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978-0-521-29014-2 - Electrophilic Halogenation: Reaction Pathways Involving Attack by Electrophilic Halogens on Unsaturated Compounds
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Excerpt
More information

1 Terminology, definitions, methods of mechanistic study

'Every schoolboy knows...' (Macaulay)

1.1 Introduction

The halogens, of which fluorine, chlorine, bromine and iodine are the most familiar, form an important group of elements which exist not only in their well-known diatomic molecular forms (e.g. Cl_2), but also as atoms, as ions, and in covalent combination with many other elements. Their reactions with unsaturated organic compounds (that is, with compounds which possess a multiple bond to carbon) are encountered early in the study of organic chemistry; thus (1.1) represents the reaction of ethylene with chlorine, and (1.2) that of benzene with bromine.

$$CH_2{:}CH_2 + Cl_2 \longrightarrow Cl.CH_2.CH_2.Cl \qquad (1.1)$$

$$C_6H_6 + Br_2 \longrightarrow C_6H_5Br + HBr \qquad (1.2)$$

Historically, these reactions and their analogues have fascinated chemists for more than a century; they have been used to distinguish between olefinic unsaturation (as in ethylene) and aromatic unsaturation (as in benzene), and in this way and in many others have played a part in the development of some of the most important ideas of chemical theory. Currently, the mechanistic considerations which, as we shall see, enable the quite different reactions of (1.1) and (1.2) to be associated and interpreted within the framework of the chemistry of carbocationic intermediates put these reactions at the centre of development of organic chemistry. Practical considerations likewise require emphasis on the importance of an understanding of the courses taken in halogenations; the introduction of halogen at a particular point in an organic molecule can often be followed by its replacement by other functional groups or by other changes directed by the introduced halogen, so that the original point of entry provides a locus for subsequent synthetic processes.

In this book, we shall be concerned mainly with reactions of the halogen molecules acting as *electrophiles*: that is, as seekers of electrons, or in other words as sources of supply of positive halogen for co-ordination with an electron-rich centre. Other related molecules which can behave similarly (e.g. chlorine acetate, Cl.OAc) will also be considered, as will the positively charged halogen ions.

The organic molecules to be discussed will be those which are formally unsaturated. Olefinic compounds, containing C═C double bonds; acetylenic compounds, containing C≡C triple bonds; aromatic compounds, containing cyclic conjugated systems of double bonds; systems involving double bonds between carbon and another element, including heterocyclic compounds; and compounds which are converted by reversible isomerism (*tautomerism*) into structures of one or other of the above kinds, will be among the important types to be considered.

The terminology to be adopted will essentially follow the conventions used by Ingold (1969). *Homolysis* involves the fission of a covalent bond into fragments in which each part carries a single electron, indicated by a heavy dot in (1.3).

$$\mathrm{A{-}B} \longrightarrow \mathrm{A}\cdot + \mathrm{B}\cdot \tag{1.3}$$

Its reverse is *colligation*.

Heterolysis involves the corresponding fission to give fragments, one of which bears both the electrons of the original electron-pair bond. This fragment must, therefore, have become formally one unit more negative, and by its nature be a *nucleophile*, with the power to donate its electron-pair for reaction with an electrophile. The other fragment is formally one unit more positive than it was in the original molecule, and must be electrophilic in character: (1.4).

$$\mathrm{A{-}B} \longrightarrow \mathrm{A}^+ + \mathrm{B}^- \tag{1.4}$$

The reverse of heterolysis is *co-ordination*. Some authors use the term ‘addition’ in the same sense; but confusion then arises when the reactions of (1.1) and (1.5) both become described as additions.

$$\mathrm{CH_2{:}CH_2} + \mathrm{Cl}^+ \longrightarrow \mathrm{Cl.CH_2.CH_2^+} \tag{1.5}$$

In generalised formulae throughout the remainder of this book, X represents halogen; E^+, an electrophile; Nu, a nucleophile; R, an unspecified substituent (often alkyl or aryl); SOH, a hydroxylic solvent.

1.2 Energy diagrams

In discussing organic reactions one is often concerned with interconversions of quite complex molecules, and with the formation of a mixture of products from a reactant or a set of reactants. Of these products, perhaps only one or two are the desired result of the attempted synthesis or degradation. Most such reactions involve the breaking of covalent bonds and the formation of other bonds. They are therefore *activated processes*; that is, they require *energy of activation* to effect them. Almost any complex organic molecule has a number of isomers; and any of these isomers could theoretically, given enough energy of activation and a suitable reaction path, be transformed one into any of the others. Such an interconversion can be described by an energy (strictly an enthalpy) diagram (fig. 1.1) involving an *initial state* (the reactant), a *transition state*, and a *final state* (the product). Occasionally, an organic reaction can be described in the simplified terms of such a diagram; the energy needed to overcome the barrier between reactants and products is supplied thermally by collision, or in other ways, and the interconversion is a smooth, *synchronous* or concerted reorganisation of the positions of the atoms and bonding electrons with no intermediate energy-minimum between reactant and product. Much more frequently, however, we encounter complicated reaction paths, involving several intermediate

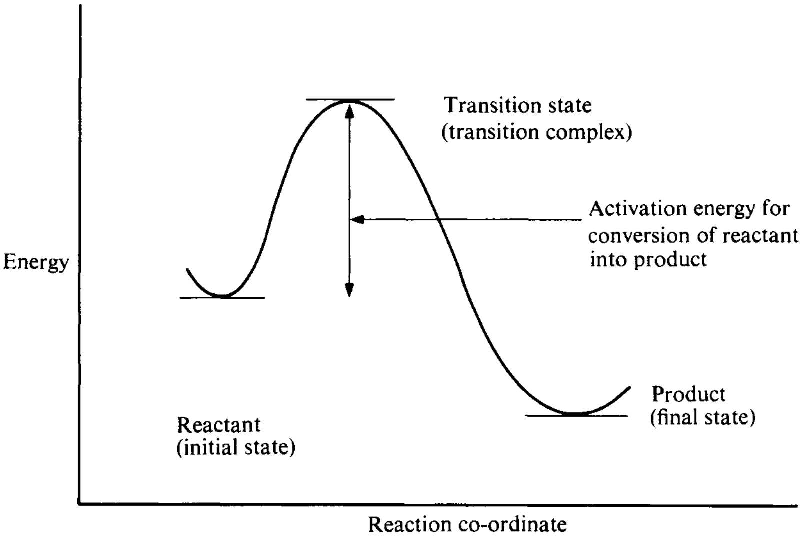

Fig. 1.1. Simplified energy diagram for interconversion of isomers through a pathway not involving an intermediate.

The scale along the reaction co-ordinate may sometimes be approximated by a single physical quantity, such as a changing interatomic distance. Strictly speaking, enthalpies rather than free energies should be represented; see text, pp. 14–15.

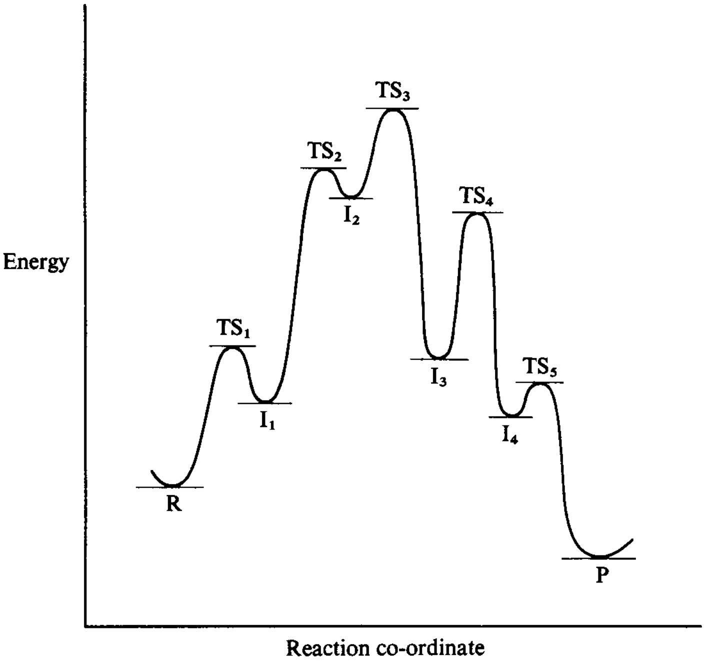

Fig. 1.2. Simplified energy diagram for a reaction involving several intermediates; the scale along the reaction co-ordinate cannot be identified with a single physical quantity. (See also caption to fig. 1.1.)

R = reactants; P = products; I_1, I_2, I_3, I_4 = intermediates; TS_1, TS_2, TS_3, TS_4, TS_5 = transition states.

stages which we need to understand if we are to control the course of the reaction. Diagrams such as that shown in fig. 1.2 are often used to discuss such sequences, which are typical of the situations that we shall encounter in a study of halogenations. Fig. 1.2 includes several *intermediates* (I_1, I_2 etc.) and several transition states, (TS_1, TS_2, etc.) the transition state of highest energy (TS_3) being that of the *rate-determining* or *rate-limiting* process. That some of these intermediates and transition states may be isomeric is hardly surprising, since isomerism of stable molecules is so common. An approach in terms of such a diagram can be helpful in enabling us to visualise the stages through which the reacting system has to pass, and the relative energetics of the various stages. It should be remembered, however, that such a description is almost always a considerable over-simplification of the proper full physical description of what happens during the reaction. More specialised texts (e.g. Leffler,

1956) should be consulted if the underlying assumptions are to be understood fully; and it is important not to read more into such a diagram than is actually implied by it.

1.3 Intermediates

One of the most difficult problems associated with such descriptions is concerned with the nature and significance of intermediates along the reaction path. It is a basic principle of transition-state theory that the transition state is in equilibrium with the reactants, being converted into products through its instability in the *reaction co-ordinate*, which represents only one of its many modes of change in the relative atomic positions. For some purposes, then, it can be held that any intermediates lying on the left of the rate-determining transition state (fig. 1.2), being themselves in equilibrium with starting materials, are irrelevant to the formation of the transition state. In some complex reactions, however, this view is not tenable, since an equilibrium pre-association may provide the only way in which all the components of the transition state can be brought together.

Not all intermediates holding reactants in pre-equilibrium will necessarily be relevant to the reaction, but to decide which are significant, and in what way they function, is not always straightforward. Fig. 1.3 provides an example. Here we postulate three isomeric positively charged intermediates, and three isomeric products. It may at first sight appear intuitively obvious that the intermediate (**1.1**) leads to product (**1.4**), and that this reaction path either is irrelevant to the formation of the other products or is a stage of diversion which may temporarily form a repository of the reactants before allowing the formation of the isomers (**1.5**) and (**1.6**), thermodynamically more stable than (**1.4**), through reversal of the stages of formation of (**1.4**). This conclusion will be wrong, however, if there exists a route or routes (shown by dashed lines in the figure) whereby (**1.2**) or (**1.5**) can be formed directly from (**1.1**) or (**1.4**). In such a case (as, for example, when $E = NO_2$ (Ingold, 1969; Hughes and Ingold, 1952)), the formation of the intermediate (**1.1**) may be especially relevant to the formation of (**1.5**), and may allow or force the bypassing of (**1.6**) which would normally be preferred over (**1.5**).

A third problem is concerned with methods of defining the intermediates lying to the right of the rate-determining transition state. Strict theory requires that a set of reactants which attain the energy of the transition state pass over the energy barrier because they are unstable only in one single vibrational co-ordinate (the reaction co-ordinate),

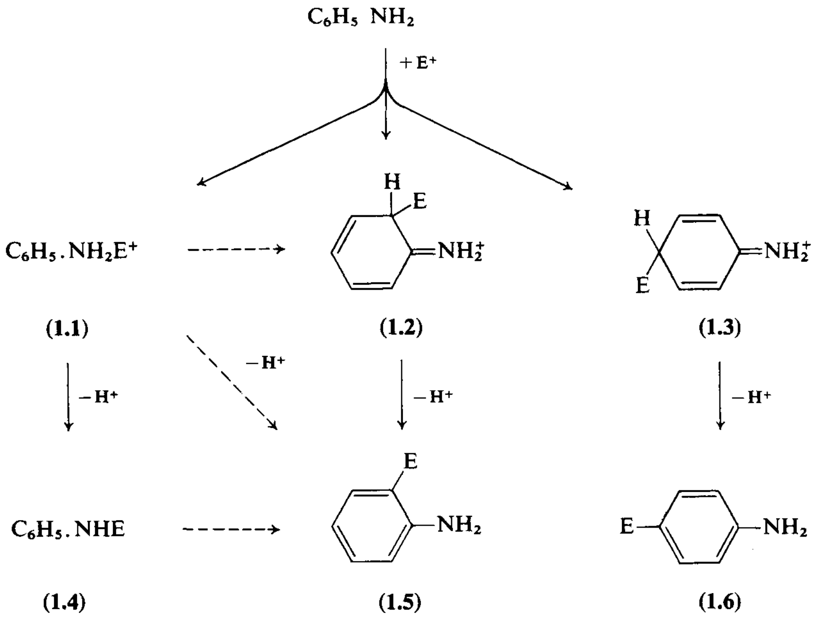

Fig. 1.3. Intermediates in a hypothetical aromatic substitution.

and so proceed onward to products to give only one mode of reaction (Leffler and Grunwald, 1963). In practice, however, some transition states are probably best thought of as a family of closely related structures, able to lose energy to the environment in more than one way, and so capable of more than one mode of decomposition. Furthermore, any intermediate to which the transition state leads may be able to react in more than one way, to give more than one product.

1.4 Methods of mechanistic study

The study of the halogenations which we shall discuss in this book can involve detailed investigations involving a wide range of physical and chemical techniques. These have of recent years been greatly extended in scope and in power through the availability of new spectrometric methods of analysis, together with devices which allow the rapid scanning of changes occurring in a reaction mixture. It will be appreciated that, whereas important examples of some reactions have been studied in very great detail, others have had only cursory or incomplete attention so far. It should be noted also that it is characteristic of many organic reactions that each new investigation produces new information, thus enabling, or requiring, that a relatively simple interpretation be replaced by a more elaborate one.

In beginning the mechanistic study of a reaction, it goes without saying that the structures of the starting materials need to be established, and that any equilibria involving them, or any of them and any component of the environment, should if possible be elucidated. Spectroscopy is often used for studies of this kind. It is then necessary to know the nature of the products, and the stoicheiometry of the reaction; that is, the proportions in which the various components are obtained. Frequently this aspect of the investigation is best associated with kinetic measurements, in which the rate of disappearance of one or more of the reactants is measured along with the rate of formation of one or more of the products. If these are the same, then a relatively simple description of the reaction may be possible. Discrepancies, if they are noted, may provide important information concerning the intervention of intermediates along the reaction path. When intermediates are suspected, they can often be detected by physical methods; as for example when calorimetric or spectrometric procedures are used to follow the course of reaction. Chemical procedures are often used also, as when intermediates can be trapped and diverted to new, recognisable products which help to define the nature of the intermediate.

1.5 Kinetic methods

Kinetic methods help also in allowing deductions to be made concerning the nature of the transition state. This state, through which the reactants must normally pass in order to become the products, cannot be examined directly by the physical methods available for study of intermediates because its lifetime is no greater than that of a molecular vibration or collision. Study of mechanism, however, requires that inferences be drawn concerning its nature. The stoicheiometry of the transition state is normally deduced from the kinetic form of the reaction. A familiar example comes through the chemistry of the alkyl halides, R.X. The reaction of (1.6) can follow the kinetic form of (1.7), in which case it would be concluded that the transition state had the composition [R.X] and did not include the nucleophile Nu^-; its structure might then be assigned as in formula (**1.7**), the dots indicating a partially broken R–X bond. Alternatively, the second-order kinetic form, (1.8), may be observed; in which case the transition state must have the composition [R.X, Nu^-], and may be assigned the structure shown in formula (**1.8**),

$$R.X + Nu^- \longrightarrow R.Nu + X^- \qquad (1.6)$$

$$d[X^-]/dt = d[R.Nu]/dt = k_1[R.X] \qquad (1.7)$$

$$\overset{\delta+}{R} \ldots \overset{\delta-}{X} \qquad [Nu \ldots R \ldots X]^-$$

(1.7) **(1.8)**

$$d[X^-]/dt = d[R.Nu]/dt = k_2[R.X]\,[Nu^-] \qquad (1.8)$$

with a partially formed bond from R to X, and negative charge shared largely between the centres X and Nu.

Powerful as the kinetic method is, yet it must be used with caution, particularly for reactions in solution. Deductions from it depend on being able to vary the concentrations of the reactants and observe changes in rate which are used to identify the composition of the transition state. If, however, this variation in concentration modifies the properties of the medium in which the reaction is occurring, a superimposed influence on the rate may be observed, and this may obscure the true kinetic form.

1.6 Environmental influences; solvent effects

Most organic reactions are carried out in the liquid state. When the solvent is not one of the reactants it may play the vital, but essentially merely mechanical role, of allowing the reactants to come rapidly into the necessary physical proximity; but in doing so it may interact with any or all of them, and it may also interact with any intermediate states between reactant and product, including the rate-determining transition state. Hughes and Ingold (1935) developed a theory of solvent action which covers also the environmental influences of added electrolytes on the basis that if a change in solvent, or other non-reacting components of the environment, stabilises the transition state more than the initial state, then the reaction will be facilitated. This theory is of wide generality; in practice it is not always easy to apply, since reactants and solvents can interact in very specific ways which are difficult to predict.

Organic chemists have a wide range of solvents available to them, including the various hydroxylic solvents (water, the alcohols, phenols, carboxylic acids, etc.), dipolar aprotic solvents (acetone, dimethyl sulphoxide, etc.), and non-polar solvents (benzene, hexane, etc.). Some of the art of organic chemistry lies in the choice of the most appropriate solvent to effect a desired transformation.

When the solvent itself is one of the reactants this introduces special difficulty into the use of the kinetic method for mechanistic deductions, since it then becomes difficult to distinguish between the function of the solvent as a reagent and its function in providing the environment for reaction (Ingold, 1969; Streitwieser, 1962).

1.7 Catalysts

The effects of particular *catalysts* are often helpful in elucidating what mechanisms are available for a reaction. Organic peroxides and other initiators of homolytic processes are often very effective catalysts; they start chain reactions involving free-radicals, and one act of initiation may result in the conversion of many molecules of reactants into products through many repetitions of the chain-propagating steps. This type of catalyst may ultimately be consumed in side reactions. Study of the products, and of the effects of possible inhibitors of the radical-chains, is often necessary to establish whether or not the uncatalysed reaction is following the same pathway as the catalysed process.

In this book we shall be concerned more often with catalysts for heterolytic processes. Acids and bases are the most important of these; their modes of functioning are reviewed by Bell (1973). Among acid catalysts we must consider the hydroxonium ion, H_3O^+; other positively charged molecules derived by protonation of the solvent (e.g. $CH_3CO_2H_2^+$, the conjugate acid obtained by protonation of the solvent acetic acid); neutral species which can act as *general acids* (e.g. the acetic acid molecule, CH_3CO_2H); and *Lewis acids* (e.g. $AlCl_3$). For all these types, the catalytic function generally involves the transference of an electrophile reversibly to one of the reactants. In this way is produced a more reactive species which can undergo heterolysis to give a more reactive intermediate; the latter then participates in further transformations. Equations (1.9) and (1.10) illustrate how a proton-donor functions in this way; (1.11) illustrates the familiar, and chemically similar, function of a Lewis acid.

$$\text{t-Bu.OH} + H^+ \rightleftharpoons \text{t-Bu.OH}_2^+ \tag{1.9}$$

$$\text{t-Bu.OH}_2^+ \longrightarrow \text{t-Bu}^+ + OH_2 \tag{1.10}$$

$$CH_3.Cl + AlCl_3 \rightleftharpoons [CH_3^+ \quad AlCl_4^-] \tag{1.11}$$

Catalysis by bases in organic chemistry usually involves the converse function: namely, the removal of a proton, (1.12), or of another electrophile, (1.13), to form an intermediate which is more reactive than the starting material.

$$CH_2(CO_2Et)_2 + OEt^- \longrightarrow [CH(CO_2Et)_2]^- + HOEt \tag{1.12}$$

$$CH_3.CO.NH_2Br^+ + Cl^- \longrightarrow CH_3.CO.NH_2 + BrCl \tag{1.13}$$

1.8 Acidity-functions

Acidity-functions have been used for some mechanistic deductions; recent reviews are given by Hammett (1970) and by Rochester (1970). Their use involves an attempt to study acid-catalysed reactions over a range of concentration sufficient to allow disentanglement of the separate influences of changing environment, of departures from ideal behaviour of electrolytes, and of the way in which the solvent is taking part in the reaction. The simplest acidity-function is the stoicheiometric concentration of hydrogen ions; but this measures the power of the medium to donate a proton to a substrate only in very dilute aqueous solution. At high concentrations of mineral acids in water significant deviations can be observed when the protonating power is measured by spectrometric measurement of the concentrations of base and conjugate acid. Typically, these deviations become important when the concentration of mineral acid exceeds about 0.5 M; they vary with the acid, with the solvent, and to some extent with the type of base used for the measurement.

The consequent definition of a useful acidity-function, and its application to a mechanistic discussion, rests on an intuitive assumption that the protonation of the organic substrate concerned in the reaction under mechanistic discussion will be paralleled by the chosen acidity-function. Certainly there are often circumstances in which correlations of this kind will lead to useful deductions, but recent research has not borne out the original hope that acidity-functions would provide information which would enable unambiguous assignment of the role of the solvent in acid-catalysed reactions generally.

1.9 Isotope effects

Potentially a more powerful approach to a study of reaction pathways involves the study of *isotope effects* on equilibria and on reactivity (Melander, 1960). Isotopes differ in their chemical properties only by virtue of their different masses, and so provide a sensitive probe of the vibrational changes experienced by an assembly of molecules undergoing reaction. In principle, a study of the effect of changing one isotope for another in a reactant gives information concerning the extent to which the bond involving the changed atom is modified in going from the initial to the transition state. The biggest differences in masses are found with the isotopes of hydrogen, so hydrogen–deuterium or hydrogen–tritium isotope effects are relatively large and can introduce rate differences of the order of a factor of ten. Heavy-atom isotope effects are much smaller,