Angew. Chem. 86,* 71-100].

c. Free-radical addition (homolytic).

$$A \overset{\frown}{=} B \ + \ \overset{\frown}{Y \overset{\frown}{-} W} \ \xrightarrow{-W \cdot} \ \overset{Y}{\underset{|}{\cdot A - B}} \ + \ W - Y \ \longrightarrow \ \overset{W \ Y}{\underset{| \ |}{A - B}} \ + \ Y \cdot$$

d. Simultaneous addition (pericyclic).

$$\overset{W \frown Y}{\underset{A \overset{\frown}{=} B}{}} \ \longrightarrow \ \overset{W \ Y}{\underset{| \ |}{A - B}}$$

The examples show Y and W coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often (again except for simultaneous addition) this cleavage takes place earlier.

3. β *Elimination* (Chapter 17).

$$\overset{W \quad X}{\underset{A \overset{\frown}{-} B}{\overset{|}{\searrow} \ \overset{|}{\swarrow}}} \ \longrightarrow \ A = B \ + \ W \ + \ \overline{X}$$
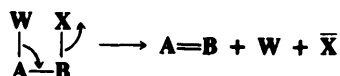
These reactions can take place by either heterolytic or pericyclic mechanisms. Examples of the latter are shown on p. 1006. Free-radical β eliminations are extremely rare. In heterolytic eliminations W and X may or may not leave simultaneously and may or may not combine.

4. *Rearrangement* (Chapter 18).   Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.
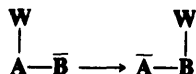
a. Migration with electron pair (nucleophilic).

$$\overset{W}{\underset{A - B}{\overset{|}{}}} \ \longrightarrow \ \overset{W}{\underset{A - B}{\overset{|}{}}}$$
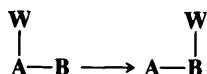
b. Migration with one electron (free-radical).

$$\overset{W}{\underset{A - \dot{B}}{\overset{|}{}}} \ \longrightarrow \ \overset{W}{\underset{\dot{A} - B}{\overset{|}{}}}$$

c. Migration without electrons (electrophilic; rare).

$$\overset{W}{\underset{A - \overline{B}}{\overset{|}{}}} \ \longrightarrow \ \overset{W}{\underset{\overline{A} - B}{\overset{|}{}}}$$

The illustrations show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements that do not involve simple migration at all (see Chapter 18). Some of the latter involve pericyclic mechanisms.

5. *Oxidation and reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation–reduction mechanistic types, see p. 1159.

6. Combinations of the above.

Note that arrows are used to show movement of *electrons*. An arrow always follows the motion of electrons and never of a nucleus or anything else (it is understood that the rest of the molecule follows the electrons). Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, though in these reactions we do not really know how or in which direction the electrons are moving.

Thermodynamic Requirements for Reaction

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; i.e., ΔG must be negative. Reactions can go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which only flows downhill and never uphill (though it can be carried or pumped uphill), molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S. These quantities are related by the equation

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

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain, and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The less order in a system, the greater the entropy. The preferred conditions in nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are small and it is the enthalpy that mainly determines whether the reaction can take place spontaneously. However, in certain types of reaction entropy is important and can dominate enthalpy. We shall discuss several examples.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy; the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.

2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, e.g., A + B → C + D, entropy effects are usually small, but if the number of molecules is increased, e.g., A → B + C, there is a large gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are therefore thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.

3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large

increases in enthalphy. An example is cleavage of ethane into two methyl radicals. In this case a bond of about 79 kcal/mol (330 kJ/mol) is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature.

4. An acyclic molecule has more entropy than a similar cyclic molecule because there are more conformations (compare hexane and cyclohexane). Ring opening therefore means a gain in entropy and ring closing a loss.

Kinetic Requirements for Reaction

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary* but not a *sufficient* condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a large negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* $\Delta G^{\ddagger}$ must be added.[2] This situation is illustrated in Figure 6.1,[3] which is an energy profile for a one-step reaction without an intermediate. In this type of diagram the horizontal axis (called the *reaction coordinate*)[4] signifies the progression of the reaction. $\Delta G_f^{\ddagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Figure 6.1 is reversible, $\Delta G_r^{\ddagger}$ must be greater than $\Delta G_f^{\ddagger}$, since it is the sum of ΔG and $\Delta G_f^{\ddagger}$.
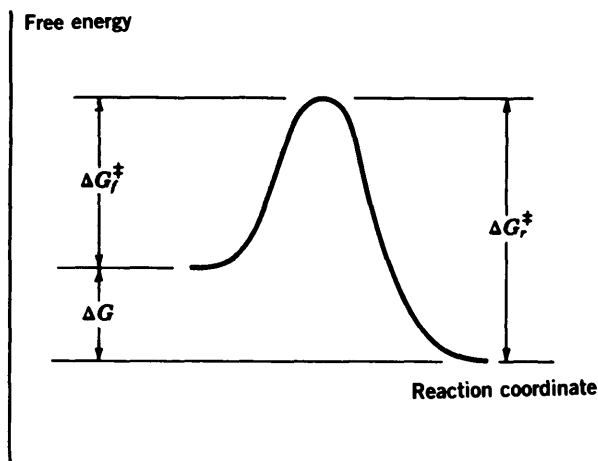

FIGURE 6.1 Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants.

[2]For mixtures of H_2 and O_2 this can be done by striking a match.
[3]Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in an approximate way, to other reactions.
[4]For a review of reaction coordinates and structure–energy relationships, see Grunwald *Prog. Phys. Org. Chem.* **1990**, *17*, 55-105.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution but has no finite existence; the system passes through it. The system at this point is called an *activated complex*.[5]

In the *transition-state theory*[6] the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, though at first sight surprising, is not unreasonable, when we consider that they are all "falling downhill") so that the rate constant (see p. 220) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, i.e., on the value of $K^{\ddagger}$. $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3RT \log K^{\ddagger}$$

so that a higher value of $\Delta G^{\ddagger}$ is associated with a smaller rate constant. The rates of nearly all reactions increase with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier. Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled*.[7]

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions bonds have been broken or partially broken by the time the transition state is reached; the energy necessary for this is $\Delta H^{\ddagger}$. It is true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

Entropy of activation $\Delta S^{\ddagger}$, which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (**7-13**) takes place only if, in the transition state, the reactants are oriented as shown.
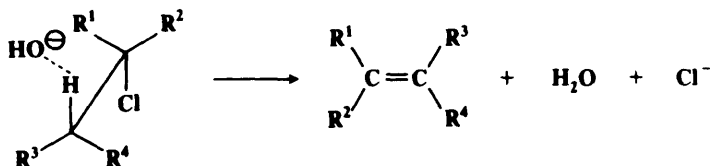
Not only must the OH⁻ be near the hydrogen, but the hydrogen must be oriented anti to the chlorine atom.[8] When the two reacting molecules collide, if the OH⁻ should be near

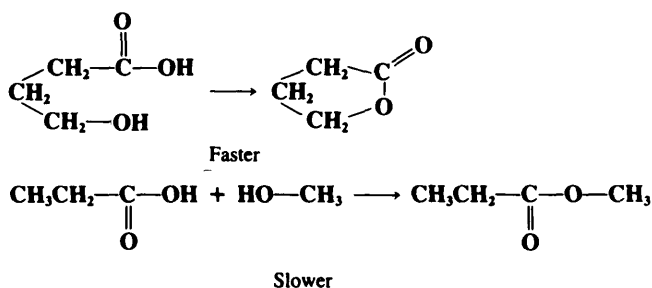[5]For a discussion of transition states, see Laidler *J. Chem. Educ.* **1988**, *65*, 540.

[6]For fuller discussions, see Kreevoy; Truhlar, in Bernasconi, Ref. 25, pt. 1, pp. 13-95; Moore; Pearson *Kinetics and Mechanism*, 3rd ed.; Wiley: New York, 1981, pp. 137-181; Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982; pp. 227-378.

[7]For a monograph on diffusion-controlled reactions, see Rice, *Comprehensive Chemical Kinetics*, Vol. 25 (edited by Bamford; Tipper; Compton); Elsevier: New York, 1985.

[8]As we shall see in Chapter 17, with some molecules elimination is also possible if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

the chlorine atom or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space and adopt only that one that leads to reaction. Thus, a considerable loss in entropy is involved, i.e., ΔS^+ is negative.

Entropy of activation is also responsible for the difficulty in closing rings[9] larger then six-membered. Consider a ring-closing reaction in which the two groups that must interact are situated on the ends of a ten-carbon chain. In order for reaction to take place, the groups must encounter each other. But a ten-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[10] This factor is also present, though less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. Though ΔH^+ is about the

Faster

$$CH_3CH_2-\overset{\underset{\displaystyle \|}{O}}{C}-OH + HO-CH_3 \longrightarrow CH_3CH_2-\overset{\underset{\displaystyle \|}{O}}{C}-O-CH_3$$

Slower

same, ΔS^+ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable ΔS^+ may not be sufficient to overcome the unfavorable ΔH^+ change. Table 6.1 shows the relative rate constants for the closing of rings of 3 to 23 members all by the same reaction.[11] Reactions in which the transition state has more disorder than the starring compounds, e.g., the pyrolytic conversion of cyclopropane to propene, have positive ΔS^+ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Figure 6.2). The deeper the well, the more stable the intermediate. In Figure 6.2a, the second peak is higher than the first. The opposite situation is shown in Figure 6.2b. Note that in reactions in which the second peak is higher than the first, the overall ΔG^+ is less than the sum of the ΔG^+ values for the two steps. Minima in free-energy-profile diagrams (*intermediates*) correspond to real species which have a finite though very short

[9]For discussions of the entropy and enthalpy of ring-closing reactions, see De Tar; Luthra *J. Am. Chem. Soc.* **1980**, *102*, 4505; Mandolini *Bull. Soc. Chim. Fr.* **1988**, 173. For a related discussion, see Menger *Acc. Chem. Res.* **1985**, *18*, 128-134.

[10]For reviews of the cyclization of acyclic molecules, see Nakagaki; Sakuragi; Mutai *J. Phys. Org. Chem.* **1989**, *2*, 187-204; Mandolini *Adv. Phys. Org. Chem.* **1986**, *22*, 1-111. For a review of the cyclization and conformation of hydrocarbon chains, see Winnik *Chem. Rev.* **1981**, *81*, 491-524. For a review of steric and electronic effects in heterolytic ring closures, see Valters *Russ. Chem. Rev.* **1982**, *51*, 788-801.

[11]The values for 4, 5, and 6 are from Mandolini *J. Am.Chem. Soc.* **1978**, *100*, 550; the others are from Galli; Illuminati; Mandolini; Tamborra *J. Am. Chem. Soc.* **1977**, *99*, 2591. See also Illuminati; Mandolini *Acc. Chem. Res.* **1981**, *14*, 95-102. See, however, van der Kerk; Verhoeven; Stirling *J. Chem. Soc., Perkin Trans. 2* **1985**, 1355; Benedetti; Stirling *J. Chem. Soc., Perkin Trans. 2* **1986**, 605.

TABLE 6.1   Relative rate constants at 50°C
(Eight-membered ring = 1) for the reaction
$Br(CH_2)_{n-2}CO_2^- \rightarrow (CH_2)_{n-2}$ C=O, where
n = the ring size[11]

Ring size	Relative rate
3	21.7
4	5.4×10^3
5	1.5×10^6
6	1.7×10^4
7	97.3
8	1.00
9	1.12
10	3.35
11	8.51
12	10.6
13	32.2
14	41.9
15	45.1
16	52.0
18	51.2
23	60.4

existence. These may be the carbocations, carbanions, free radicals, etc., discussed in Chapter 5 or molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^{\ddagger}$ is small) but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.[12]

The Baldwin Rules for Ring Closure

In previous sections, we discussed, in a general way, the kinetic and thermodynamic aspects of ring-closure reactions. J. E. Baldwin has supplied a more specific set of rules for certain closings of 3- to 7-membered rings.[13] These rules distinguish two types of ring closure, called
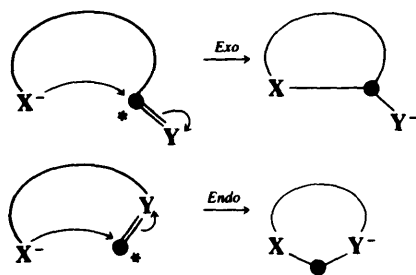
[12]Despite their transient existences, it is possible to study transition states of certain reactions in the gas phase with a technique called laser femtochemistry: Zewall; Bernstein *Chem. Eng. News* **1988,** 66, No. 45 (Nov. 7), 24-43. For another method, see Collings; Polanyi; Smith; Stolow; Tarr *Phys. Rev. Lett.* **1987,** 59, 2551.
[13]Baldwin *J. Chem. Soc., Chem. Commun.* **1976,** 734; Baldwin in *Further Perspectives in Organic Chemistry (Ciba Foundation Symposium 53)*; Elsevier North Holland: Amsterdam, 1979, pp. 85-99. See also Baldwin; Thomas; Kruse; Silberman *J. Org. Chem.* **1977,** 42, 3846; Baldwin; Lusch *Tetrahedron* **1982,** 38, 2939; Anselme *Tetrahedron Lett.* **1977,** 3615; Fountain; Gerhardt *Tetrahedron Lett.* **1978,** 3985.
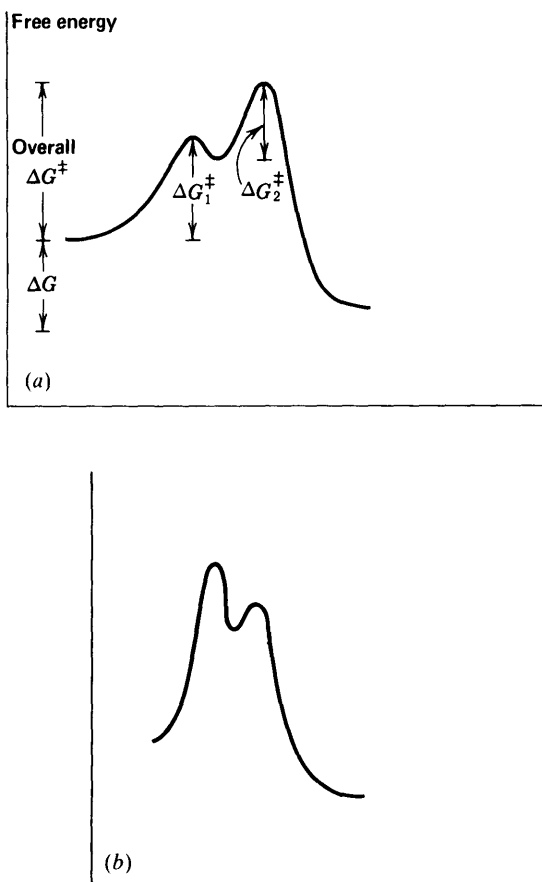
FIGURE 6.2 (a) Free-energy profile for a reaction with an intermediate. $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ are the free energy of activation for the first and second stages, respectively. (b) Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

Exo and *Endo*, and three kinds of atoms at the starred positions: *Tet* for sp^3, *Trig* for sp^2, and *Dig* for *sp*. The following are Baldwin's rules for closing rings of 3 to 7 members.

Rule 1. Tetrahedral systems
    (a) 3 to 7-*Exo-Tet* are all favored processes
    (b) 5 to 6-*Endo-Tet* are disfavored

Rule 2. Trigonal systems
    (a) 3 to 7-*Exo-Trig* are favored
    (b) 3 to 5-*Endo-Trig* are disfavored[14]
    (c) 6 to 7-*Endo-Trig* are favored

[14]For some exceptions to the rule in this case, see Trost; Bonk *J. Am. Chem. Soc.* **1985**, *107*, 1778; Auvray; Knochel; Normant *Tetrahedron Lett.* **1985**, *26*, 4455; Torres; Larson *Tetrahedron Lett.* **1986**, *27*, 2223.

Rule 3. Digonal systems
  (a) 3 to 4-*Exo-Dig* are disfavored
  (b) 5 to 7-*Exo-Dig* are favored
  (c) 3 to 7-*Endo-Dig* are favored

"Disfavored" does not mean it cannot be done—only that it is more difficult than the favored cases. These rules are empirical and have a stereochemical basis. The favored pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavored cases require severe distortion of bond angles and distances. Many cases in the literature are in substantial accord with these rules.

Kinetic and Thermodynamic Control

There are many cases in which a compound under a given set of reaction conditions can undergo competing reactions to give different products:

$$A \underset{\searrow C}{\overset{\nearrow B}{}}$$

Figure 6.3 shows a free-energy profile for a reaction in which B is thermodynamically more stable than C (lower ΔG), but C is formed faster (lower ΔG^*). If neither reaction is reversible, C will be formed in larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be B. Under these conditions the C that is first formed reverts to A,
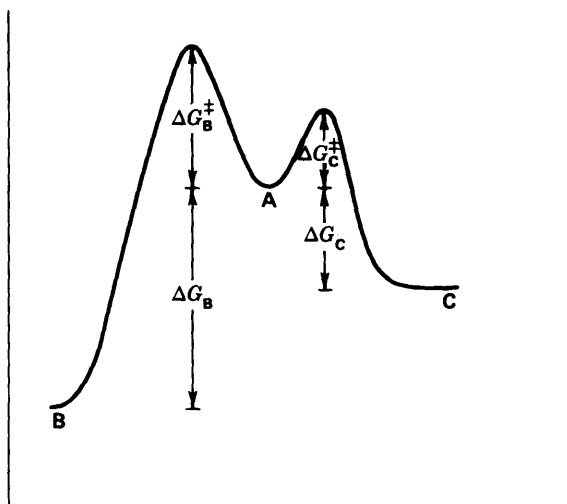

FIGURE 6.3 Free-energy profile illustrating kinetic versus thermodynamic control of product. The starting compound (**A**) can react to give either **B** or **C**.

while the more stable B does so much less. We say the product is *thermodynamically controlled*.[15] Of course, Figure 6.3 does not describe all reactions in which a compound A can give two different products. In many cases the more stable product is also the one that is formed faster. In such cases the product of kinetic control is also the product of thermodynamic control.

The Hammond Postulate

Since transition states have zero lifetimes, it is impossible to observe them directly and information about their geometries must be obtained from inference. In some cases our inferences can be very strong. For example, in the Sₙ2 reaction (p. 294) between CH_3I and I^- (a reaction in which the product is identical to the starting compound), the transition state should be perfectly symmetrical. In most cases, however, we cannot reach such easy conclusions, and we are greatly aided by the *Hammond postulate*,[16] which states that for any single reaction step, *the geometry of the transition state for that step resembles the side to which it is closer in free energy*. Thus, for an exothermic reaction like that shown in Figure 6.1, the transition state resembles the reactants more than the products, though not much more because there is a substantial ΔG^* on both sides. The postulate is most useful in dealing with reactions with intermediates. In the reaction illustrated in Figure 6.2a, the first transition state lies much closer in energy to the intermediate than to the reactants, and we can predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions that involve very reactive intermediates. Since we usually know more about the structure of intermediates than of transition states, we often use our knowledge of intermediates to draw conclusions about the transition states (for examples, see pp. 340, 750).

Microscopic Reversibility

In the course of a reaction the nuclei and electrons assume positions that at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction A → B there is an intermediate C, then C must also be an intermediate in the reaction B → A. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule that has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

Marcus Theory

It is often useful to compare the reactivity of one compound with that of similar compounds. What we would like to do is to find out how a reaction coordinate (and in particular the

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[15]For a discussion of thermodynamic vs. kinetic control, see Klumpp, Ref. 6, pp. 36-89.

[16]Hammond *J. Am. Chem. Soc.* **1955**, *77*, 334. For a discussion, see Fǎrcasiu *J. Chem. Educ.* **1975**, *52*, 76-79.

transition state) changes when one reactant molecule is replaced by a similar molecule. Marcus theory is a method for doing this.[17]

In this theory the activation energy ΔG^{+} is thought of as consisting of two parts.

1. An *intrinsic* free energy of activation, which would exist if the reactants and products had the same $\Delta G°$.[18] This is a kinetic part, called the *intrinsic barrier* ΔG_{int}^{+}.

2. A thermodynamic part, which arises from the $\Delta G°$ for the reaction.

The Marcus equation says that the overall ΔG^{+} for a one-step reaction is[19]
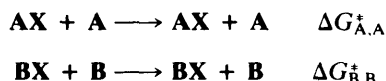
$$\Delta G^{+} = \Delta G_{int}^{+} + \tfrac{1}{2}\Delta G^{\Delta} + \frac{(\Delta G^{\Delta})^{2}}{16(\Delta G_{int}^{+} - w^{R})}$$

where the term ΔG^{Δ} stands for

$$\Delta G^{\Delta} = \Delta G° - w^{R} + w^{P}$$

w^{R}, a work term, is the free energy required to bring the reactants together and w^{P} is the work required to form the successor configuration from the products.
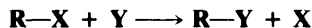
For a reaction of the type $AX + B \rightarrow BX$, the intrinsic barrier[20] ΔG_{int}^{+} is taken to be the average ΔG^{+} for the two symmetrical reactions

$$AX + A \longrightarrow AX + A \qquad \Delta G_{A,A}^{+}$$

$$BX + B \longrightarrow BX + B \qquad \Delta G_{B,B}^{+}$$

so that

$$\Delta G^{+} = \tfrac{1}{2}(\Delta G_{A,A}^{+} + \Delta G_{B,B}^{+})$$

One type of process that can successfully be treated by the Marcus equation is the S_N2 mechanism (p. 294)

$$R—X + Y \longrightarrow R—Y + X$$

When R is CH_3 the process is called *methyl transfer*.[21] For such reactions the work terms w^{R} and w^{P} are assumed to be very small compared to $\Delta G°$, and can be neglected, so that the Marcus equation simplifies to

$$\Delta G^{+} = \Delta G_{int}^{+} + \tfrac{1}{2}\Delta G° + \frac{(\Delta G°)^{2}}{16\Delta G_{int}^{+}}$$

The Marcus equation allows ΔG^{+} for $RX + Y \rightarrow RY + X$ to be calculated from the barriers of the two symmetrical reactions $RX + X \rightarrow RX + X$ and $RY + Y \rightarrow RY + Y$. The results of such calculations are generally in agreement with the Hammond postulate.

Marcus theory can be applied to any single-step process where something is transferred

[17]For reviews, see Albery *Annu. Rev. Phys. Chem.* **1980**, *31*, 227-263; Kreevoy; Truhlar, in Bernasconi, Ref. 25, pt. 1, pp. 13-95.
[18]$\Delta G°$ is the standard free energy; that is, ΔG at atmospheric pressure.
[19]Albery; Kreevoy, Ref. 21, pp. 98-99.
[20]For discussions of intrinsic barriers, see Lee *J. Chem. Soc., Perkin Trans. 2* **1989**, 943, *Chem. Soc. Rev.* **1990**, *19*, 133-145.
[21]For a review of Marcus theory applied to methyl transfer, see Albery; Kreevoy *Adv. Phys. Org. Chem.* **1978**, *16*, 87-157. See also Ref. 20; Lewis; Kukes; Slater *J. Am. Chem. Soc.* **1980**, *102*, 1619; Lewis, Hu *J. Am. Chem. Soc.* **1984**, *106*, 3292; Lewis; McLaughlin; Douglas *J. Am.Chem. Soc.* **1985**, *107*, 6668; Lewis *Bull. Soc. Chim. Fr.* **1988**, 259.

from one particle to another. It was originally derived for electron transfers,[22] and then extended to transfers of H^+ (see p. 258), H^-,[23] and $H\cdot$[24] as well as methyl transfers.

## METHODS OF DETERMINING MECHANISMS

There are a number of commonly used methods for determining mechanisms.[25] In most cases one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (3-25) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions. For example, any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$
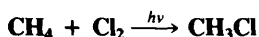
that fails to account for the formation of a small amount of ethane cannot be correct (see 4-1), and any mechanism proposed for the Hofmann rearrangement (8-14):

$$CH_3CH_2-\underset{\underset{O}{\|}}{C}-NH_2 \xrightarrow[H_2O]{NaOBr} CH_3CH_2NH_2$$
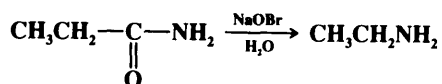
must account for the fact that the missing carbon appears as CO_2.

Determination of the Presence of an Intermediate

Intermediates are postulated in many mechanisms. There are several ways, none of them foolproof,[26] for attempting to learn whether or not an intermediate is present and, if so, its structure.

    1. *Isolation of an intermediate.* It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the Neber rearrangement (8-13)

$$R-CH_2-\underset{\underset{N-OTs}{\|}}{C}-R' \xrightarrow{OEt^-} R-\underset{\underset{NH_2}{|}}{CH}-\underset{\underset{O}{\|}}{C}-R'$$
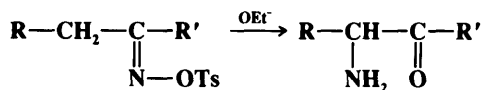
[22]Marcus *J. Phys. Chem.* **1963,** *67,* 853, *Annu. Rev. Phys. Chem.* **1964,** *15,* 155-196; Eberson *Electron Transfer Reactions in Organic Chemistry*; Springer: New York, 1987.

[23]Kreevoy; Lee *J. Am. Chem. Soc.* **1984,** *106,* 2550; Lee; Ostović; Kreevoy *J. Am. Chem. Soc.* **1988,** *110,* 3989; Kim; Lee; Kreevoy *J. Am. Chem. Soc.* **1990,** *112,* 1889.

[24]See for example Dneprovskii; Eliseenkov *J. Org. Chem. USSR* **1988,** *24,* 243.

[25]For a treatise on this subject, see Bernasconi *Investigation of Rates and Mechanisms of Reactions,* 4th ed. (vol. 6 of Weissberger *Techniques of Chemistry*), 2 pts.; Wiley: New York, 1986. For a monograph, see Carpenter *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.

[26]For a discussion, see Martin *J. Chem. Educ.* **1985,** *62,* 789.

the intermediate **1** has been isolated. If it can be shown that the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than

$$R—CH—C—R'$$

1
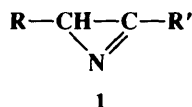
the starting compound, this constitutes strong evidence that the reaction involves that intermediate, though it is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.

2. *Detection of an intermediate.* In many cases an intermediate cannot be isolated but can be detected by ir, nmr, or other spectra.[27] The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see **1-2**). Free radical and triplet intermediates can often be detected by esr and by CIDNP (see Chapter 5). Free radicals (as well as radical ions and EDA complexes) can also be detected by a method that does not rely on spectra. In this method a double-bond compound is added to the reaction mixture, and its fate traced.[28] One possible result is cis-trans conversion. For example, *cis*–stilbene is isomerized to the trans isomer in the presence of RS• radicals, by this mechanism:

cis-stilbene   *trans*-stilbene
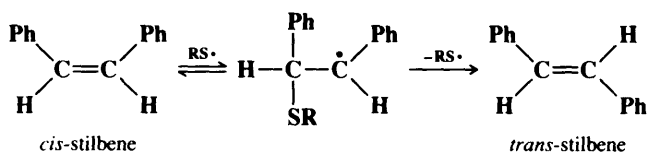
Since the trans isomer is more stable than the cis, the reaction does not go the other way, and the detection of the isomerized product is evidence for the presence of the RS• radicals.

3. *Trapping of an intermediate.* In some cases, the suspected intermediate is known to be one that reacts in a given way with a certain compound. The intermediate can then be trapped by running the reaction in the presence of that compound. For example, benzynes (p. 646) react with dienes in the Diels–Alder reaction (**5-47**). In any reaction where a benzyne is a suspected intermediate, the addition of a diene and the detection of the Diels–Alder adduct indicate that the benzyne was probably present.

4. *Addition of a suspected intermediate.* If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the correct products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The von Richter reaction (**3-25**) provides us with a good example here too. For many years it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (**6-5**). In fact, in 1954, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under normal von Richter conditions.[29] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although

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[27]For a review on the use of electrochemical methods to detect intermediates, see Parker *Adv. Phys. Org. Chem.* **1983**, *19*, 131-222. For a review of the study of intermediates trapped in matrixes, see Sheridan *Org. Photochem.* **1987**, *8*, 159-248.

[28]For a review, see Todres *Tetrahedron* **1987**, *43*, 3839-3861.

[29]Bunnett; Rauhut; Knutson; Bussell *J. Am. Chem. Soc.* **1954**, *76*, 5755.

2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[30] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route that does not involve 1-cyanonaphthalene. It also showed that even the conclusion that p-chlorobenzonitrile was an intermediate in the conversion of m-nitrochlorobenzene to p-chlorobenzoic acid must now be suspect, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.

The Study of Catalysis[31]

Much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, catalysts perform their actions by providing an alternate pathway for the reaction in which ΔG^* is less than it would be without the catalyst. Catalysts do not change ΔG.

Isotopic Labeling[32]

Much useful information has been obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction

$$\text{RCOO}^- + \text{BrCN} \longrightarrow \text{RCN}$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $R^{14}CO_2^-$ gave *radioactive* RCN.[33] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of CO_2 by CN (see **6-59**). Other radioactive isotopes are also frequently used as tracers, but even stable isotopes can be used. An example is the hydrolysis of esters

$$\text{R—C—OR'} + \text{H}_2\text{O} \longrightarrow \text{R—C—OH} + \text{R'OH}$$
$$\overset{\|}{\text{O}} \qquad\qquad\qquad \overset{\|}{\text{O}}$$
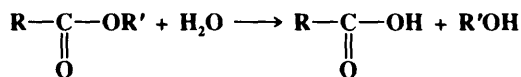
Which bond of the ester is broken, the acyl—O or the alkyl—O bond? The answer is found by the use of $H_2{}^{18}O$. If the acyl—O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see **0-10**). Although neither compound is radioactive, the one that contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case it is not necessary to use mass spectrometry, since ir and nmr spectra can be used to determine when deuterium has been substituted for hydrogen. ^{13}C is also nonradioactive; it can be detected by ^{13}C nmr.[34]

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient.

[30]Bunnett; Rauhut *J. Org. Chem.* **1956**, *21*, 944.

[31]For treatises, see Jencks *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Bender *Mechanisms of Homogeneous Catalysis from Protons to Proteins*; Wiley: New York, 1971. For reviews, see Coenen *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 57-64; and in Bernasconi, Ref. 25, pt. 1, the articles by Keeffe; Kresge, pp. 747-790; Haller; Delgass, pp. 951-979.

[32]For reviews see Wentrup, in Bernasconi, Ref. 25, pt. 1, pp. 613-661; Collins *Adv. Phys. Org. Chem.* **1964**, *2*, 3-91. See also the series *Isotopes in Organic Chemistry*.

[33]Douglas; Eccles; Almond *Can. J. Chem.* **1953**, *31*, 1127; Douglas; Burditt *Can. J. Chem.* **1958**, *36*, 1256.

[34]For a review, see Hinton; Oka; Fry *Isot. Org. Chem.* **1977**, *3*, 41-104.

Stereochemical Evidence[35]

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden[36] to give (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$, showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 295, 327). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with $KMnO_4$ gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction **5-35**).

Kinetic Evidence[37]

The rate of a homogeneous reaction[38] is the rate of disappearance of a reactant or appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) that does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

If the rate is proportional to the change in concentration of only one reactant (A), the *rate law* (the rate of change of concentration of A with time t) is

$$\text{Rate} = \frac{-d[A]}{dt} = k[A]$$

where k is the *rate constant* for the reaction. There is a minus sign because the concentration of A decreases with time. A reaction that follows such a rate law is called a *first-order reaction*. The units of k for a first-order reaction are sec^{-1}. The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\frac{-d[A]}{dt} = k[A][B] \qquad \text{or} \qquad \frac{-d[A]}{dt} = k[A]^2$$

For a second-order reaction the units are liters mol^{-1} sec^{-1} or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to [A] and to [B] is said to be first order in A and in B, second order overall.

[35]For lengthy treatments of the relationship between stereochemistry and mechanism, see Billups; Houk; Stevens, in Bernasconi, Ref. 25, pt. 1, pp. 663-746; Eliel *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; Newman *Steric Effects in Organic Chemistry*; Wiley, New York, 1956.
[36]Walden *Ber.* **1896**, *29*, 136, **1897**, *30*, 3149, **1899**, *32*, 1833.
[37]For the use of kinetics in determining mechanisms, see Connors *Chemical Kinetics*; VCH: New York, 1990; Zuman; Patel *Techniques in Organic Reaction Kinetics*; Wiley: New York, 1984; Drenth; Kwart *Kinetics Applied to Organic Reactions*; Marcel Dekker: New York, 1980; Hammett *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1970, pp. 53-100; Gardiner *Rates and Mechanisms of Chemical Reactions*; W.A. Benjamin: New York, 1969; Leffler; Grunwald *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; Jencks, Ref. 31, pp. 555-614; Refs. 6 and 25.
[38]A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

A reaction rate can be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is $2A + B \rightarrow C + D$ then, on a molar basis, A must disappear twice as fast as B, so that $-d[A]/dt$ and $-d[B]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. From this fact we attempt to learn the *molecularity*, which may be defined as the number of molecules that come together to form the activated complex. It is obvious that if we know how many (and which) molecules take part in the activated complex, we know a good deal about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions that take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order, one-step reaction is always unimolecular; a one-step reaction that is second order in A always involves two molecules of A; if it is first order in A and in B, then a molecule of A reacts with one of B, etc. For reactions that take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, though the calculations may get lengthy at times.[39] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.[40]

For reactions that take place in two or more steps, two broad cases can be distinguished:

1. The first step is slower than any subsequent step and is consequently rate-determining. In such cases, the rate law simply includes the reactants that participate in the slow step. For example, if the reaction $A + 2B \rightarrow C$ has the mechanism

$$A + B \xrightarrow{\text{slow}} I$$

$$I + B \xrightarrow{\text{fast}} C$$
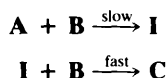
where I is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[A]}{dt} = k[A][B]$$

2. When the first step is not rate-determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I$$

$$I + B \xrightarrow{k_2} C$$
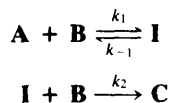
where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give C. The rate of disappearance of A is

$$\frac{-d[A]}{dt} = k_1[A][B] - k_{-1}[I]$$

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[39]For a discussion of how order is related to molecularity in many complex situations, see Szabó, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 2; Elsevier: New York, 1969, pp. 1-80.

[40]Many chemists prefer to use the term *rate-limiting step* or *rate-controlling step* for the slow step, rather than *rate-determining step*. See the definitions in Gold; Loening; McNaught; Sehmi *IUPAC Compendium of Chemical Terminology*; Blackwell Scientific Publications: Oxford, 1987, p. 337. For a discussion of rate-determining steps, see Laidler *J. Chem. Educ.* **1988**, *65*, 250.

Both terms must be included because A is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of I is

$$\frac{d[\text{I}]}{dt} = k_1[\text{A}][\text{B}] - k_{-1}[\text{I}] - k_2[\text{I}][\text{B}]$$

At first glance we seem no better off with this equation, but we can make the assumption that *the concentration of I does not change with time*, since it is an intermediate that is used up (going either to A + B or to C) as fast as it is formed. This assumption, called the assumption of the *steady state*,[41] enables us to set $d[\text{I}]/dt$ equal to zero and hence to solve for [I] in terms of the measurable quantities [A] and [B]:

$$[\text{I}] = \frac{k_1[\text{A}][\text{B}]}{k_2[\text{B}] + k_{-1}}$$

We now insert this value for [I] into the original rate expression to obtain

$$\frac{-d[\text{A}]}{dt} = \frac{k_1 k_2[\text{A}][\text{B}]^2}{k_2[\text{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\text{A}][\text{B}] \gg k_2[\text{I}][\text{B}]$$

Since the first step is an equilibrium

$$k_1[\text{A}][\text{B}] = k_{-1}[\text{I}]$$

we have

$$k_{-1}[\text{I}] \gg k_2[\text{I}][\text{B}]$$

Canceling [I], we get

$$k_{-1} \gg k_2[\text{B}]$$

We may thus neglect $k_2[\text{B}]$ in comparison with k_{-1} and obtain

$$\frac{-d[\text{A}]}{dt} = \frac{k_1 k_2}{k_{-1}} [\text{A}][\text{B}]^2$$

The overall rate is thus third order: first order in A and second order in B. Incidentally, if the first step is rate-determining (as was the case in the preceding paragraph), then

$$k_2[\text{B}] \gg k_{-1} \quad \text{and} \quad \frac{-d[\text{A}]}{dt} = k_1[\text{A}][\text{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate-determining, the rate law includes the reactants that participate in that step.

It is possible for a reaction to involve A and B in the rate-determining step, though only [A] appears in the rate law. This occurs when a large excess of B is present, say 100 times

[41]For a discussion, see Raines; Hansen *J. Chem. Educ.* **1988,** *65,* 757.

the molar quantity of A. In this case the complete reaction of A uses up only 1 mole of B, leaving 99 moles. It is not easy to measure the change in concentration of B with time in such a case, and it is seldom attempted, especially when B is also the solvent. Since [B], for practical purposes, does not change with time, the reaction appears to be first order in A though actually both A and B are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions can also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium that keeps the concentration of a reactant constant, e.g., in a buffer solution where H^+ or OH^- is a reactant. Pseudo-first-order conditions are frequently used in kinetic investigations for convenience in experimentation and calculations.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements.[42] The choice of a method depends on its convenience and its applicability to the reaction being studied. Among the most common methods are:

1. *Periodic or continuous spectral readings.*   In many cases the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be read, periodically or continuously. Among the methods used are ir and uv spectroscopy, polarimetry, nmr, and esr.[43]

2. *Quenching and analyzing.*   A series of reactions can be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed by spectral readings, titrations, chromatography, polarimetry, or any other method.

3. *Removal of aliquots at intervals.*   Each aliquot is then analyzed as in method 2.

4. *Measurement of changes in total pressure, for gas-phase reactions.*[44]

5. *Calorimetric methods.*   The output or absorption of heat can be measured at time intervals.

Special methods exist for kinetic measurements of very fast reactions.[45]

In any case what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted[46] to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is A_0, the first-order rate law

$$\frac{-d[A]}{dt} = k[A] \qquad \text{or} \qquad \frac{-d[A]}{[A]} = k \, dt$$

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln \frac{[A]}{A_0} = kt \qquad \text{or} \qquad \ln [A] = -kt + \ln A_0$$

[42]For a monograph on methods of interpreting kinetic data, see Zuman; Patel, Ref. 37. For a review of methods of obtaining kinetic data, see Batt, in Bamford; Tipper, Ref. 39, vol. 1, 1969, pp. 1-111.

[43]For a review of esr to measure kinetics, see Norman *Chem. Soc. Rev.* **1979**, *8*, 1-27.

[44]For a review of the kinetics of reactions in solution at high pressures, see le Noble *Prog. Phys. Org. Chem.* **1967**, *5*, 207-330. For reviews of synthetic reactions under high pressure, see Matsumoto; Sera; Uchida *Synthesis* **1985**, 1-26; Matsumoto; Sera *Synthesis* **1985**, 999-1027.

[45]For reviews, see Connors, Ref. 37, pp. 133-186; Zuman; Patel, Ref. 37, pp. 247-327; Krüger *Chem. Soc. Rev.* **1982**, *11*, 227-255; Hague, in Bamford; Tipper, Ref. 39, vol. 1, pp. 112-179, Elsevier, New York, 1969; Bernasconi, Ref. 25, pt. 2. See also Bamford; Tipper, Ref. 39, vol. 24, 1983.

[46]For discussions, much fuller than that given here, of methods for interpreting kinetic data, see Connors, Ref. 37, pp. 17-131; Ritchie *Physical Organic Chemistry*, 2nd ed.; Marcel Dekker: New York, 1990, pp. 1-35; Zuman; Patel, Ref. 37; Margerison, in Bamford; Tipper, Ref. 39, vol. 1, pp. 343-421, 1969; Moore; Pearson, Ref. 6, pp. 12-82; in Bernasconi, Ref. 25, pt. 1, the articles by Bunnett, pp. 251-372, Noyes, pp. 373-423, Bernasconi, pp. 425-485, Wiberg, pp. 981-1019.

Therefore, if a plot of ln [A] against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions it is customary to express the rate not only by the rate constant k but also by the *half-life*, which is the time required for half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for [A] to reach $A_0/2$, we may say that

$$\ln \frac{A_0}{2} = kt_{1/2} + \ln A_0$$

so that

$$t_{1/2} = \frac{\ln\left(\dfrac{A_0}{A_0/2}\right)}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in A and first order in B, second order overall, integration is complicated, but it can be simplified if equimolar amounts of A and B are used, so that $A_0 = B_0$. In this case

$$\frac{-d[A]}{dt} = k[A][B]$$

is equivalent to

$$\frac{-d[A]}{dt} = k[A]^2 \qquad \text{or} \qquad \frac{-d[A]}{[A]^2} = k\, dt$$

Integrating as before gives

$$\frac{1}{[A]} - \frac{1}{A_0} = kt$$

Thus, under equimolar conditions, if a plot of $1/[A]$ against t is linear, the reaction is second order with a slope of k. It is obvious that the same will hold true for a reaction second order in A.[47]

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases a reaction may be first order at low concentrations but second order at higher concentrations. In other cases fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetics are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining precise enough measurements.[48]

Nmr spectra can be used to obtain kinetic information in a completely different manner from that mentioned on p. 223. This method, which involves the study of nmr line shapes,[49] depends on the fact that nmr spectra have an inherent time factor: if a proton changes its environment less rapidly than about 10^3 times per second, an nmr spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the

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[47]We have given the integrated equations for simple first- and second-order kinetics. For integrated equations for a large number of kinetic types, see Margerison, Ref. 46, p. 361.

[48]See Hammett, Ref. 37, pp. 62-70.

[49]For a monograph, see Oki *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: New York, 1985. For reviews, see Fraenkel, in Bernasconi, Ref. 25, pt. 2, pp. 547-604; Aganov; Klochkov; Samitov *Russ. Chem. Rev.* **1985**, *54*, 931-947; Roberts *Pure Appl. Chem.* **1979**, *51*, 1037-1047; Binsch *Top. Stereochem.* **1968**, *3*, 97-192; Johnson *Adv. Magn. Reson.* **1965**, *1*, 33-102.

C—N bond of N,N-dimethylacetamide is slower than 10^3 rotations per second, the two N-methyl groups each have separate chemical shifts since they are not equivalent, one being
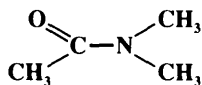
cis to the oxygen and the other trans. However, if the environmental change takes place more rapidly than about 10^3 times per second, only one line is found, at a chemical shift that is the weighted average of the two individual positions. In many cases, two or more lines are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes. This method is not limited to changes in proton line shapes but can also be used for other atoms that give nmr spectra and for esr spectra.

Several types of mechanistic information can be obtained from kinetic studies.

1. From the order of a reaction, information can be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. For any mechanism that can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed on pp. 221-223. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable, i.e., they predict the same rate law.

2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they can tell us the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, etc.

3. If the rate is measured at several temperatures, in most cases a plot of ln k against $1/T$ (T stands for absolute temperature) is nearly linear[50] with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A a constant called the *frequency factor*. This permits the calculation of E_a, which is the Arrhenius activation energy of the reaction. $\Delta H^{\ne}$ can then be obtained by

$$E_a = \Delta H^{\ne} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ne}$ by the formula[51]

$$\frac{\Delta S^{\ne}}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

[50]For a review of cases where such a plot is nonlinear, see Blandamer; Burgess; Robertson; Scott *Chem. Rev.* **1982,** *82,* 259-286.
[51]For a derivation of this equation, see Bunnett, in Bernasconi, Ref. 25, pt. 1, p. 287.

for energies in calorie units. For joule units the formula is

$$\frac{\Delta S^*}{19.15} = \log k - 10.753 - \log T + \frac{E_a}{19.15T}$$

One then obtains ΔG^* from $\Delta G^* = \Delta H^* - T\Delta S^*$.

Isotope Effects

When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*[52] and are expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[53] Therefore, D—C, D—O, D—N bonds, etc., have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, etc. Complete dissociation of a deuterium bond consequently requires more energy than that for a corresponding hydrogen bond in the same environment (Figure 6.4). If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but
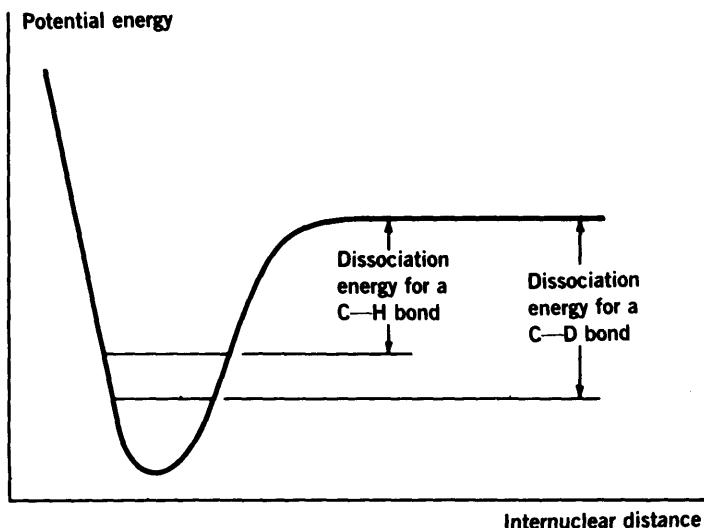

FIGURE 6.4 A C—D bond has a lower zero-point energy than does a corresponding C—H bond; thus the dissociation energy is higher.

[52]For a monograph, see Melander; Saunders *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980. For reviews, see Isaacs *Physical Organic Chemistry*; Longman Scientific and Technical: Essex, 1987, pp. 255-281; Lewis *Top. Curr. Chem.* **1978**, *74*, 31-44; Saunders, in Bernasconi, Ref. 25, pp. 565-611; Bell *The Proton in Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1973, pp. 226-296, *Chem. Soc. Rev.* **1974**, *3*, 513-544; Bigeleisen; Lee; Mandel *Annu. Rev. Phys. Chem.* **1973**, 24, 407-440; Wolfsberg *Annu. Rev. Phys. Chem.* **1969**, *20*, 449-478; Saunders *Surv. Prog. Chem.* **1966**, *3*, 109-146; Simon; Palm *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 920-933 [*Angew. Chem. 78*, 993-1007]; Jencks, Ref. 31, pp. 243-281. For a review of temperature dependence of primary isotope effects as a mechanistic criterion, see Kwart *Acc. Chem. Res.* **1982**, 15, 401-408. For a review of the effect of pressure on isotope effects, see Isaacs, *Isot. Org. Chem.* **1984**, 6, 67-105. For a review of isotope effects in the study of reactions in which there is branching from a common intermediate, see Thibblin; Ahlberg *Chem. Soc. Rev.* **1989**, *18*, 209-224. See also the series *Isotopes in Organic Chemistry*.
[53]The reduced mass μ of two atoms connected by a covalent bond is $\mu = m_1 m_2/(m_1 + m_2)$.

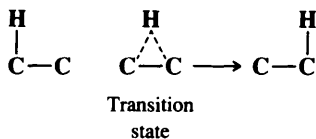if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (2-4)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$
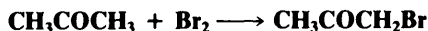
the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was prior tautomerization of the acetone:

$$\overset{\displaystyle OH}{\underset{\displaystyle |}{CH_3COCH_3}} \rightleftharpoons CH_3\overset{|}{C}{=}CH_2$$
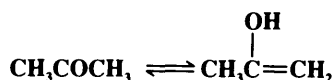
In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see 2-3). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, k_H/k_D was found to be about 7.[54] Deuterium isotope effects usually range from 1 (no isotope effect at all) to about 7 or 8, though in a few cases, larger[55] or smaller values have been reported.[56] Values of k_H/k_D smaller that 1 are called *inverse isotope effects*. Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[57] Also, calculations show that isotope effects are at a maximum when the hydrogen in the transition state is on the straight line connecting the two atoms between which the hydrogen is being transferred and that for sufficiently nonlinear configurations they decrease to $k_H/k_D = 1$ to 2.[58] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms, e.g., in a 1,2 migration of a hydrogen

$$\overset{\displaystyle H}{\underset{\displaystyle |}{C}}{-}C \qquad \overset{\displaystyle H}{\underset{\displaystyle C{-}C}{\overset{\displaystyle \wedge}{}}} \longrightarrow C{-}\overset{\displaystyle H}{\underset{\displaystyle |}{C}}$$

Transition
state

To measure isotope effects it is not always necessary to prepare deuterium-enriched starting compounds. It can also be done by measuring the change in deuterium concentration at specific sites between a compound containing deuterium in natural abundance and the reaction product, using a high field nmr instrument.[59]

[54]Reitz; Kopp *Z. Phys. Chem., Abt. A* **1939**, *184*, 429.

[55]For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis; Funderburk *J. Am. Chem. Soc.* **1967**, *89*, 2322. The high isotope effect in this case has been ascribed to *tunneling* of the proton: because it is so small a hydrogen atom can sometimes get through a thin potential barrier without going over the top, i.e., without obtaining the usually necessary activation energy. A deuterium, with a larger mass, is less able to do this. The phenomenon of tunneling is a consequence of the uncertainty principle. k_H/k_T for the same reaction is 79: Lewis; Robinson *J. Am. Chem. Soc.* **1968**, *90*, 4337. An even larger deuterium isotope effect (~50) has been reported for the oxidation of benzyl alcohol. This has also been ascribed to tunneling: Roecker; Meyer *J. Am. Chem. Soc.* **1987**, *109*, 746. For discussions of high isotope effects, see Kresge; Powell *J. Am. Chem. Soc.* **1981**, *103*, 201; Caldin; Mateo; Warrick *J. Am. Chem. Soc.* **1981**, *103*, 202. For arguments that high isotope effects can be caused by factors other than tunneling, see McLennan *Aust. J. Chem.* **1979**, *32*, 1883; Thibblin *J. Phys. Org. Chem.* **1988**, *1*, 161; Kresge; Powell *J. Phys. Org. Chem.* **1990**, *3*, 55.

[56]For a review of a method for calculating the magnitude of isotope effects, see Sims; Lewis *Isot. Org. Chem.* **1984**, *6*, 161-259.

[57]Kwart; Latimore *J. Am. Chem. Soc.* **1971**, *93*, 3770; Pryor; Kneipp *J. Am. Chem Soc.* **1971**, *93*, 5584; Bell; Cox *J. Chem. Soc. B* **1971**, 783; Bethell; Hare; Kearney *J. Chem. Soc.. Perkin Trans. 2* **1981**, 684, and references cited in these papers. See, however, Motell; Boone; Fink *Tetrahedron* **1978**, *34*, 1619.

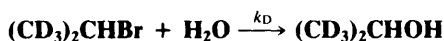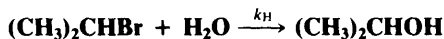[58]More O'Ferrall *J. Chem. Soc. B* **1970**, 785, and references cited therein.

[59]Pascal; Baum; Wagner; Rodgers; Huang *J. Am. Chem. Soc.* **1986**, *108*, 6477.

The substitution of tritium for hydrogen gives isotope effects that are numerically larger. Isotope effects have also been observed with other elements, but they are much smaller, about 1.02 to 1.10. For example, $k_{^{12}C}/k_{^{13}C}$ for

$$\text{Ph*CH}_2\text{Br} + \text{CH}_3\text{O}^- \xrightarrow{\text{CH}_3\text{OH}} \text{Ph*CH}_2\text{OCH}_3$$
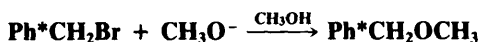
is 1.053.[60] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.[61]

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects*,[62] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided into α and β effects. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:

$$\text{(CH}_3)_2\text{CHBr} + \text{H}_2\text{O} \xrightarrow{k_\text{H}} \text{(CH}_3)_2\text{CHOH}$$

$$\text{(CD}_3)_2\text{CHBr} + \text{H}_2\text{O} \xrightarrow{k_\text{D}} \text{(CD}_3)_2\text{CHOH}$$

where k_H/k_D was found to be 1.34.[63] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbocation character.[64] Although the C—H bond in question is not broken in the transition state, the carbocation is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is anti to the leaving group[65] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[66] There is evidence that at least some β isotope effects are steric in origin[67] (e.g., a CD$_3$ group has a smaller steric requirement than a CH$_3$ group) and a field-effect explanation has also been suggested (CD$_3$ is apparently a better electron donor than CH$_3$[68]), but hyperconjugation is the most probable cause in most instances.[69] Part of the difficulty in attempting to explain these effects is their small size,

[60]Stothers; Bourns *Can. J. Chem.* **1962**, *40*, 2007. See also Ando; Yamataka; Tamura; Hanafusa *J. Am. Chem. Soc.* **1982**, *104*, 5493.

[61]For a review of carbon isotope effects, see Willi *Isot. Org. Chem.* **1977**, *3*, 237-283.

[62]For reviews, see Westaway *Isot. Org. Chem.* **1987**, 7, 275-392; Sunko; Hehre *Prog. Phys. Org. Chem.* **1983**, 14, 205-246; Shiner, in Collins; Bowman *Isotope Effects in Chemical Reactions*; Van Nostrand-Reinhold: Princeton, 1970, pp. 90-159; Laszlo; Welvart *Bull. Soc. Chim. Fr.* **1966**, 2412-2438; Halevi *Prog. Phys. Org. Chem.* **1963**, *1*, 109-221. For a review of model calculations of secondary isotope effects, see McLennan *Isot. Org. Chem.* **1987**, 7, 393-480. See also Ref. 56.

[63]Leffek; Llewellyn; Robertson *Can. J. Chem.* **1960**, *38*, 2171.

[64]Bender; Feng *J. Am. Chem. Soc.* **1960**, *82*, 6318; Jones; Bender *J. Am. Chem. Soc.* **1960**, *82*, 6322.

[65]Shiner; Murr; Heinemann *J. Am. Chem. Soc.* **1963**, *85*, 2413; Shiner; Humphrey *J. Am. Chem. Soc.* **1963**, *85*, 2416; Shiner; Jewett *J. Am. Chem. Soc.* **1964**, *86*, 945; DeFrees; Hehre; Sunko *J. Am. Chem. Soc.* **1979**, *101*, 2323. See also Siehl; Walter *J. Chem. Soc., Chem. Commun.* **1985**, 76.

[66]Shiner; Kriz *J. Am. Chem. Soc.* **1964**, *86*, 2643.

[67]Bartell *J. Am. Chem. Soc.* **1961**, *83*, 3567; Brown; Azzaro; Koelling; McDonald *J. Am. Chem. Soc.* **1966**, *88*, 2520; Kaplan; Thornton *J. Am. Chem. Soc.* **1967**, *89*, 6644; Carter; Dahlgren *Acta Chem. Scand.* **1970**, *24*, 633; Leffek; Matheson *Can. J. Chem.* **1971**, *49*, 439; Sherrod; Boekelheide *J. Am. Chem. Soc.* **1972**, *94*, 5513.

[68]Halevi; Nussim; Ron *J. Chem. Soc.* **1963**, 866; Halevi; Nussim *J. Chem. Soc.* **1963**, 876.

[69]Karabatsos; Sonnichsen; Papaioannou; Scheppele; Shone *J. Am. Chem. Soc.* **1967**, *89*, 463; Kresge; Preto *J. Am. Chem. Soc.* **1967**, *89*, 5510; Jewett; Dunlap *J. Am. Chem. Soc.* **1968**, *90*, 809; Sunko; Szele; Hehre *J. Am. Chem. Soc.* **1977**, *99*, 5000; Kluger; Brandl *J. Org. Chem.* **1986**, *51*, 3964.

ranging only as high as about 1.5.[70] Another complicating factor is that they can change with temperature. In one case[71] k_H/k_D was 1.00 ± 0.01 at 0°C, 0.90 ± 0.01 at 25°C, and 1.15 ± 0.09 at 65°C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbocation character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called α *secondary isotope effects*) are varied, with values so far reported[72] ranging from 0.87 to 1.26.[73] These effects are also correlated with carbocation character. Nucleophilic substitutions that do not proceed through carbocation intermediates (SN2 reactions) have α isotope effects near unity.[74] Those that do involve carbocations (SN1 reactions) have higher α isotope effects, which depend on the nature of the leaving group.[75] The accepted explanation for α isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[76] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. α isotope effects on SN2 reactions can vary with concentration,[77] an effect attributed to a change from a free nucleophile to one that is part of an ion pair[78] (see p. 350). This illustrates the use of secondary isotope effects as a means of studying transition state structure. γ secondary isotope effects have also been reported.[79]

Another kind of isotope effect is the *solvent isotope effect*.[80] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them.

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds that are not breaking.

2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.

3. The extent or nature of solvent-solute interactions may be different in the deuterated and nondeuterated solvents; this may change the energies of the transition state and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[81]

[70]A value for k_{CH_3}/k_{CD_3} of 2.13 was reported for one case: Liu; Wu *Tetrahedron Lett.* **1986**, *27*, 3623.

[71]Halevi; Margolin *Proc. Chem. Soc.* **1964**, 174.

[72]A value of 2.0 has been reported in one case, for a cis-trans isomerization, rather than a nucleophilic substitution: Caldwell; Misawa; Healy; Dewar *J. Am. Chem. Soc.* **1987**, *109*, 6869.

[73]Shiner; Buddenbaum; Murr; Lamaty *J. Am. Chem. Soc.* **1968**, *90*, 418; Harris; Hall; Schleyer *J. Am. Chem. Soc.* **1971**, *93*, 2551.

[74]For reported exceptions, see Tanaka; Kaji; Hayami *Chem. Lett.* **1972**, 1223; Westaway *Tetrahedron Lett.* **1975**, 4229.

[75]Shiner; Dowd *J. Am. Chem. Soc.* **1971**, *93*, 1029; Shiner; Fisher *J. Am. Chem. Soc.* **1971**, *93*, 2553; Willi; Ho; Ghanbarpour *J. Org. Chem.* **1972**, *37*, 1185; Shiner; Neumann; Fisher *J. Am. Chem. Soc.* **1982**, *104*, 354; and references cited in these papers.

[76]Streitwieser; Jagow; Fahey; Suzuki *J. Am. Chem. Soc.* **1958**, *80*, 2326.

[77]Westaway; Waszczylo; Smith; Rangappa *Tetrahedron Lett.* **1985**, *26*, 25.

[78]Westaway; Lai *Can. J. Chem.* **1988**, *66*, 1263.

[79]Leffek; Llewellyn; Robertson *J. Am. Chem. Soc.* **1960**, *82*, 6315, *Chem. Ind. (London)* **1960**, 588; Werstiuk; Timmins; Cappelli *Can. J. Chem.* **1980**, *58*, 1738.

[80]For reviews, see Alvarez; Schowen *Isot. Org. Chem.* **1987**, *7*, 1-60; Kresge; More O'Ferrall, Powell *Isot. Org. Chem.* **1987**, *7*, 177-273; Schowen *Prog. Phys. Org. Chem.* **1972**, *9*, 275-332; Gold *Adv. Phys. Org. Chem.* **1969**, *7*, 259-331; Laughton; Robertson, in Coetzee; Ritchie *Solute–Solvent Interactions;* Marcel Dekker: New York, 1969, pp. 399-538. For a review of the effect of isotopic changes in the solvent on the properties of nonreacting solutes, see Arnett; McKelvey, in Coetzee; Ritchie, cited above, pp. 343-398.

[81]Swain; Bader *Tetrahedron* **1960**, *10*, 182; Bunton; Shiner *J. Am. Chem. Soc.* **1961**, *83*, 42, 3207, 3214; Swain; Thornton *J. Am. Chem. Soc.* **1961**, *83*, 3884, 3890. See also Mitton; Gresser; Schowen *J. Am. Chem. Soc.* **1969**, *91*, 2045.

It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[82]

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by his or her ingenuity.

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[82]More O'Ferrall; Koeppl; Kresge *J. Am. Chem. Soc.* **1971**, *93*, 9.