

1 Classification and investigation of reaction mechanisms

The aim of this book is to describe the mechanisms and the synthetic applications of several important types of organic reactions, which include cycloadditions and many molecular rearrangements. The unifying feature of the reactions is that they can go by way of *cyclic* transition states.

Such processes involve the breaking and formation of more than one bond. These bonding changes can be *concerted*; that is, they occur by a mechanism in which the nature and type of new bond formation is coupled to and controlled by the movement of the electrons in the bonds which are being broken. Alternatively the bond making and breaking processes can be *stepwise*, in which case a discrete intermediate (a diradical or a zwitterion) is involved. The concerted or stepwise nature of a reaction is amenable to experimental investigation; the major part of this chapter is devoted to discussing the experimental criteria which have been used to determine the mechanisms, and the related terminology.

Experimental evidence supporting stepwise and concerted mechanisms for different types of cycloadditions and cyclic rearrangements has been available for several years. It was not until the mid 1960s, however, that any comprehensive rationalisation of these experimental observations was available. At that time R. B. Woodward and R. Hoffmann began to develop a general theory of concerted reactions which proceed through a cyclic transition state – processes which they termed *pericyclic*. They used the concept of orbital symmetry to predict which types of cyclic transition state are energetically feasible.¹ This and related theories are described in chapter 2, and form the mechanistic basis for the chemistry which follows in later chapters.

1.1. Free energy, enthalpy and entropy²

Two factors are important in determining the stability of a molecule: the stabilising energy resulting from the formation of bonds between the atoms and the destabilising energy due to the loss of freedom involved in constraining the atoms within the molecular structure. The thermodynamic

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function which embraces both of these factors is the *free energy* (G) now called Gibbs Function in SI terminology. Free energy is the fundamental quantity which controls the feasibility and the rates of all reactions.

The reactants in a chemical system usually have a higher free energy than the products and the forward reaction can then, in principle, proceed spontaneously. If the products have a higher free energy than the reactants, energy has to be supplied from some external source for the forward reaction to go. However, even when the reactants have a higher free energy than the products, the forward reaction is rarely spontaneous, but proceeds at a finite rate which may be extremely slow except at high temperatures. Theories which attempt to explain this use the concept of an *energy barrier* which has to be surmounted.

A reaction involves a gradual breaking of some bonds and/or formation of others. According to *transition state theory*, the reaction course can be considered as an infinite series of equilibria between one structure and another.

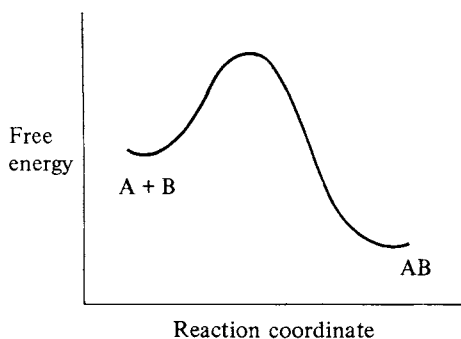
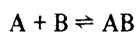


Fig. 1.1

The structure of highest free energy on the reaction path is called the *transition state* or *activated complex*. Although there is an infinite number of such routes from reactants to products, we are concerned only with the one of lowest energy - the so-called *reaction profile*. The free energy in such a process is illustrated in fig. 1.1 for the simple reaction.



The free energy is shown as a function of *reaction coordinate*. This is a rather loose term which indicates progress of change from reactants to products: for the example shown, it could be the length of the A-B bond.

The equilibrium constant K for any reversible reaction is determined by the difference in free energy ΔG between reactants and products. For the system

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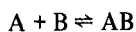
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1.1] Free energy, enthalpy and entropy

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$$K = \frac{[AB]}{[A][B]}$$

$$\text{and } \Delta G = -RT \ln K = -RT \ln \frac{[AB]}{[A][B]}$$

The relative proportions of products and reactants at equilibrium are therefore determined by their difference in free energy.

Transition state theory also enables the rate of a reaction to be linked to free energy differences. The theory assumes an equilibrium between the reactants $A + B$ and the activated complex $A \dots B$. The concentration of the activated complex is therefore determined by ΔG^\ddagger , the difference in free energy between the reactants and the transition state. ΔG^\ddagger is called the *free energy of activation*, because it is the free energy barrier which must be surmounted for reaction to occur. In transition state theory the further assumption is made that all activated complexes break down at the same rate. This can be shown to be reasonable by a statistical argument which gives kT/h as the rate constant for the breakdown (k = Boltzmann's constant; h = Planck's constant). Thus, the rate of the forward reaction $A + B \rightarrow AB$ is

$$\frac{akT}{h} [A \dots B]$$

where a is the fraction of activated complex passing on to product; it is assumed to be close to one. Putting

$$K^\ddagger = \frac{[A \dots B]}{[A][B]}$$

this expression becomes

$$\text{rate} = \frac{kT}{h} \cdot K^\ddagger [A][B]$$

The rate constant for the reaction k_r is therefore

$$k_r = \frac{kT}{h} \cdot K^\ddagger = \frac{kT}{h} \cdot e^{-\Delta G^\ddagger/RT}$$

The rate constant at any particular temperature is thus determined by the free energy of activation ΔG^\ddagger . The rate constant for the reverse reaction is similarly determined by the difference in free energy between products and transition state.

The discussion so far has concerned *reversible* reactions, but in fact not all reactions are found experimentally to be reversible. An *irreversible* reaction is one in which ΔG^\ddagger for the reverse reaction is large compared with ΔG^\ddagger for

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the forward reaction so that the rate of the reverse reaction is negligible in comparison with the rate of the forward reaction.

It is useful to split ΔG^\ddagger into its component enthalpy (ΔH^\ddagger) and entropy (ΔS^\ddagger) factors:

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

Enthalpy is essentially a bond energy term and entropy reflects the ordering of the system, so that ΔH^\ddagger and ΔS^\ddagger give more insight into the nature of the transition state. This idea of the energy barrier for a reaction as a combination of two factors is derived naturally from an alternative, and pictorially simpler, approach to the theory of reaction rates - *collision theory*. This assumes that only that fraction of molecules which collide with sufficient energy to surmount the transition state barrier can react (the ΔH term), and that even sufficiently energetic collisions will only lead to reaction if the colliding molecules are correctly aligned (the ΔS term).

Experimental values of ΔH^\ddagger , ΔS^\ddagger and ΔG^\ddagger are obtained by measuring the reaction rate constant at several different temperatures. The *Arrhenius equation*

$$k_r = A e^{-E_a/RT} \quad (k_r = \text{rate constant})$$

is an empirical relationship between rate constant and temperature which fits well for most reactions. A and E_a are constants which are, to a first approximation, independent of temperature. E_a is called the *Arrhenius activation energy* and A the *pre-exponential factor*. It can be shown that for a reaction in solution

$$\Delta H^\ddagger = E_a - RT$$

and for a gas phase reaction

$$\Delta H^\ddagger = E_a - nRT \quad (n = \text{molecularity})$$

At room temperature RT is about 2.5 kJ mol^{-1} so there is little difference in the value of E_a and ΔH^\ddagger .

Since $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$, the expression for the rate constant for a reaction derived from transition state theory

$$k_r = \frac{kT}{h} \cdot e^{-\Delta G^\ddagger/RT}$$

can be rewritten in a form very similar to that of the empirical Arrhenius equation:

$$k_r = \left(\frac{kT}{h} \cdot e^{\Delta S^\ddagger/R} \right) e^{-E_a/RT}$$

the expression within the brackets being equivalent to the pre-exponential

factor A . Thus, ΔH^\ddagger and ΔS^\ddagger can be obtained from the experimentally determined values of E_a and A , respectively.

1.2. Concerted and stepwise reactions

Reactions in which more than one bond is broken or formed can be divided into two classes. The first is one in which all the bond forming and breaking processes occur simultaneously so that a one-step transformation of reactants to products occurs without the intervention of an intermediate. Such reactions are called *concerted* or *multicentre* since the bond changes occur in concert or at the same time at more than one centre. The energy curve for such processes is shown in fig. 1.1; it involves only one energy barrier and one transition state.

The second broad class of reactions is one in which the bond forming and breaking processes occur consecutively so that one or more intermediates is involved. These intermediates may be stable molecules capable of isolation, or they may be highly reactive species of only transient existence. Where the intermediate is a stable molecule it is often more convenient to consider the overall process as two or more consecutive concerted reactions. Where the intermediates are unstable the process is normally considered as one reaction which proceeds in a stepwise manner. This distinction is purely arbitrary and one of convenience.

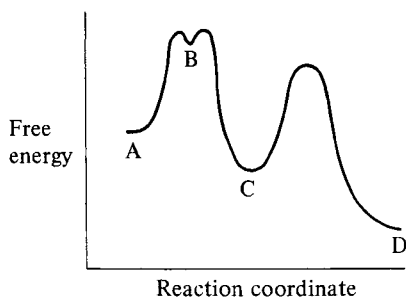


Fig. 1.2

The energy curve for a simple stepwise reaction could be as in fig. 1.2. In such a reaction C is formed from A via an unstable intermediate B which has a discrete, though short, lifetime. The instability of B is indicated by the fact that it lies in a shallow energy well. It has only a small energy barrier to surmount in order to pass over to products or to revert to reactants. The more stable such an intermediate is, the deeper the energy well. C is relatively stable and lies in a deep energy well.

Although C is the first isolable product to be formed, it may subsequently pass over to the more stable D in the reaction conditions. C is called the

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kinetically controlled product of reaction of A. D, which is the product isolated after the system reaches equilibrium, is called the *thermodynamically controlled* product. This is the type of situation where kinetic and thermodynamic control is most frequently encountered.

Kinetic and thermodynamic control can also operate in systems of the type $Q \rightleftharpoons P \rightleftharpoons R$. If the reactions $P \rightarrow Q$ and $P \rightarrow R$ have energy profiles as shown in fig. 1.3, Q is formed faster than R because the energy barrier for its formation is lower than that for R. However, if the reacting system reaches thermodynamic equilibrium, the proportions of products Q and R will be determined by their relative free energies, and R will predominate. In this type of situation, Q is the kinetically controlled product and R is the thermodynamically controlled product.

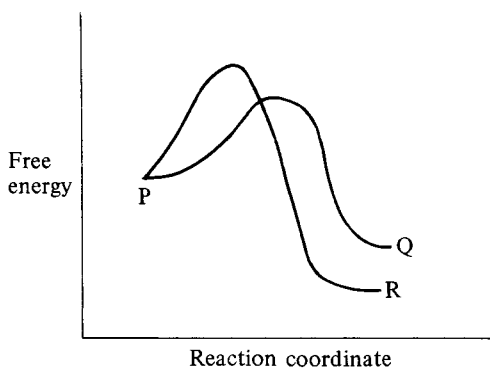


Fig. 1.3

If a reaction is reversible and a particular pathway is energetically the most favourable route from reactants to products, the lowest energy pathway for the reverse reaction will be along the same route but with all bond making and breaking processes reversed. Forward and reverse reactions will therefore pass through the same transition states and will involve the same mechanism. This is the *principle of microscopic reversibility*.

Throughout the book we are concerned with reactions in which cyclic structures are formed or cleaved or which, at least formally, involve a cyclic transition state. The extreme mechanisms by which such reactions can occur can conveniently be discussed with reference to a hypothetical fragmentation:



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Concerted mechanism

In the concerted fragmentation the breaking of the a–c bond is coupled with, and depends on, the breaking of the b–d bond, so that both processes are going on at the same time. The overall reaction does not involve an intermediate and the energy profile is of the type shown in fig. 1.1. There is only one energy barrier with a transition state in which both σ bonds are partially broken and the new π bonds in a=b and c=d are partially formed.

The two σ bonds can break simultaneously and at exactly the same rate (a *synchronous* process). It is reasonable that the bonds do not break at the same rate, however, especially if the reactant is unsymmetrical. In the latter case the two bonds will be broken to different extents in the transition state. However, no matter how lopsided the transition state may be, the process is still considered to be concerted if the breaking of the a–c bond is coupled with and controlled by the breaking of the b–d bond (fig. 1.4).

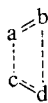


Fig. 1.4

Woodward and Hoffmann¹ have introduced the term *pericyclic* to cover all concerted reactions which involve a cyclic transition state, and define it as follows: 'a pericyclic reaction is a reaction in which all first order changes in bonding relationships take place in concert on a closed curve'.

Stepwise mechanism

The bonds a–c and b–d may break in two successive independent steps. The reaction then involves an intermediate in which only one of the σ bonds is broken. The energy profile will be as in fig. 1.5, with two transition states.

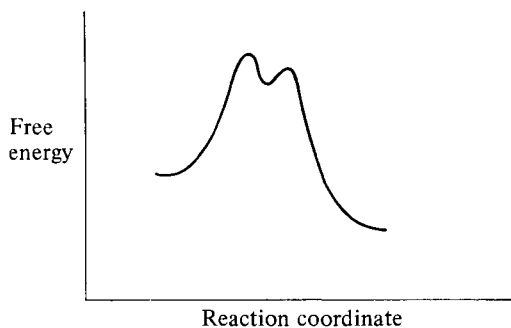


Fig. 1.5

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Stepwise breaking and formation of bonds can be detected experimentally (§1.3). The intermediates fall into two categories; those which are highly polar, and those which are essentially non-polar. The first type is normally considered to be a *zwitterion*; that is, a species bearing both a positive and a negative charge; and the second type, a *diradical* (fig. 1.6).



Fig. 1.6

Zwitterions. In the fragmentation shown a zwitterion results from heterolytic cleavage of one of the bonds. Such a process is favoured if the resulting charges are stabilised inductively or mesomerically. Collapse of the zwitterion to reform the bond b—d gives back the starting material. Other courses are open to the zwitterion; the bond a—c may cleave, or the zwitterion may react with other species present. Bond rotation about the a—b, a—c, or c—d bonds in the intermediate may occur before re-closure or cleavage. It is the experimental observation of these competing processes which enables the reaction to be identified as a stepwise one.

*Diradicals.*³ If the bond b—d cleaves homolytically, this leads to a diradical intermediate. Such a process is favoured if the structure is such that the separate monoradicals are stabilised by delocalisation. As the separation of the centres b and d increases, the correlation between the electrons decreases. At some point the separation is sufficiently large for the species to be considered as a diradical rather than as a vibrationally excited ring. Conversely, a diradical $\cdot b-a-c-d \cdot$ only becomes equivalent to a vibrationally excited ring when conformational changes bring b and d within bonding distance. The diradical is therefore a discrete intermediate; it can re-close, or fragment by cleavage of the bond a—c, both processes competing with bond rotation.

If the centres bearing the unpaired electrons in a diradical are well separated (for example, by a long carbon chain) there is little interaction between them and each might be expected to act as an independent monoradical function. Usually the centres are close enough for intramolecular interaction to preclude their reaction as separate chemical entities.

The concept of electron spin has proved very useful to organic chemists, and the question of relative spins of the unpaired electrons in a diradical is often alluded to. This is reasonable if the separation between the radical centres is small, but not otherwise. The species is referred to as a singlet if the electron spins are opposed, but as a triplet if the spins are parallel. As the bond b—d is cleaved, the electrons initially have antiparallel spins, so that the

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radical should be generated as a singlet. This singlet state may not be the ground state of the intermediate, however. The relationship between structure and reactivity of diradicals is a complex one, and further discussion is deferred until §6.3.

*Photochemical reactions*⁴

In a photochemical reaction, a reactant absorbs radiation (generally ultraviolet) which causes excitation of an electron to a higher vacant orbital. Most frequently, lone pair electrons or π electrons are promoted to low-lying π^* antibonding orbitals. σ Electrons are more tightly held and less easily excited. The type of transition can be controlled by the wavelength of light used, since the energy of the light quanta is given by $E = h\nu$.

In the excitation step the electron is promoted with retention of spin to give a singlet excited state. Excited states of higher energy rapidly decay to the lowest excited singlet. This may undergo chemical reaction or it can emit a quantum of light and collapse to the ground state (fluoresce). The singlet excited molecule may also undergo intersystem crossing, with spin inversion, to give a lower energy triplet state. This again may undergo chemical reactions, which are likely to be quite different from those of the singlet, or it may collapse to the ground state with emission of light (phosphoresce). Since this involves spin inversion it is a forbidden process and occurs more slowly than collapse of the excited singlet. The lifetime of an excited singlet is very short since both emission of light and intersystem crossing are fast. (The rate constants for these processes are of the order 10^7 – 10^8 s⁻¹ and 10^8 – 10^{10} s⁻¹ giving lifetimes of 10^{-7} – 10^{-8} s and 10^{-8} – 10^{-10} s, respectively.) The lowest triplet state has a relatively long lifetime ($\sim 10^{-3}$ s). Thus, intramolecular photochemical reactions may involve the singlet excited state, but intermolecular reactions are more likely to involve triplet states since intersystem crossing competes favourably with intermolecular collision.

Both singlet and triplet excited molecules may lose their energy by intermolecular transfer to other molecules. This type of process is utilised in photosensitised reactions where reactant molecules are excited not by direct absorption of light, but through energy transfer from photosensitisers. Light is absorbed by the sensitizer molecule which then transfers its energy to the reactant, if the latter has a lower-lying excited state available. If the sensitizer transfers its energy from a singlet state, a singlet excited reactant is produced. If the excited photosensitizer undergoes intersystem crossing to its triplet state and then transfers its energy, a triplet reactant molecule is produced.

Other processes are also possible; for example, triplet* + triplet \rightarrow singlet* + singlet, as in the generation of singlet oxygen. Thus by careful choice of reaction conditions, the chemist can exercise considerable control over the nature of the excited species involved in a photochemical process.

1.3. Experimental investigation of mechanism²

The first step in any mechanistic investigation is to determine what all the reactants and products are. This may seem obvious, but incomplete knowledge of all products has often hampered investigations, and has led to wrong conclusions about a mechanism. Minor side products can sometimes provide clues to possible mechanisms.

It must be established that the observed products are actually formed in the reaction studied and not in some subsequent step. Thus, it must be known whether kinetic or thermodynamic control is operative. The fate of particular atoms in a reaction must be known. This is usually evident from the relative positions of substituents in the reactants and products but in more subtle cases atoms can be labelled by isotopes. Detailed stereochemistries of reactants and products must be known since the mechanism has to be able to account for the stereochemical course of the process. For example, we must know whether configuration is retained, inverted or lost at an atom to which a bond is broken and formed.

The second major type of information in a mechanistic investigation comes from rate measurements. Measurement of the rate at varying concentrations of reactants gives an empirical rate equation. In simple cases this gives directly the number of molecules of each type involved in the transition state. In other cases the rate equations are complex and can fit more than one mechanistic scheme. However, for any proposed reaction scheme it is possible to formulate a theoretical rate expression, and this must be compatible with the observed one.

The effects of changing substituents, replacement of atoms by their isotopes, and solvent polarity on the rate of a reaction all give additional useful information. Determination of the rate constant at several different temperatures leads to estimates of enthalpy and entropy of activation.

The information thus obtained can often enable a distinction to be made between concerted and stepwise mechanisms and if the reaction is stepwise it can indicate what sort of intermediate is involved. The following types of experiment have most commonly been used.

Isolation or detection of an intermediate⁵

Stepwise reactions involve intermediates which have widely differing stabilities. At one end of the stability scale these may be isolable; at the other end they may be extremely unstable and their presence only proved indirectly. If an intermediate can be detected by a method which does not affect the mechanism then the stepwise nature of the reaction is proved. The converse does not apply; if no intermediate is detectable the reaction is not necessarily concerted - it may be that the methods of detecting the intermediate are not sufficiently refined.