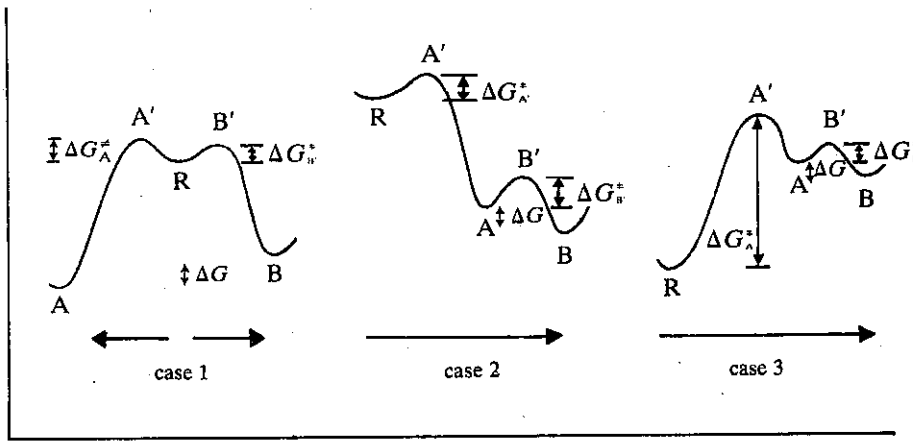


Fig. 4.4. Kinetic versus thermodynamic control.

discuss these methods but there are reviews available which can be consulted for information about this area.[29]

4.4. Basic Mechanistic Concepts: Kinetic versus Thermodynamic Control, Hammond's Postulate, and the Curtin–Hammett Principle

Use of two-dimensional potential energy diagrams can provide insight into the important general concepts listed in the heading of this section. There are many organic reactions in which the energy requirements for competing reaction paths are rather similar. It is important to be able to analyze the factors that may permit a particular reaction path to dominate.

4.4.1. Kinetic versus Thermodynamic Control

Product composition may be governed by the equilibrium thermodynamics of the system. When this is true, the product composition is governed by *thermodynamic control.* Alternatively, product composition may be governed by competing rates of formation of products. This is called *kinetic control.*

Let us consider cases 1–3 in Fig. 4.4. In case 1, $\Delta G^{\ddagger}$'s for formation of transition states A′ and B′ from the reactant R are much less than $\Delta G^{\ddagger}$'s for formation of A′ and B′ from A and B, respectively. If the latter two $\Delta G^{\ddagger}$'s are sufficiently large that the competitively formed products B and A do not return to R, the ratio of the products A and B at the end of the reaction will not depend on their relative

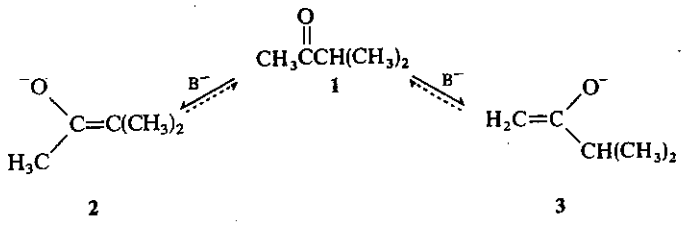
29. J. Hine, *Physical Organic Chemistry,* McGraw-Hill, New York, 1962, pp. 95–98; P. R. Wells, *Linear Free Energy Relationships,* Academic Press, New York, 1968, pp. 35–44; M. Charton, *Prog. Phys. Org. Chem.* **10,** 81 (1973).

stabilities, but only on their relative rates of formation. The formation of A and B is effectively irreversible in these circumstances. The energy plot in case 1 corresponds to this situation. This is a case of kinetic control. The relative amounts of products A and B will depend on the heights of the activation barriers $\Delta G_A^{\ddagger}$ and $\Delta G_b^{\ddagger}$.

In case 2, the lowest $\Delta G^{\ddagger}$ is that for formation of A′ from R. However, the $\Delta G^{\ddagger}$ for formation of B′ from A is not much larger. System 2 might be governed by either kinetic or thermodynamic factors. Conversion of R to A will be only slightly more favorable than conversion of A to B. If the reaction conditions are carefully adjusted, it will be possible for A to accumulate and not proceed to B. Under such conditions, A will be the dominant product and the reaction will be under kinetic control. Under somewhat more energetic conditions, for example, at a higher temperature, A will be transformed to B, and under these conditions the reaction will be under thermodynamic control. A and B will equilibrate, and the product ratio will depend on the equilibrium constant determined by ΔG.

In case 3, the barrier separating A and B is very small relative to that for formation of A′ from R. In this case, A and B will equilibrate more rapidly than R is converted to A. Adjustment of temperature or other reaction conditions would not change the A:B ratio at the end of the reaction very much.

The idea of kinetic versus thermodynamic control can be illustrated by discussing briefly the case of formation of enolate anions from unsymmetrical ketones. This is a very important case for synthesis and will be discussed more fully in Chapter 1 of Part B. Any ketone with more than one type of α-hydrogen can give rise to more than one enolate. Many studies have shown that the ratio of the possible enolates depends on the reaction conditions.[30] This can be illustrated for the case of methyl isopropyl ketone (3-methyl-2-butanone). If the base chosen is a strong, sterically hindered one and the solvent is aprotic, the major enolate formed is **3**. If a protic solvent is used or if a weaker base (one comparable in basicity to the ketone enolate) is used, the dominant enolate is **2**. Enolate **3** is the "kinetic enolate" while **2** is the thermodynamically favored enolate.



2 **3**

The structural and mechanistic basis for the relationships between kinetic versus thermodynamic control and the reaction conditions is as follows. The α-hydrogens of the methyl group are less hindered sterically than the α-hydrogen of the isopropyl group. As a result, abstraction of one of these hydrogens as a proton is faster than

30. J. d'Angelo, *Tetrahedron* **32**, 2979 (1976); H. O. House, *Modern Synthetic Reactions*, Second Edition, W. A. Benjamin, Menlo Park, California, 1972.

for the isopropyl hydrogen. This effect is magnified when the base is sterically hindered so that it is particularly sensitive to the difference in the steric situation of the competing hydrogens. If the base is very strong, the enolate will not be reconverted to the ketone because the enolate will be too weak a base to regain the proton. These conditions correspond to case 1 in Fig. 4.4 and represent a case of kinetic control. If a weaker base is used or if the solvent is protic, protons can be transferred reversibly between the isomeric enolates and the base (because the base strengths of the enolate and the base are comparable). Under these conditions, the more stable enolate will be the predominant one because the enolates are equilibrated. The more substituted enolate **2** is the more stable of the pair, just as more substituted alkenes are more stable than terminal alkenes.

4.4.2. Hammond's Postulate

Because of the crucial role played by the energy of the transition state in determining the rates of chemical reactions, information about the structure of transition states is crucial to understanding reaction mechanisms. However, because transition states have only transitory existence, it has not been possible to make experimental measurements that would provide direct information about the structure of transition states. Hammond has discussed the circumstances under which it is valid to relate transition state structure to the structure of reactants, intermediates, and products.[31] His statements concerning transition state structure are known as *Hammond's postulates.* Discussing individual steps in a reaction mechanism, Hammond's postulate states "if two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of molecular structure."

This statement can best be discussed with reference to potential energy diagrams. Case 1 in Fig. 4.5 represents a highly exothermic step with a low activation energy. It follows from Hammond's postulate that in this step the transition state will structurally resemble the reactant since they are close in energy and therefore interconverted by a small structural change. This is depicted in the potential energy diagram by a small displacement toward product along the reaction coordinate. Case 2 describes a step in which the transition state is a good deal higher in energy than either the reactant or the product. In this case, neither the reactant nor the product will be a good model of the transition state. Case 3 illustrates an endothermic step such as would occur in the formation of an unstable intermediate. In this case, the energy of the transition state is similar to that of the intermediate and the transition state should be similar in structure to the intermediate.

The significance of the concept incorporated in Hammond's postulate then is that, in appropriate cases, it permits discussion of transition state structure in terms

31. G. S. Hammond, *J. Am. Chem. Soc.* 77, 334 (1955).

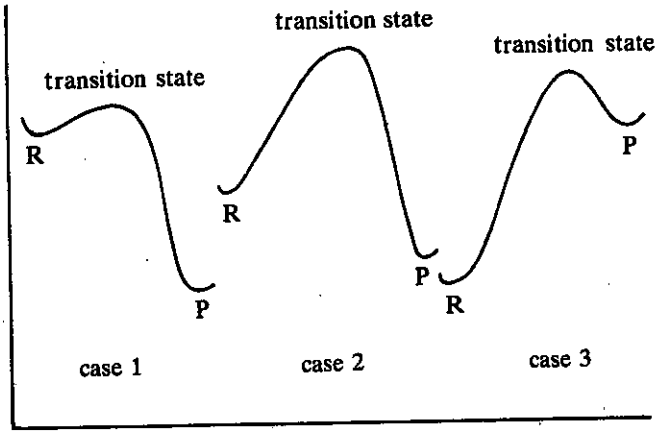
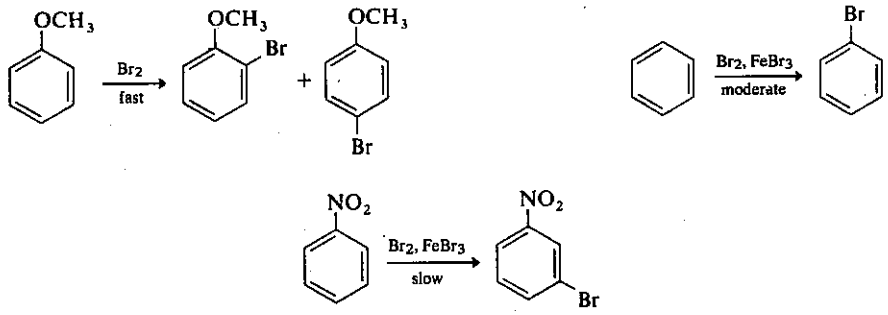


Fig. 4.5. Some typical potential energy diagrams that illustrate the application of Hammond's postulate.

of the reactants, intermediates, or products in a multistep reaction sequence. The postulate indicates that the cases where such comparison is appropriate are those in which the transition state is close in energy to the reactant, intermediate, or product.

The case of electrophilic aromatic substitution can illustrate a situation in which it is useful to discuss transition state structure in terms of a reaction intermediate. The *ortho–para-* and *meta*-directing effects of aromatic substituents were among the first structure–reactivity relationships to be developed in organic chemistry. Certain functional groups were found to activate aromatic rings toward substitution and to direct the entering electrophile to the *ortho* and *para* positions whereas others were deactivating and led to substitution in the *meta* position. The bromination of anisole (methoxybenzene), benzene, and nitrobenzene can serve as cases for discussion.

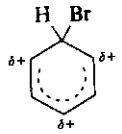


It can be demonstrated that the reactions are kinetically controlled. It is therefore the $\Delta G^{\ddagger}$ value that holds the key to the connection between the rate effects and the substituent's directing effects. But to discuss $\Delta G^{\ddagger}$ satisfactorily, we must know something about the reaction mechanism and the nature of the competing transition states. Electrophilic aromatic substitution will be discussed in detail in Chapter 10.

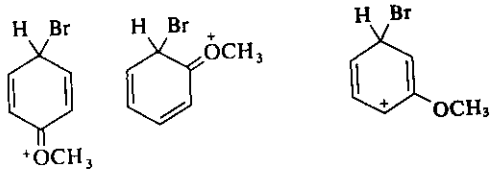
Evidence presented there will indicate that electrophilic aromatic substitution involves a distinct intermediate and two less well-defined states. The potential energy diagram in Fig. 4.6 is believed to be a good representation of the energy changes that occur during bromination. By application of the Hammon postulate, we can conclude that the rate-determining step involves formation of a transition state that should closely resemble the intermediate σ complex. It is therefore legitimate to discuss effects of substituents on the transition state in terms of the structure of this intermediate.

Since the product composition is kinetically controlled, the isomer ratio will be governed by the relative magnitudes of $\Delta G_o^{\ddagger}$, $\Delta G_m^{\ddagger}$, and $\Delta G_p^{\ddagger}$, the energies of activation for the *ortho*, *meta*, and *para* transition states, respectively. In Fig. 4.7 a qualitative comparison of these $\Delta G^{\ddagger}$ values is made.

At the transition state, a considerable positive charge is present on the benzene ring, primarily at positions 2, 4, and 6 in relation to the entering bromine.



The electron-releasing methoxy group can interact directly to delocalize the charge and stabilize the intermediates leading to *o*- and *p*-bromoanisole. It cannot stabilize the intermediate leading to *m*-bromoanisole.



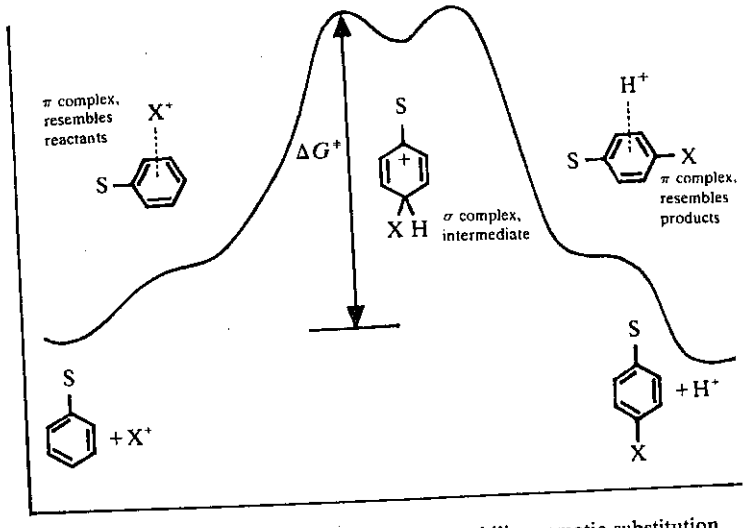
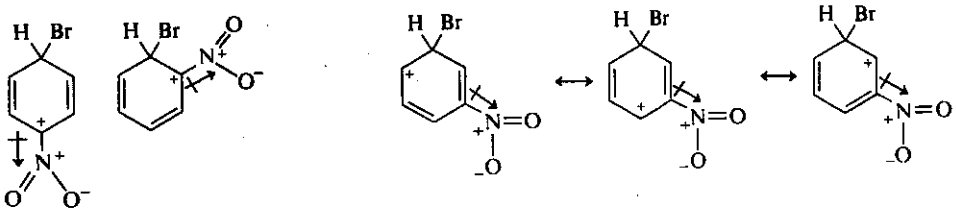


Fig. 4.6. Potential energy diagram for electrophilic aromatic substitution.

The *ortho* and *para* intermediates are therefore stabilized relative to benzene but the *meta* intermediate is not, as is illustrated in Fig. 4.7. As a result, anisole reacts faster than benzene, and the products are mainly the *ortho* and *para* isomers.

In the case of nitrobenzene, the electron-withdrawing nitro group is not able to stabilize the positive charge in the σ-complex intermediate. In fact, it strongly destabilizes the intermediate. This destabilization is greatest in the *ortho* and *para* intermediates, which place positive charge on the nitro-substituted carbon. The *meta* transition state is also destablized relative to benzene, but not as much as the *ortho* and *para* transition states. As a result, nitrobenzene is less reactive than benzene and the product is mainly the *meta* isomer



The substituent effects in aromatic electrophilic substitution can be analyzed in terms of resonance effects. In other systems, stereoelectronic effects or steric

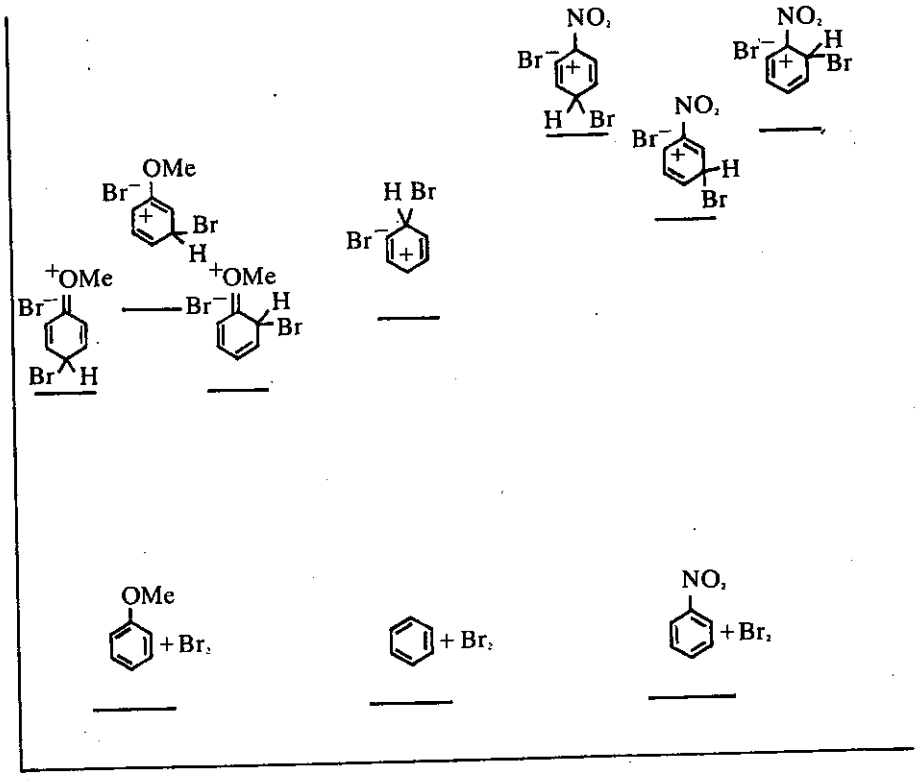


Fig. 4.7. Transition state energies in bromination.

effects might be more important. Whatever the nature of the substituent effects, the Hammond postulate insists that structural discussion of transition states in terms of reactants, intermediates, or products is valid only when their energies are similar.

4.4.3. The Curtin–Hammett Principle

In Chapter 3, equilibria among conformers of organic molecules were discussed. At this point, let us consider in a general way the effect that conformational equilibria can have on a chemical reaction. Under what circumstances can the position of the conformational equilibrium for a reactant determine which of two competing reaction paths will be followed? A potential energy diagram is shown in Fig. 4.8. In most cases, the energy of activation for a chemical reaction will be greater than that for a conformational equilibrium as is illustrated in the figure. If this is the case, $\Delta G_a^{\ddagger}$ and $\Delta G_b^{\ddagger} \gg \Delta G_c$. The conformers of the reactant are in equilibrium and are interconverted at a rate much faster than that at which the competing reactions occur.

$$\mathrm{B} \rightleftharpoons \mathrm{A} \qquad K_c = \frac{[\mathrm{A}]}{[\mathrm{B}]}$$

$$\text{rate of formation of product } P_\mathrm{A} = \frac{dP_\mathrm{A}}{dt} = k_a[\mathrm{A}] = k_a K_c[\mathrm{B}]$$

$$\text{rate of formation of product } P_\mathrm{B} = \frac{dP_\mathrm{B}}{dt} = k_b[\mathrm{B}]$$

$$\text{product ratio} = \frac{dP_\mathrm{A}/dt}{dP_\mathrm{B}/dt} = \frac{k_a K_c[\mathrm{B}]}{k_b[\mathrm{B}]} = \frac{k_a K_c}{k_b}$$

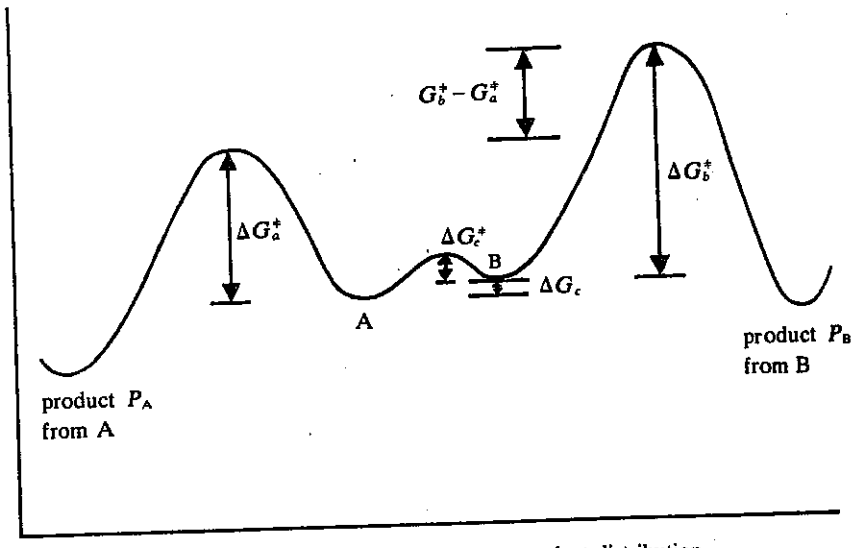


Fig. 4.8. Effect of conformation on product distribution.

According to transition state theory,

$$k_r = \frac{\kappa kT}{h} e^{-\Delta G^{\ddagger}/RT} \qquad \text{and} \qquad K_c = e^{-(-\Delta G_c)/RT}$$

$$\text{product ratio} = \frac{(\kappa kT/h)\, e^{-\Delta G_a^{\ddagger}/RT}\, e^{+\Delta G_c/RT}}{(\kappa kT/h)\, e^{-\Delta G_b^{\ddagger}/RT}}$$

$$= e^{(-\Delta G_a^{\ddagger}+\Delta G_b^{\ddagger}+\Delta G_c)/RT}$$

But from Fig. 4.8,

$$\Delta G_b^{\ddagger} - \Delta G_a^{\ddagger} + \Delta G_c = G_b^{\ddagger} - G_a^{\ddagger}$$

The product ratio is therefore not determined by ΔG_c but instead primarily on the relative energy of the two transition states leading to A and B.

The conclusion that the ratio of products formed from conformational isomers is not determined by the conformation population ratio is known as the *Curtin–Hammett principle.*[32] While the rate of the formation of the products is dependent upon the relative concentration of the two conformers, since $\Delta G_b^{\ddagger}$ is decreased relative to $\Delta G_a^{\ddagger}$ to the extent of the difference in the two conformational energies, the conformational preequilibrium is established rapidly, relative to the two competing product-forming steps.[33] The position of the conformational equilibrium cannot control the product ratio. The reaction may proceed through a minor conformation if it is the one which provides access to the lowest-energy transition state.

The same arguments can be applied to other energetically facile interconversions of two potential reactants. For example, many organic molecules undergo rapid proton shifts (tautomerism) and the chemical reactivity of the two isomers may be quite different. It is not valid, however, to deduce the ratio of two tautomers on the basis of subsequent reactions which have activation energies greater than that of the tautomerism. Just as in the case of conformational isomerism, the ratio of products formed in subsequent reactions will not primarily be controlled by the position of the facile equilibrium.

4.5. Isotope Effects

A special type of substituent effect that has proved very valuable in the study of reaction mechanisms is the replacement of an atom by one of its isotopes. Isotopic substitution has most often involved replacing protium by deuterium (or tritium),

32. D. Y. Curtin, *Rec. Chem. Prog.* **15**, 111 (1954); E. L. Eliel, *Stereochemistry of Carbon Compounds*, Mc-Graw-Hill, New York, 1962, pp. 151–152, 237–238.
33. For a more complete discussion of the relationship between conformational equilibria and reactivity, see J. I. Seeman, *Chem. Rev.* **83**, 83 (1983).