A guidebook to mechanism in organic chemistry

Peter Sykes M.Sc., Ph.D., F.R.S.C., C.Chem.
Fellow and Vice-Master, Christ's College, Cambridge

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Contents*

* A detailed list of contents will be found at the beginning of each chapter.

Foreword

Fifty years ago the student taking up organic chemistry—and I speak from experience—was almost certain to be referred to one or other of a few textbooks generally known by the name of their authors—e.g. Holleman, Bernthsen, Schmidt, Karrer and Gattermann. On these texts successive generations of chemists were nurtured, and not in one country alone, for they were translated into several languages. These, the household names of fifty years ago, have for the most part gone. In past times of course the total number of books available was rather small and it is only in the last quarter of a century that we have seen a veritable flood of organic chemical textbooks pouring into booksellers' lists. The increase in the number of texts may be in part due to the rise in student numbers but the primary reason for it is the revolutionary impact of mechanistic studies on our approach to organic chemistry at the elementary level. With the plethora of books available, however, it is now much more difficult for an author to become a household name wherever the subject is taught. Yet this has indeed happened to Dr. Peter Sykes through his *Guidebook to Mechanism in Organic Chemistry*.

In the Foreword which I was privileged to write for the First Edition in 1961 I described not only my own view of what was happening in organic chemistry but also the type of approach to teaching it which was favoured by Dr. Sykes. Having known and watched him over many years first as student, then as colleague, and always as friend, I was confident that he had written an excellent book which, in my view at least, would add new interest to the study of organic chemistry. But its success has far exceeded even my high expectations and in its later editions it has been revised and refined without ever losing the cutting edge of the original.

The present volume continues the tradition. Once again the recent literature has been combed for new examples the better to exemplify principles of reactions. Of particular interest is an admirable chapter dealing with reactions controlled by orbital symmetry. Until I read it I was not convinced that this very important new development in the theory of organic reactions could be simply yet usefully communicated to students at an elementary level. To have succeeded in doing so only underlines further Dr. Sykes' gifts as a teacher and writer and I am sure that this new edition of the Guidebook will more than equal the success of its predecessors.

Cambridge TODD

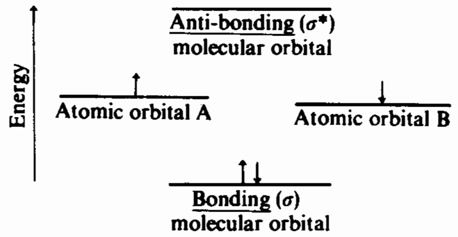


Fig. 1.1

The molecular orbital of lower energy is called the *bonding orbital*, and its occupancy results in the formation of a stable bond between the two atoms. In the above case, the pair of electrons constituting the bond tend to be concentrated between the two positively charged atomic nuclei, which can thus be thought of as being held together by the negative charge between them. The molecular orbital of higher energy is called the *anti-bonding orbital*; this corresponds to a state in which the internuclear space remains largely empty of electrons, and thus results in repulsion between the two positively charged atomic nuclei. The anti-bonding orbital remains empty in the ground state of the molecule, and need not here be further considered in the formation of stable bonds between atoms.

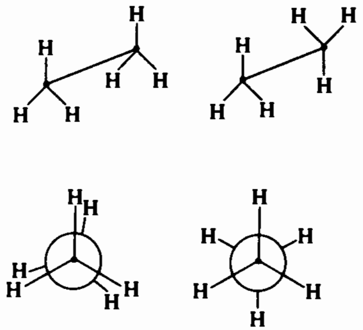
If overlap of the two atomic orbitals has taken place along their major axes, the resultant bonding molecular orbital is referred to as a σ orbital,* and the bond formed as a σ bond. The σ molecular orbital, and the electrons occupying it, are found to be *localised* symmetrically about the internuclear axis of the atoms that are bonded to each other. Thus on combining with hydrogen, the four hybrid sp^3 atomic orbitals of carbon overlap with the 1*s* atomic orbitals of four hydrogen atoms to form four identical, strong σ bonds, making angles of 109° 28′ with each other (the regular tetrahedral angle), in methane. A similar, exactly regular, tetrahedral structure will result with, for example, CCl_4, but where the atoms bonded to carbon are not all the same, e.g. CH_2Cl_2, the spatial arrangement may depart slightly from the exactly symmetrical while remaining essentially tetrahedral (*cf.* p. 5).

1.3.1 Carbon–carbon single bonds

The combination of two carbon atoms, for example in ethane, results from the axial overlap of two sp^3 atomic orbitals, one from each carbon atom, to form a strong σ bond between them. The carbon–carbon bond length in saturated compounds is found to be pretty constant—0·154 nm (1·54 Å). This refers, however, to a carbon–carbon single bond between sp^3 hybridised carbons. A similar single bond between two sp^2 hybridised carbons, =CH—CH=, is found on average to be about 0·147 nm (1·47 Å) in length, and one between two sp^1 hybridised carbons, ≡C—C≡, about 0·138 nm (1·38 Å). This is not really surprising, for an *s* orbital and any electrons in it are held closer to, and more tightly by, the nucleus than is a *p* orbital and any electrons in it. The same effect will be observed with hybrid orbitals as their *s* component increases, and for two carbon atoms bonded to each other the nuclei are drawn inexorably closer together on going from

$$sp^3\text{–}sp^3 \longrightarrow sp^2\text{–}sp^2 \longrightarrow sp^1\text{–}sp^1.$$

We have not, however, defined a unique structure for ethane; the σ bond joining the two carbon atoms is symmetrical about a line joining the two nuclei, and, theoretically, an infinite variety of different structures is still possible, defined by the position of the hydrogens on one carbon atom relative to the position of those on the other. The two extremes, of all the possible species, are known as the *eclipsed* and *staggered* forms:



Eclipsed Staggered

The above quasi three-dimensional representations are known as 'sawhorse' and Newman projections, respectively. The eclipsed and staggered forms, and the infinite variety of possible structures lying between them as extremes, are known as *conformations* of the ethane molecule; conformations being defined as different arrangements of the same group of atoms that can be converted into one another without the breaking of any bonds.

The staggered conformation is likely to be the more stable of the two as hydrogen atoms on one carbon are then as far away from those on the other as they can get (0·310 nm; 3·1 Å), and any so-called 'non-bonded' interaction between them is thus at a

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* The anti-bonding molecular orbital is referred to as a σ^* orbital.

to as a *Lewis acid.* Electrophiles and nucleophiles in organic reactions can be looked upon essentially as acceptors and donors, respectively, of electron pairs, from and to other atoms—most frequently *carbon.* Electrophiles and nucleophiles also, of course, bear a relationship to oxidising and reducing agents, for the former can be looked upon as electron acceptors and the latter as electron donors. A number of the more common electrophiles and nucleophiles are listed below:

Electrophiles:

$H^{\oplus}$, $H_3O^{\oplus}$, ${}^{\oplus}NO_2$, ${}^{\oplus}NO$, $PhN_2{}^{\oplus}$, $R_3C^{\oplus}$

$\overset{*}{S}O_3$, $\overset{*}{C}O_2$, $\overset{*}{B}F_3$, $\overset{*}{A}lCl_3$, $\overset{*}{I}Cl$, Br_2, O_3

Nucleophiles:

$H^{\ominus}$, $BH_4{}^{\ominus}$, $H\overset{*}{S}O_3{}^{\ominus}$, $HO^{\ominus}$, $RO^{\ominus}$, $RS^{\ominus}$, ${}^{\ominus}CN$, $RCO_2{}^{\ominus}$, $RC{\equiv}C^{\ominus}$, ${}^{\ominus}CH(CO_2Et)_2$

$O\!:$, $N\!:$, $S\!:$, $\overset{*}{R}MgBr$, $\overset{*}{R}Li$ (41)

Where a reagent is starred, the star indicates the atom that accepts electrons from, or donates electrons to, the substrate as the case may be. No clear distinction can necessarily be made between what constitutes a reagent and what a substrate, for though ${}^{\oplus}NO_2$, ${}^{\ominus}OH$, etc., are normally thought of as reagents, the carbanion (41) could, at will, be either reagent or substrate, when reacted with, for example, an alkyl halide. The reaction of the former on the latter is a nucleophilic attack, while that of the latter on the former would be looked upon as an electrophilic attack; but no matter from which reactant's standpoint a reaction is viewed, its essential nature is not for a moment in doubt.

It should be remembered that reactions involving radicals as the reactive entities are also known. These are much less susceptible to variations in electron density in the substrate than are reactions involving polar intermediates, but they are greatly affected by the addition of small traces of substances that either liberate or remove radicals. They are considered in detail below (p. 313).

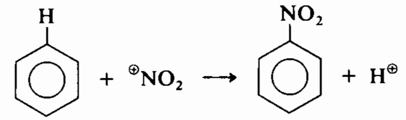
1.8 REACTION TYPES

There are essentially four general types of reaction which organic compounds can undergo:

(*a*) Displacement (substitution)
(*b*) Addition
(*c*) Elimination
(*d*) Rearrangement

In (*a*) it is displacement from carbon that is normally referred to, but the atom displaced can be either hydrogen or another atom or group.

In electrophilic substitution it is often hydrogen that is displaced, classical aromatic substitution (p. 132) being a good example:

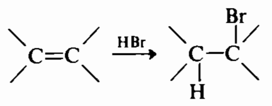


In nucleophilic substitution it is often an atom other than hydrogen that is displaced (p. 77),

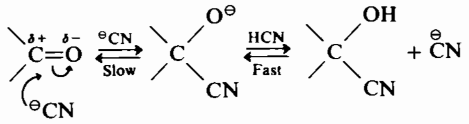
$$NC^{\ominus} + R{-}Br \longrightarrow NC{-}R + Br^{\ominus}$$

but nucleophilic displacement of hydrogen is also known (p. 167). Radical-induced displacement is also known, for example the halogenation of alkanes (*cf.* p. 323).

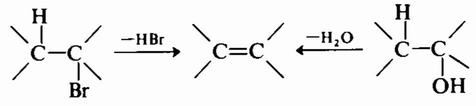
Addition reactions, too, can be electrophilic, nucleophilic or radical in character, depending on the type of species that initiates the process. Addition to simple carbon–carbon double bonds is normally either electrophile-, or radical-, induced; e.g. addition of HBr,



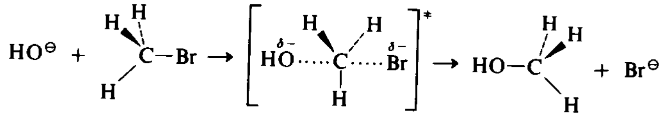
which can be initiated by the attack of either $H^{\oplus}$ (p. 184) or Br· (p. 317) on the double bond. By contrast, the addition reactions exhibited by the carbon–oxygen double bond, in simple aldehydes and ketones, are usually nucleophilic in character (p. 204). An example is the base-catalysed formation of cyanohydrins in liquid HCN:



Elimination reactions are, of course, essentially the reversal of addition reactions; the most common type is the loss of hydrogen and another atom or group from adjacent carbon atoms to yield alkenes (p. 246):



to as an *activated complex* or *transition state*. It should be emphasised that this is merely a highly unstable state that is passed through in a dynamic process, and not a discrete molecular species, an intermediate, that can actually be detected or even isolated (*cf.* p. 49). An example is (1) in the alkaline hydrolysis of bromomethane, in which the HO—C bond is being formed at the same time as the C—Br bond is being broken,



(1)

and the three hydrogen atoms attached to carbon are passing through a configuration in which they all lie in one plane (at right-angles to the plane of the paper). This reaction is discussed in detail below (p. 77).

The height of the barrier in (Fig. 2.3), $\Delta G^{\ddagger}$, is called the *free energy of activation* for the reaction (the higher it is the slower the reaction), and can be considered as being made up of enthalpy ($\Delta H^{\ddagger}$) and entropy ($T\Delta S^{\ddagger}$) terms:

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

$\Delta H^{\ddagger}$ (the *enthalpy of activation*) corresponds to the energy necessary to effect the stretching or even breaking of bonds that is an essential prerequisite for reaction to take place (e.g. stretching of the C—Br bond in 1). Thus reacting molecules must bring with them to any collision a certain minimum threshold of energy for reaction to be possible (often called simply the *activation energy*, E_{act}, but related to $\Delta H^{\ddagger}$); the well-known increase in the rate of a reaction as the temperature is raised is, indeed, due to the growing proportion of molecules with an energy above this minimum as the temperature rises.

The magnitude of E_{act} for a reaction may be calculated from values of k, the rate constant (*cf.* p. 39), determined experimentally at two different temperatures, T_1 and T_2, using the Arrhenius expression which relates k to T, the absolute temperature:

$$k = Ae^{-E/RT} \quad \text{or} \quad \log_{10} k = -\frac{E_{act}}{2{\cdot}303RT} + \log_{10} A$$

Where R is the gas constant (8·32 joules $\text{mol}^{-1}\,\text{deg}^{-1}$), and A is a constant for the reaction—independent of temperature—that is related to the proportion of the total number of collisions between reactant molecules that result in successful conversion into products. The value

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‡ The symbol ‡ will often be applied to a structure to indicate that it is intended as an attempted representation of a transition state (T.S.).

of E_{act} may then be obtained graphically by plotting values of $\log_{10} k$ against 1/T, or by conversion of the above equation into,

$$\log_{10} k_1/k_2 = -\frac{E_{act}}{2{\cdot}303R}\left[\frac{1}{T_1} - \frac{1}{T_2}\right]$$

and subsequent calculation.

The $\Delta S^{\ddagger}$ term (the *entropy of activation*) again relates to randomness. It is a measure of the change in degree of organisation, or ordering, of both the reacting molecules themselves and of the distribution of energy within them, on going from starting materials to the transition state; $\Delta S^{\ddagger}$ is related to the A factor in the Arrhenius equation above. If formation of the transition state requires the imposition of a high degree of organisation in the way the reactant molecules must approach each other, and also of the concentration of their energy in particular linkages so as to allow of their ultimate breakage, then the attainment of the transition state is attended by a sizeable decrease in entropy (randomness), and the probability of its formation is correspondingly decreased.

2.2.2 Kinetics and the rate-limiting step

Experimentally, the measurement of reaction rates consists in investigating the rate at which starting materials disappear and/or products appear at a particular (constant) temperature, and seeking to relate this to the concentration of one, or all, of the reactants. The reaction may be monitored by a variety of methods, e.g. directly by the removal of aliquots followed by their titrimetric determination, or indirectly by observation of colorimetric, conductimetric, spectroscopic, etc., changes. Whatever method is used the crucial step normally involves matching the crude kinetic data against variable possible functions of concentration, either graphically or by calculation, until a reasonable fit is obtained. Thus for the reaction,

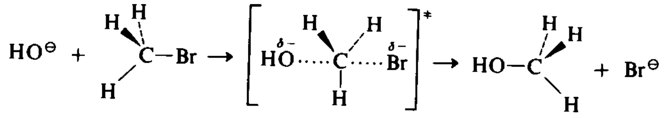
$$CH_3Br + {}^{\ominus}OH \longrightarrow CH_3OH + Br^{\ominus}$$

it comes as no surprise to find a rate equation,

$$\text{Rate} = k[CH_3Br][{}^{\ominus}OH]$$

where k is known as the *rate constant* for the reaction. The reaction is said to be *second order* overall; *first order* with respect to CH_3Br, and *first order* with respect to ${}^{\ominus}OH$.

Such coincidence of stoichiometry and rate law is fairly uncommon, the former is commonly no guide at all to the latter, which can only be obtained by experiment. Thus for the base catalysed bromination to as an *activated complex* or *transition state*. It should be emphasised that this is merely a highly unstable state that is passed through in a dynamic process, and not a discrete molecular species, an intermediate, that can actually be detected or even isolated (*cf.* p. 49). An example is (1) in the alkaline hydrolysis of bromomethane, in which the HO—C bond is being formed at the same time as the C—Br bond is being broken,



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general one that might otherwise have been assumed for the series. Thus the observed rates of hydrolysis of the chloromethanes with strong bases are found, under comparable conditions, to vary as follows,

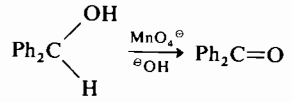
$$CH_3Cl \gg CH_2Cl_2 \ll CHCl_3 \gg CCl_4$$

clearly suggesting that trichloromethane undergoes hydrolysis in a different manner from the other compounds (*cf.* p. 267).

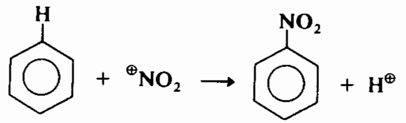
2.3.3 The use of isotopes

It is often a matter of some concern to know whether a particular bond has, or has not, been broken in a step up to and including the rate-limiting step of a reaction: simple kinetic data cannot tell us this, and further refinements have to be resorted to. If, for example, the bond concerned is C—H, the question may be settled by comparing the rates of reaction, under the same conditions, of the compound in which we are interested, and its exact analogue in which this bond has been replaced by a C—D linkage. The two bonds will have the same chemical nature as isotopes of the same element are involved, but their vibration frequencies, and hence their dissociation energies, will be slightly different because atoms of different *mass* are involved: the greater the mass, the stronger the bond. This difference in bond strength will, of course, be reflected in different rates of breaking of the two bonds under comparable conditions: the weaker C—H bond being broken more rapidly than the stronger C—D bond; quantum-mechanical calculation suggests a maximum rate difference, k_H/k_D, of ≈7 at 25°.

Thus in the oxidation



it is found that Ph_2CHOH is oxidised 6·7 times as rapidly as Ph_2CDOH; the reaction is said to exhibit a *primary kinetic isotope effect*, and breaking of the C—H bond must clearly be involved in the rate-limiting step of the reaction. By contrast benzene, C_6H_6, and hexadeuterobenzene, C_6D_6, are found to undergo nitration at essentially the same rate, and C—H bond-breaking, that must occur at some stage in the overall process,



thus cannot be involved in the rate-limiting step (*cf.* p. 136).

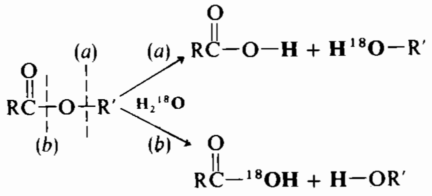
Primary kinetic isotope effects are also observable with pairs of isotopes other than hydrogen/deuterium, but as the relative mass difference must needs be smaller their maximum values will be correspondingly smaller. Thus the following have been observed:

$$HO^{\ominus} + \overset{(14)}{{}^{12}}CH_3{-}I \rightarrow HO{-}\overset{(14)}{{}^{12}}CH_3 + I^{\ominus} \qquad \frac{k_{^{12}C}}{k_{^{14}C}} = 1{\cdot}09\ (25°)$$

$$PhCH_2{-}\overset{(37)}{{}^{35}}Cl + H_2O \rightarrow PhCH_2{-}OH + H^{\oplus}\,\overset{(37)}{{}^{35}}Cl^{\ominus} \qquad \frac{k_{^{35}Cl}}{k_{^{37}Cl}} = 1{\cdot}0076\ (25°)$$

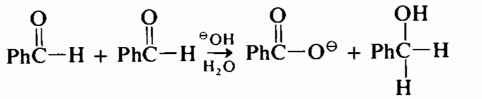
It should be emphasised that primary kinetic isotope effects are observed experimentally with values intermediate between the maximum calculated value and unity (i.e. *no* isotope effect): these too can be useful, as they may supply important information about the breaking of particular bonds in the transition state.

Isotopes can also be used to solve mechanistic problems that are non-kinetic. Thus the aqueous hydrolysis of esters to yield an acid and an alcohol could, in theory, proceed by cleavage at (*a*) alkyl/oxygen fission, or (*b*) acyl/oxygen fission:



If the reaction is carried out in water enriched in the heavier oxygen isotope ^{18}O, (*a*) will lead to an alcohol which is ^{18}O enriched and an acid which is not, while (*b*) will lead to an ^{18}O enriched acid but a normal alcohol. Most simple esters are in fact found to yield an ^{18}O enriched acid indicating that hydrolysis, under these conditions, proceeds *via* (*b*) acyl/oxygen fission (p. 238). It should of course be emphasised that these results are only valid provided that neither acid nor alcohol, once formed, can itself exchange its oxygen with water enriched in ^{18}O, as has indeed been shown to be the case.

Heavy water, D_2O, has often been used in a rather similar way. Thus in the Cannizzaro reaction of benzaldehyde (p. 216),



(9)

the question arises of whether the second hydrogen atom that becomes attached to carbon, in the molecule of phenylmethanol (benzyl alcohol, general one that might otherwise have been assumed for the series. Thus the observed rates of hydrolysis of the chloromethanes with strong bases are found, under comparable conditions, to vary as follows,

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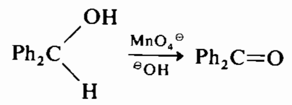

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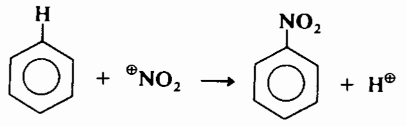

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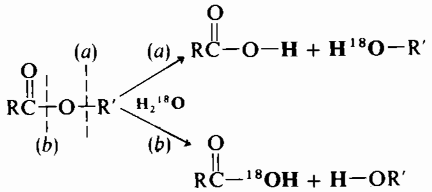
$$PhCH_2{-}\overset{(37)}{{}^{35}}Cl + H_2O \rightarrow PhCH_2{-}OH + H^{\oplus}\,\overset{(37)}{{}^{35}}Cl^{\ominus} \qquad \frac{k_{^{35}Cl}}{k_{^{37}Cl}} = 1{\cdot}0076\ (25°)$$

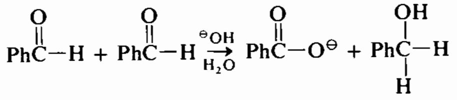
It should be emphasised that primary kinetic isotope effects are observed experimentally with values intermediate between the maximum calculated value and unity (i.e. *no* isotope effect): these too can be useful, as they may supply important information about the breaking of particular bonds in the transition state.

Isotopes can also be used to solve mechanistic problems that are non-kinetic. Thus the aqueous hydrolysis of esters to yield an acid and an alcohol could, in theory, proceed by cleavage at (*a*) alkyl/oxygen fission, or (*b*) acyl/oxygen fission:



If the reaction is carried out in water enriched in the heavier oxygen isotope ^{18}O, (*a*) will lead to an alcohol which is ^{18}O enriched and an acid which is not, while (*b*) will lead to an ^{18}O enriched acid but a normal alcohol. Most simple esters are in fact found to yield an ^{18}O enriched acid indicating that hydrolysis, under these conditions, proceeds *via* (*b*) acyl/oxygen fission (p. 238). It should of course be emphasised that these results are only valid provided that neither acid nor alcohol, once formed, can itself exchange its oxygen with water enriched in ^{18}O, as has indeed been shown to be the case.

Heavy water, D_2O, has often been used in a rather similar way. Thus in the Cannizzaro reaction of benzaldehyde (p. 216),

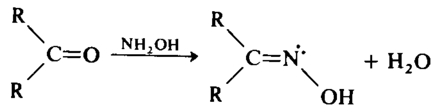


$$Ph\overset{O}{\overset{\|}{C}}{-}H + Ph\overset{O}{\overset{\|}{C}}{-}H \xrightarrow[H_2O]{^{\ominus}OH} Ph\overset{O}{\overset{\|}{C}}{-}O^{\ominus} + Ph\underset{H}{\underset{|}{\overset{OH}{\overset{|}{C}}}}{-}H$$

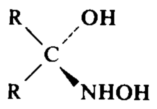
(9)

the question arises of whether the second hydrogen atom that becomes attached to carbon, in the molecule of phenylmethanol (benzyl alcohol, reaction pathway, and not merely in equilibrium with the true intermediate.

It is much more common not to be able to isolate any intermediates at all, but this does not necessarily mean that none are formed, merely that they may be too labile or transient to permit of their isolation. Their occurrence may then often be inferred from physical, particularly spectroscopic, measurements made on the system. Thus in the formation of oximes from a number of carbonyl compounds by reaction with hydroxylamine (p. 219),



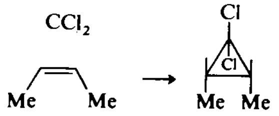
the infra-red absorption band characteristic of C=O in the starting material disappears rapidly, and may have gone completely before the band characteristic of C=N in the product even begins to appear. Clearly an intermediate must be formed, and further evidence suggests that it is the *carbinolamine* (10),



(10)

which forms rapidly and then breaks down only slowly to yield the products, the oxime and water.

Where we have reason to suspect the involvement of a particular species as a labile intermediate in the course of a reaction, it may be possible to confirm our suspicions by introducing into the reaction mixture, with malice aforethought, a reactive species which we should expect our postulated intermediate to react with particularly readily. It may then be possible to divert the labile intermediate from the main reaction pathway—to *trap* it—and to isolate a stable species into which it has been unequivocally incorporated. Thus in the hydrolysis of trichloromethane with strong bases (*cf.* p. 46), the highly electron-deficient *dichlorocarbene*, CCl_2, which has been suggested as a labile intermediate (p. 267), was 'trapped' by introducing into the reaction mixture the electron-rich species *cis* but-2-ene (11), and then isolating the resultant stable cyclopropane derivative (12), whose formation can hardly be accounted for in any other way:

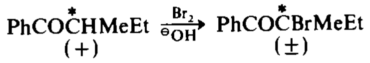


(11) (12)

The successful study of intermediates not only provides one or more signposts which help define the detailed pathway traversed by a reaction, the intermediates themselves may also provide inferential evidence about the transition states for which they are often taken as models (*cf.* p. 41).

2.3.5 Stereochemical criteria

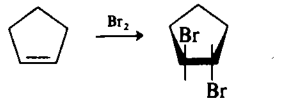
Information about the stereochemical course followed by a particular reaction can also provide useful insight into its mechanism, and may well introduce stringent criteria that any suggested mechanistic scheme will have to meet. Thus the fact that the base-catalysed bromination of an optically active stereoisomer of the ketone (13)



$$\underset{(+)}{PhCO\overset{*}{C}HMeEt} \xrightarrow[^{\ominus}OH]{Br_2} \underset{(\pm)}{PhCO\overset{*}{C}BrMeEt}$$

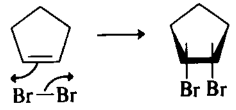
(13)

leads to an optically inactive racemic product (p. 295), indicates that the reaction must proceed through a planar intermediate, which can undergo attack equally well from either side leading to equal amounts of the two mirror-image forms of the product. Then again, the fact that cyclopentene (14) adds on bromine under polar conditions to yield the *trans* dibromide (15) only, indicates that the mechanism of



(14) (15)

the reaction cannot simply be direct, one-step addition of the bromine molecule to the double bond, for this must lead to the *cis* dibromide (16):

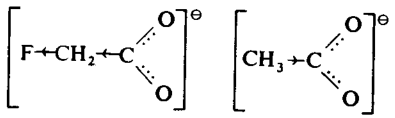


(14) (16)

The addition must be at least a two-step process (*cf.* p. 179). Reactions like this, which proceed so as to give largely—or even wholly—one

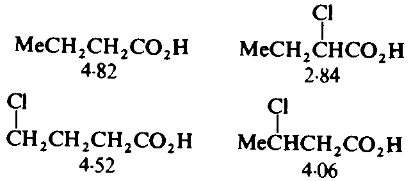
The relative effect of the different halogens is in the expected order, fluorine being the most electronegative (electron-withdrawing) and producing a hundredfold increase in strength of fluoroethanoic acid as compared with ethanoic acid itself. The effect is very much greater than that produced, in the opposite direction, by the introduction of an alkyl group, and the introduction of further halogens still produces large increases in acid strength: trichloroethanoic is thus a very strong acid.

Here again it is important to remember that K_a (and hence pK_a) is related to $\Delta G^{\ominus}$ for the ionisation, and that $\Delta G^{\ominus}$ includes both $\Delta H^{\ominus}$ and $\Delta S^{\ominus}$ terms. In this series of halogen-substituted ethanoic acids $\Delta H^{\ominus}$ is found to differ little from one compound to another, the observed change in $\Delta G^{\ominus}$ along the series being due largely to variation in $\Delta S^{\ominus}$. This arises from the substituent halogen atom effecting delocalisation of the negative charge over the whole of the anion,



the latter thus imposes correspondingly less powerful restriction on the water molecules surrounding it than does the unsubstituted ethanoate anion whose charge is largely concentrated, being confined substantially to $CO_2^{\ominus}$. There is therefore a smaller decrease in entropy on ionisation of the halogen-substituted ethanoic acids than with ethanoic acid itself. This is particularly pronounced with CF_3CO_2H (pK_a 0·23) for whose ionisation $\Delta G^{\ominus} = 1{\cdot}3$ kJ (0·3 kcal) compared with 27·2 kJ (6·5 kcal) for CH_3CO_2H, while the $\Delta H^{\ominus}$ values for these two acids differ very little from each other.

The introduction of a halogen atom further away from the carboxyl group than the adjacent α-position has much less influence. Its inductive effect quickly dies away down a saturated chain, with the result that the negative charge becomes progressively less spread, i.e. more concentrated, in the carboxylate anion. The acid thus increasingly resembles the corresponding simple aliphatic acid itself, as the following pK_a values show:



$MeCH_2CH_2CO_2H$ 4·82

$MeCH_2\underset{}{\overset{\overset{\textstyle Cl}{|}}{C}}HCO_2H$ 2·84

$\overset{\overset{\textstyle Cl}{|}}{C}H_2CH_2CH_2CO_2H$ 4·52

$Me\overset{\overset{\textstyle Cl}{|}}{C}HCH_2CO_2H$ 4·06

Other electron-withdrawing groups, e.g. $R_3N^{\oplus}$, CN, NO_2, SO_2R, CO, CO_2R increase the strength of simple aliphatic acids, as also do

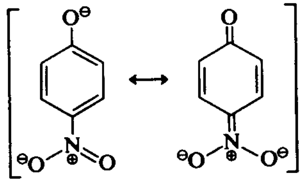
hydroxyl and methoxyl groups. The unshared electrons on the oxygen atoms of the last two groups are not able to exert a mesomeric effect, in the opposite direction to their inductive effect, owing to the intervening saturated carbon atoms. All this is seen in the pK_a values:

$O_2N\leftarrow CH_2\leftarrow CO_2H$ 1·68	$EtO_2C\leftarrow CH_2\leftarrow CO_2H$ 3·35
$Me_3\overset{\oplus}{N}\leftarrow CH_2\leftarrow CO_2H$ 1·83	$MeCO\leftarrow CH_2\leftarrow CO_2H$ 3·58
$NC\leftarrow CH_2\leftarrow CO_2H$ 2·47	$Me\ddot{O}\leftarrow CH_2\leftarrow CO_2H$ 3·53
$H\ddot{O}\leftarrow CH_2\leftarrow CO_2H$ 3·83	

3.1.6 Phenols

Analogous effects can be observed with substituted phenols, the presence of electron-withdrawing groups in the nucleus increasing their acidity. In the case of a nitro substituent, the inductive effect would be expected to fall off with distance on going *o*- → *m*- → *p*-nitrophenol, but there would also be an electron-withdrawing mesomeric effect when the nitro group is in the *o*- or *p*-, but not in the *m*-position; and this too would promote ionisation by stabilisation (though delocalisation) of the resultant anion. We might therefore expect *o*- and *p*-nitrophenols to be more acidic than the *m*-compound which is, in fact, found to be the case. Introduction of further NO_2 groups promotes acidity markedly, thus 2,4,6-trinitrophenol (picric acid) is found to be a very strong acid:

	pK_a
C_6H_5OH	9·95
o-$O_2NC_6H_4OH$	7·23
m-$O_2NC_6H_4OH$	8·35
p-$O_2NC_6H_4OH$	7·14
2,4-$(O_2N)_2C_6H_3OH$	4·01
2,4,6-$(O_2N)_3C_6H_2OH$	1·02

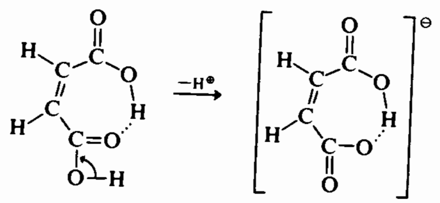


Here again $\Delta H^{\ominus}$ is found to vary only very slightly between *o*-, *m*- and *p*- nitrophenols, the differing $\Delta G^{\ominus}$ values observed for the three arising from differences in the $T\Delta S^{\ominus}$ terms, i.e. from variations in the solvation patterns of the three anions, due to the differing distribution of negative charge in them.

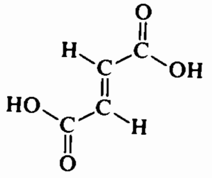
The effect of introducing electron-donating alkyl groups into the benzene nucleus is found to be small:

	pK_a
C_6H_5OH	9·95
o-MeC_6H_4OH	10·28
m-MeC_6H_4OH	10·08
p-MeC_6H_4OH	10·19

The effect is very pronounced, but falls off sharply as soon as the carboxyl groups are separated by more than one saturated carbon atom. *Cis*-butenedioic(maleic) acid (5, $pK_a^1 = 1{\cdot}92$) is a much stronger acid than *trans*-butenedioic(fumaric) acid (6, $pK_a^1 = 3{\cdot}02$), due to the intramolecular hydrogen bonding that can take place with the former, but not with the latter, leading to relative stabilisation of the *cis* (maleate, 7) mono-anion (*cf. o*-hydroxybenzoic acid above):

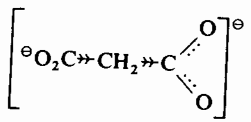


(5) (7)

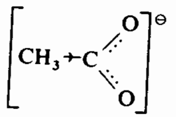


(6)

The second dissociation of *trans*-butenedioic acid ($pK_a^2 = 4{\cdot}38$) occurs more readily than that of the *cis*-acid ($pK_a^2 = 6{\cdot}23$), however, because of the greater difficulty in removing a proton from the negatively charged cyclic system in the anion (7) derived from the latter. Ethanedioic(oxalic), propane-1,3-dioic(malonic) and butane-1,4-dioic(succinic) acids are each weaker in their second dissociations than methanoic, ethanoic and propanoic acids, respectively. This is because the second proton has to be removed from a negatively charged species containing an electron-donating substituent, i.e. $CO_2^{\ominus}$, which might be expected to destabilise the anion with respect to the undissociated acid, as compared with the unsubstituted system:



$$\left[{}^{\ominus}O_2C\!\twoheadrightarrow\!CH_2\!\twoheadrightarrow\!C\begin{smallmatrix}O\\ \\ O\end{smallmatrix}\right]^{\ominus}$$



$$\left[CH_3\!\rightarrow\!C\begin{smallmatrix}O\\ \\ O\end{smallmatrix}\right]^{\ominus}$$

3.1.9 pK_a and temperature

We have already seen (p. 56) that the K_a, and hence pK_a, value for an acid is not an intrinsic attribute of the species itself, because it varies from one solvent to another: the value depending on the overall system of which the acid is a constituent. Values are normally quoted for aqueous solution, unless otherwise specified, because most data are available for that solvent. Most values are also quoted as at 25°, again because most data were obtained at this temperature. A constant temperature has to be specified as K_a, an equilibrium constant, varies with temperature. We have been concerned above with the *relative* acidity of various categories of acids, and in trying to correlate relative acidity sequences with structure in a rational way—with some degree of success. It is, however, pertinent to point out that not only do individual K_a values vary with temperature, they also vary *relative* to each other: thus ethanoic is a weaker acid than Et_2CHCO_2H below 30°, but a stronger acid above that temperature. Such reversals of relative acidity with change of temperature are found to be fairly common; it thus behoves us not to split too many fine hairs about correlating relative acidity with structure at 25°!

3.2 BASES

3.2.1 pK_b, p$K_{BH^{\oplus}}$ and pK_a

The strength of a base, B:, in water, may be determined by considering the equilibrium:

$$B\!: + HOH \rightleftarrows BH^{\oplus} + {}^{\ominus}OH$$

The equilibrium constant in water, K_b, is then given by:

$$K_b \approx \frac{[BH^{\oplus}][{}^{\ominus}OH]}{[B:]}$$

The $[H_2O]$ term is incorporated into K_b, because water is present in such excess that its concentration does not change significantly; here again, concentrations can commonly be used instead of the more correct activities provided the solution is reasonably dilute.

It is, however, now more usual to describe the strength of bases also in terms of K_a and pK_a, thereby establishing a single continuous scale for both acids and bases. To make this possible we use, as our reference reaction for bases, the equilibrium

$$BH^{\oplus} + H_2O\!: \rightleftarrows B\!: + H_3O^{\oplus}$$

for which we can then write,

$$K_a \approx \frac{[B:][H_3O^{\oplus}]}{[BH^{\oplus}]}$$

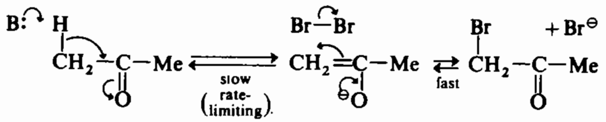
where K_a (and pK_a) is a measure of the acid strength of the conjugate acid, $BH^{\oplus}$, of the base, B:. This measure of the readiness with which $BH^{\oplus}$ will part with a proton is, conversely, a measure of the lack of readiness with which the base, B:, will accept one: the stronger $BH^{\oplus}$ is as an acid, the weaker B: will be as a base. Thus the smaller the numerical value of pK_a for $BH^{\oplus}$, the weaker B: is as a base. When using pK to quote the strength of a base, B:, $pK_{BH^{\oplus}}$ should actually be specified but it has become common—though incorrect—to write it simply as pK_a.

By analogy with acids above, specific basic catalysis is found to be characteristic of reactions in which there is rapid, reversible proton-removal from the substrate *before* the slow, rate-limiting step.

In *general base catalysis*, bases other than $^{\ominus}OH$ are involved. Thus in the base catalysed bromination of acetone (*cf.* p. 295) in an acetate buffer it is found that,

$$\text{Rate} = k_{^{\ominus}OH}[^{\ominus}OH][MeCOMe] + k_{MeCO_2^{\ominus}}[MeCO_2^{\ominus}][MeCOMe]$$

and the reaction is believed to proceed:



(B: = $^{\ominus}OH$ or $MeCO_2^{\ominus}$)

Again by analogy with acids above, general base catalysis is found to be characteristic of reactions in which removal of proton from the substrate is slow, i.e. rate-limiting, and is followed by rapid conversion of the intermediate into products.

4

Nucleophilic substitution at a saturated carbon atom

A type of reaction that has probably received more detailed study than any other—largely due to the monumental work of Ingold and his school—is nucleophilic substitution at a saturated carbon atom: the classical displacement reaction exemplified by the conversion of an alkyl halide into an alcohol by the action of aqueous base:

$$HO^{\ominus} + R{-}Hal \rightarrow HO{-}R + Hal^{\ominus}$$

Kinetic measurements on reactions in which alkyl halides are attacked by a wide variety of different nucleophiles, Nu:, have revealed two, essentially extreme, types: one in which,

$$\text{Rate} = k_2[\text{RHal}][\text{Nu:}] \qquad [1]$$

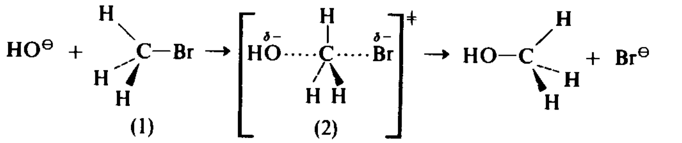
and another in which,

$$\text{Rate} = k_1[\text{RHal}] \qquad [2]$$

i.e. the rate is independent of [Nu:]. In some cases the rate equations are found to be 'mixed' or are otherwise complicated, but examples are known which exactly follow the simple relations above.

4.1 RELATION OF KINETICS TO MECHANISM

Hydrolysis of the primary halide bromomethane (methyl bromide) in aqueous base has been shown to proceed according to equation [1] above, and this has been interpreted as involving the participation of both alkyl halide and hydroxyl ion in the rate-limiting (i.e. slowest) step of the reaction. Ingold has suggested a transition state in which the attacking hydroxyl ion becomes partially bonded to the reacting carbon atom before the incipient bromide ion has become wholly detached from it; thus part of the energy necessary to effect the breaking of the C—Br bond is then supplied by that produced in forming the HO—C bond. Quantum mechanical calculation shows that an approach by the hydroxyl ion along the line of centres of the carbon and bromine atoms is that of lowest energy requirement. This can be represented:

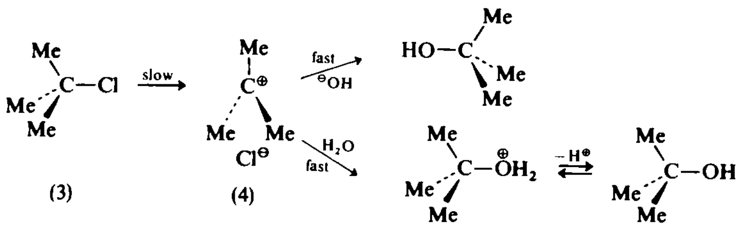


(1) (2)

Transition state

The negative charge is spread in the transition state in the course of being transferred from hydroxyl to bromine, and the hydrogen atoms attached to the carbon atom attacked pass through a position in which they all lie in one plane (at right angles to the plane of the paper as drawn above). The initially sp^3 hybridised carbon atom becomes sp^2 hybridised in the transition state, the HO and Br being associated with the two lobes of the unhybridised *p* orbital that is thereby made available. This type of mechanism has been designated by Ingold as S_N2: Substitution Nucleophilic bimolecular.

By contrast, hydrolysis of the tertiary halide 2-chloro-2-methylpropane (3,*t*-butyl chloride) in base is found kinetically to follow equation [2], i.e. as the rate is independent of [$^{\ominus}$OH], this can play no part in the rate-limiting step. This has been interpreted as indicating that the halide undergoes slow ionisation (in fact, completion of the R$\rightarrow$Cl polarisation that has already been shown to be present in such a molecule) as the rate-limiting step to yield the ion pair R$^{\oplus}$Cl$^{\ominus}$ (4); followed by rapid, non rate-limiting attack by $^{\ominus}$OH or, if that is suitable, by solvent, the latter often predominating because of its very high concentration:



(3) (4)

This type of mechanism has been designated S_N1: Substitution Nucleophilic unimolecular. The energy necessary to effect the initial ionisation is largely recovered from the energy evolved through solvation of the resultant ion pair. The entropy of activation, $\Delta S^{\ddagger}$, for such a dissociative process (*cf.* p. 39) is also advantageous; thus $\Delta S^{\ddagger}$ for the hydrolysis of Me_3CCl is found to be $+51\ J\ K^{-1}\ mol^{-1}$, compared with $-17\ J\ K^{-1}\ mol^{-1}$ for hydrolysis of CH_3Cl. The cation in the ion pair (4), in which the central carbon atom carries the +ve charge, is of course a carbocation intermediate, and during its formation the initially sp^3 hybridised carbon atom collapses to a more stable planar (sp^2) state, in which the three methyl groups are as far apart from each other as they can get. Attack by $^{\ominus}$OH or solvent (e.g. H_2O:) can then take place from either side of this planar intermediate. If attainment of this planar state is inhibited by steric or other factors (*cf.* p. 87), the carbocation intermediate will be formed only with difficulty, if at all; i.e. ionisation, and hence reaction by the S_N1 pathway, may then not take place.

Thus the salient difference between reaction by the S_N2 and S_N1 pathways is that S_N2 proceeds in one step only, *via* a transition state; while S_N1 proceeds in two steps, *via* an actual (carbocation) intermediate.

A certain element of confusion is to be met with both in textbooks, and in the literature, over the use and meaning of the terms *order* (*cf.* p. 39) and *molecularity* as applied to reactions. The order is an experimentally determined quantity, the overall order of a reaction being the sum of the powers of the concentration terms that appear in the rate equation:

Rate = $k_3[A][B][C]$ Third order overall

Rate = $k_3[A]^2[B]$ Third order overall

Rate = $k_2[A]^2$ Second order overall

Generally, however, it is the order with respect to a particular reactant (or reactants) that is of more interest and significance than the overall order, i.e. that the above reactions are first order, second order, and second order, respectively, with respect to A. Examples of both zero order, and non-integral orders, with respect to a particular reactant are also known.

The molecularity refers to the number of species (molecules, ions, etc.) that are undergoing bond-breaking and/or bond-making in one step of the reaction, usually in the rate-limiting step. It is important to realise that the molecularity is not an experimentally determined quantity, and has significance only in the light of the particular mechanism chosen for the reaction: it is an integral part of the mechanistic interpretation of the reaction and is susceptible to rebecause it is a bond other than that carrying the isotopic label that is being broken (*cf.* p. 46). The relative contributions of hyperconjugation and inductive effects to the stabilisation of carbocations is open to debate, but it is significant that a number of carbocations will only form at all if they can take up a planar arrangement, the state in which hyperconjugation will operate most effectively (*cf.* p. 104).

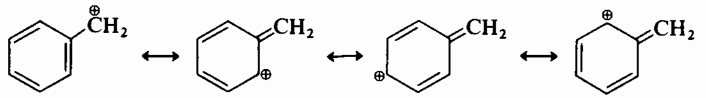
In steric terms there is a relief of crowding on going from the initial halide, with a tetrahedral disposition of four substituents about the sp^3 hybridised carbon atom, to the carbocation, with a planar disposition of only *three* substituents (*cf. five* for the S_N2 T.S.) about the now sp^2 hybridised carbon atom. The three substituents are as far apart from each other as they can get in the planar carbocation, and the relative relief of crowding (halide → carbocation) will increase as the substituents increase in size ($H \rightarrow Me \rightarrow Me_3C$). The S_N1 reaction rate would thus be expected to increase markedly (on both electronic and steric grounds) as the series of halides is traversed. It has not, however, proved possible to confirm this experimentally by setting up conditions such that the four halides of Fig. 4.1 (p. 82) all react *via* the S_N1 pathway.

Thus, as the S_N2 rate is expected to *decrease*, and the S_N1 rate to *increase*, across the series in Fig. 4.1, the reason for the observed pattern of reaction rates, and changeover in reaction pathway, becomes apparent.

A similar mechanistic changeover is observed, though considerably sooner, in traversing the series:

$CH_3{-}Cl$	$C_6H_5CH_2{-}Cl$	$(C_6H_5)_2CH{-}Cl$	$(C_6H_5)_3C{-}Cl$
(9)	(10)	(11)	(12)

Thus for hydrolysis in 50% aqueous acetone, a mixed second and first order rate equation is observed for phenylchloromethane (benzyl chloride, 10)—moving over almost completely to the S_N1 mode in water alone. Diphenylchloromethane (11) is found to follow a first order rate equation, with a very large increase in total rate, while with triphenylchloromethane (trityl chloride, 12) the ionisation is so pronounced that the compound exhibits electrical conductivity when dissolved in liquid SO_2. The main reason for the greater promotion of ionisation—with consequent earlier changeover to the S_N1 pathway in this series—is the considerable stabilisation of the carbocation, by delocalisation of its positive charge, that is now possible:



This is a classical example of an ion stabilised by charge delocalisation *via* the agency of the delocalised π orbitals of the benzene nucleus (*cf.* the negatively charged phenoxide ion, p. 23). The effect will become progressively more pronounced, and S_N1 attack further facilitated, with $(C_6H_5)_2CHCl(11)$ and $(C_6H_5)_3CCl(12)$, as the possibilities for delocalising the positive charge are increased in the carbocations to which these latter halides give rise.

S_N2 attack on the CH_2 in (10) is found to proceed at very much the same rate as on that in $MeCH_2Cl$, suggesting that any adverse steric crowding in the T.S. by the bulky C_6H_5 group is compensated by a small electronic (inductive?) effect promoting reaction.

Similar carbocation stabilisation can also occur in the hydrolysis of allyl halides, e.g. 3-chloropropene:

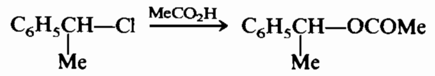
$$CH_2{=}CH{-}CH_2Cl \rightarrow [CH_2{=}CH{-}\overset{\oplus}{C}H_2 \leftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2]\ Cl^{\ominus}$$

S_N1 attack is thus promoted and allyl, like benzyl, halides are normally more reactive than such species, e.g. $CH_3CH_2CH_2Cl$ and $C_6H_5CH_2CH_2CH_2Cl$, in which such carbocation stabilisation cannot take place. S_N2 attack is also speeded up, compared with $CH_3CH_2CH_2Cl$, presumably because any electronic effect of the double bond—promoting reaction—is not here nullified by an adverse steric effect, as with the bulky C_6H_5 group in $C_6H_5CH_2Cl$ (*cf.* above). The proportion of the total reaction proceeding by each of the two pathways is found to depend on the conditions: more powerful nucleophiles promoting the S_N2 mode (*cf.* p. 96).

By contrast, vinyl halides such as chloroethene, $CH_2{=}CHCl$, and halogenobenzenes are very unreactive towards nucleophiles. This stems from the fact that the halogen atom is now bonded to an sp^2 hybridised carbon, with the result that the electron pair of the C—Cl bond is drawn closer to carbon than in the bond to an sp^3 hybridised carbon. The C—Cl is found to be stronger, and thus less easily broken, than in, for example, CH_3CH_2Cl, and the C—Cl dipole is smaller; there is thus less tendency to ionisation (S_N1) and a less positive carbon for $^{\ominus}OH$ to attack (S_N2); the π electrons of the double bond also inhibit the close approach of an attacking nucleophile. The double bond would not help to stabilise either the S_N2 transition state or the carbocation involved in the S_N1 pathway. Very much the same considerations apply to halogenobenzenes, with their sp^2 hybridised carbons and the π orbital system of the benzene nucleus; their reactions, which though often bimolecular are not in fact simply S_N2 in nature, are discussed further below (p. 170).

The influence of steric factors on the reaction pathway is particularly observed when substitution takes place at the β-position. Thus for the excess. This raises the question whether the mixture of racemisation/inversion observed in such cases stems from the simultaneous operation of S_N1 and S_N2 pathways for solvolysis, rather than *via* the relatively elaborate, variable ion pair hypothesis advanced above.

In some cases at least it is possible to demonstrate that a 'mixed' S_N1+S_N2 pathway is *not* operating. Thus solvolysis of the halide, $(+)C_6H_5CHMeCl$, mentioned above, but this time in $MeCO_2H$,



$$C_6H_5\underset{\displaystyle Me}{CH}—Cl \xrightarrow{MeCO_2H} C_6H_5\underset{\displaystyle Me}{CH}—OCOMe$$

(+)

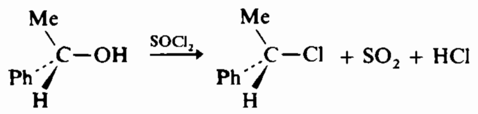
88% racemisation
12% net inversion

was found to lead to 88% racemisation, and 12% net inversion. Adding the much more powerfully nucleophilic $MeCO_2^{\ominus}$ (as $MeCO_2^{\ominus}Na^{\oplus}$) to the reaction mixture was found to result in: (*a*) no increase in the overall reaction rate, and (*b*) no increase in the proportion of net inversion. This strongly suggests that the inversion that is observed does *not* stem from part of the overall reaction proceeding *via* an S_N2 pathway simultaneously with the (major) S_N1 mode. If it did, we would expect the change to a much more powerful nucleophile ($MeCO_2H \rightarrow MeCO_2^{\ominus}$) to lead to marked increases in both (*a*) and (*b*) above.

A good deal of interest, and controversy, has centred on whether in the last analysis there is perhaps a continuous spectrum of mechanistic pathways intermediate between S_N2 and S_N1: these imperceptibly shading into each other *via* gradually varying transition states from the pure S_N2 side, and *via* gradually varying ion pair/solvent combinations from the pure S_N1 side. It is an area in which theory has shaded over into semantics if, indeed, not even into theology!

4.4.5 S_Ni mechanism: retention of configuration

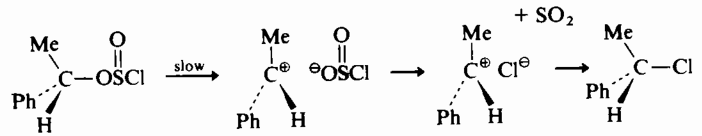
Despite what has been said above about displacement reactions leading to inversion of configuration, to racemisation, or to a mixture of both, a number of cases are known of reactions that proceed with actual retention of configuration, i.e. in which the starting material and product have the same configuration. One reaction in which this has been shown to occur is in the replacement of OH by Cl through the use of thionyl chloride, $SOCl_2$:



(29) (30*a*)

The reaction has been shown to follow a second order rate equation, rate = $k_2[ROH][SOCl_2]$, but clearly cannot proceed by the simple S_N2 mode for this would lead to inversion of configuration (p. 87) in the product, which is not observed.

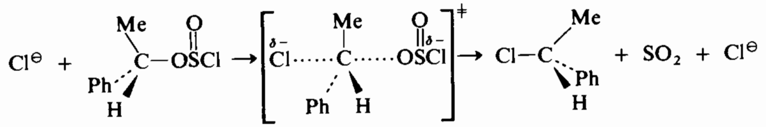
Carrying out the reaction under milder conditions allows of the isolation of an alkyl chlorosulphite, ROSOCl (31), and this can be shown to be a true intermediate. The chlorosulphite is formed with retention of configuration, the R—O bond not being broken during the reaction. The rate at which the alkyl chlorosulphite intermediate (31) breaks down to the product, RCl (30*a*), is found to increase with increasing polarity of the solvent, and also with increasing stability of the carbocation $R^{\oplus}$: an ion pair, $R^{\oplus\ominus}OSOCl$ (32), is almost certainly involved. Provided collapse of the ion pair to products then occurs rapidly, i.e. in the intimate ion pair (33) within a solvent cage (*cf.* p. 90), then attack by $Cl^{\ominus}$ is likely to occur on the same side of $R^{\oplus}$ from which $^{\ominus}OSOCl$ departed, i.e. with retention of configuration:



(31) (32) (33) (30*a*)

Whether the breaking of the C—O and the S—Cl bonds occurs simultaneously, or whether the former occurs first, is still a matter of debate.

It is interesting that if the $SOCl_2$ reaction on ROH (29) is carried out in the presence of pyridine, the product RCl is found now to have undergone inversion of configuration (30*b*). This occurs because the HCl produced during the formation of (31) from ROH and $SOCl_2$ is converted by pyridine into $C_5H_5NH^{\oplus}Cl^{\ominus}$ and $Cl^{\ominus}$, being an effective nucleophile, attacks (31) 'from the back' in a normal S_N2 reaction with inversion of configuration:



(31) (30*b*)

4.4.6 Neighbouring group participation: 'retention'

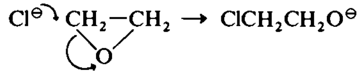
There are also some examples of retention of configuration in nucleophilic displacement reactions where the common feature is an atom or group—close to the carbon undergoing attack—which has an electron and non-charged nucleophiles on positively charged species (N_2 is probably the best leaving group there is):

$$H_2O\colon + PhN_2^{\oplus} \longrightarrow PhOH + N_2 + H^{\oplus}$$

We have also seen good leaving groups other than halide ion, e.g. tosylate anion (*cf.* p. 88),

$$MeCO_2^{\ominus} + ROSO_2C_6H_4Me\text{-}p \rightarrow MeCO_2R + p\text{-}MeC_6H_4SO_3^{\ominus}$$

and 'internal' leaving groups (*cf.* p. 94):



There are also nucleophilic displacement reactions, of considerable synthetic importance, in which the attacking atom in the nucleophile is carbon in either a carbanion (p. 288) or a source of negatively polarised carbon (*cf.* p. 221); new carbon–carbon bonds are thus formed:

$$HC{\equiv}CH \overset{^{\ominus}NH_2}{\rightleftarrows} HC{\equiv}C^{\ominus} + Pr{-}Br \longrightarrow HC{\equiv}C{-}Pr + Br^{\ominus}$$

$$CH_2(CO_2Et)_2 \overset{EtO^{\ominus}}{\rightleftarrows} (EtO_2C)_2CH^{\ominus} + PhCH_2{-}Br \longrightarrow (EtO_2C)_2CH{-}CH_2Ph + Br^{\ominus}$$

$$Br\overset{\delta+}{Mg}\overset{\delta-}{Ph} + C_6H_{13}{-}Br \longrightarrow MgBr_2 + Ph{-}C_6H_{13}$$

It should be remembered that in the above examples what is nucleophilic attack from the viewpoint of one participant is electrophilic attack from the viewpoint of the other. Any designation of the process as a whole tends therefore to be somewhat arbitrary, reflecting as it does our preconceptions about what constitutes a reagent as opposed to a substrate (*cf.* p. 30).

Hardly surprisingly, not all nucleophilic displacement reactions proceed so as to give 100% yields of the desired products! Here, as elsewhere, side-reactions occur yielding unexpected, and in preparative terms unwanted, products. A major side-reaction is *elimination* to yield unsaturated compounds: this is discussed in detail below (p. 246).

5

Carbocations, electron-deficient N and O atoms and their reactions

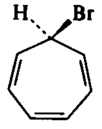
Reference has already been made in the last chapter to the generation of carbocations, in ion pairs, as intermediates in some displacement reactions at a saturated carbon atom, e.g. the solvolysis of an alkyl halide *via* the S_N1 mechanism. Carbocations are, however, fairly widespread in occurrence and, although their existence is often only transient, they are of considerable importance in a wide variety of chemical reactions.

5.1 METHODS OF FORMING CARBOCATIONS

5.1.1 Heterolytic fission of neutral species

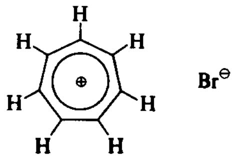
The obvious example is simple *ionisation*, the group attached to carbon departing with its bonding electrons to form an ion pair, $R^{\oplus}Y^{\ominus}$:

Stabilisation, through delocalisation, can also occur through *aromatisation*. Thus 1-bromocyclohepta-2,4,6-triene(tropylium bromide, 6),



(6)

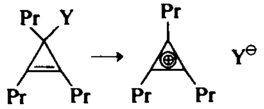
which is isomeric with $C_6H_5CH_2Br$, is found, unlike the latter compound, to be a crystalline solid (m.p. 208°) which is highly soluble in water yielding bromide ions in solution, i.e. it has not the above covalent structure but is an ion pair. The reason for this behaviour resides in the fact that the cyclic cation (7) has 6πe which can be accommodated in three delocalised molecular orbitals spread over the seven atoms. It is thus a Hückel $4n + 2$ system ($n = 1$) like benzene (*cf.* p. 17) and exhibits quasi-aromatic stability:



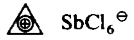
(7)

thus the planar carbocation is here stabilised by aromatisation. The above delocalised structure is confirmed by the fact that its n.m.r. spectrum exhibits only a single proton signal, i.e. all seven hydrogen atoms are equivalent. The effectiveness of such aromatic stabilisation is reflected in its being $\approx 10^{11}$ times more stable than the highly delocalised $Ph_3C^{\oplus}$. The generation of (7) by the action of $Ph_3C^{\oplus}$ on cycloheptatriene itself has already been referred to (p. 104).

A particularly interesting case of carbocation stabilisation occurs with Hückel $4n+2$ systems when $n = 0$, i.e. cyclic systems with 2πe (p. 18). Thus derivatives of 1,2,3-tripropylcyclopropene (8) are found to yield ion pairs containing the corresponding cyclopropenyl cation (9) extremely readily,



(8) (9)



(10)

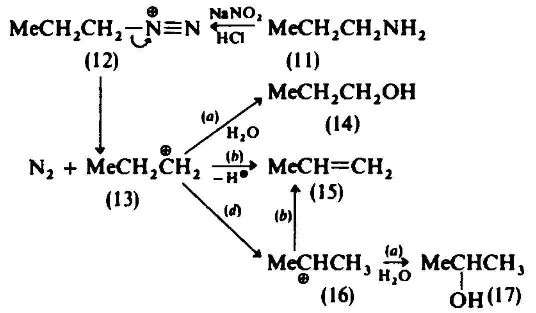
and the latter is found to be even more stable ($\approx 10^3$ times) than (7) above: it is still present as a carbocation to the extent of $\approx 50\%$ in water at pH 7! More recently it has also proved possible to isolate an ion pair containing the parent cyclopropenyl cation (10) itself, as a white crystalline solid. ^{13}C n.m.r. (*cf.* p. 48) has proved useful in this field as the position of the signal from the +ve carbon correlates with the electron density at this atom (*cf.* p. 393).

5.3 CARBOCATION REACTIONS

Carbocations are found to undergo four basic types of reaction:

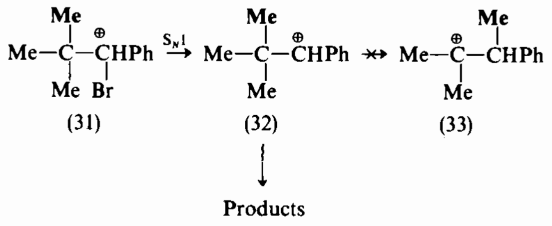
(*a*) Combination with a nucleophile.
(*b*) Elimination of a proton.
(*c*) Addition to an unsaturated linkage.
(*d*) Rearrangement of their structure.

The first two reaction types often lead to the formation of stable end-products, but (*c*) and (*d*) lead to the formation of new carbocations to which the whole spectrum of reaction types is still open. Most of these possibilities are neatly illustrated in the reaction of 1-aminopropane (11) with sodium nitrite and dilute hydrochloric acid [the behaviour of diazonium cations, e.g. (12), will be discussed further below, p. 119]:



Thus reaction of the 1-propyl cation (13) with water (reaction type *a*) will yield propan-1-ol (14), elimination of a proton from (13) will yield propene (15, reaction type *b*), while rearrangement of (13, reaction type *d*)—in this case migration of $H^{\ominus}$—will yield the 2-propyl cation (16). Type (*b*) reaction on this rearranged cation (16) will yield more propene (15), while type (*a*) reaction with water will yield propan-2-ol (17). The product mixture obtained in a typical experiment was 7% propan-1-ol, 28% propene, and 32% propan-2-ol: the relative proportions of propan-1-ol and propan-2-ol reflecting the relative stability of the two cations (13) and (16).

The sum of the above products still represents only 67% conversion of the original 1-aminopropane, however, and we have clearly not

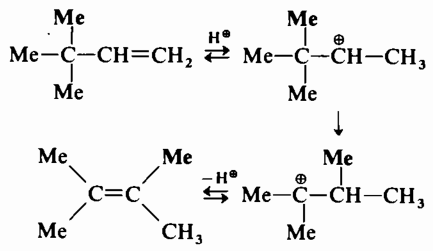


This reflects the greater stability of the benzylic cation (32), though only secondary, compared with the tertiary cation (33) that would be—but in fact is not—obtained by its rearrangement (*cf.* p. 105).

5.4.2.2 Rearrangement of hydrocarbons

Wagner–Meerwein type rearrangements are also encountered in the cracking of petroleum hydrocarbons when catalysts of a Lewis acid type are used. These generate carbocations from the straight chain alkanes (*cf.* the isomerisation of ^{13}C labelled propane, p. 108), which then tend to rearrange to yield branched-chain products. Fission also takes place, but this branching is important because the resultant alkanes cause less knocking in the cylinders of internal combustion engines than do their straight-chain isomers. It should be mentioned, however, that petroleum cracking can also be induced by catalysts that promote reaction *via* radical intermediates (p. 305).

Rearrangement of alkenes takes place readily in the presence of acids:

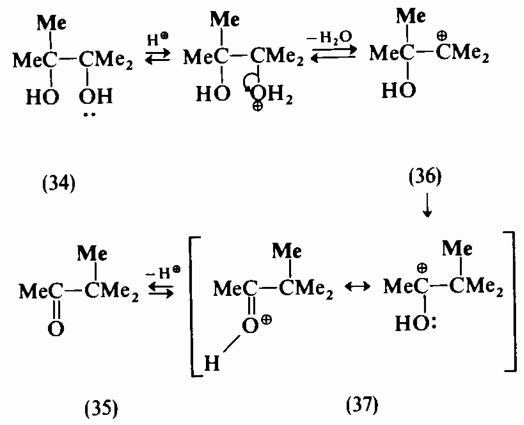


This relatively ready rearrangement can be a nuisance in the preparative addition of acids, e.g. hydrogen halides (p. 184) to alkenes, or in their acid-catalysed hydration (p. 187): mixed products that are difficult to separate may result or, in unfavourable cases, practically none of the desired product may be obtained. Further, addition of carbocations to initial, or product, alkenes may also take place (p. 188).

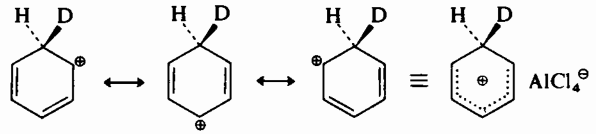
Rearrangement of di- and poly-alkylbenzenes also takes place readily in the presence of Lewis acid catalysts (p. 163), and in the dienone/phenol rearrangement (p. 115).

5.4.2.3 Pinacol/pinacolone rearrangements

Another example of migration of a group, in the original case Me, to a cationic carbon atom occurs in the acid-catalysed rearrangement of 1,2-diols, e.g. pinacol (*cf.* p. 218) $Me_2C(OH)C(OH)Me_2$ (34) to ketones, e.g. pinacolone, $MeCOCMe_3$ (35):



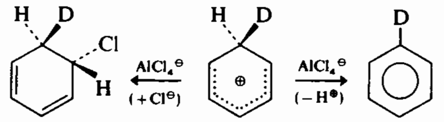
The fact that a 1,2-shift of Me takes place in (36), which is already a tertiary carbocation, results from the extra stabilisation conferred on the rearranged carbocation (37) by delocalisation of charge through an electron pair on the oxygen atom; (37) can also readily lose a proton to yield a stable end-product (35). It might be expected that an analogous reaction would occur with other compounds capable of forming the crucial carbocation (36): this is, in fact, found to be the case. Thus the corresponding 1,2-bromohydrin (38) and 1,2-amino-alcohol (39) are found to yield pinacolone (35) when right angles to that of the ring in the carbocation intermediate:



(2*a*) (2*b*) (2*c*) (2)

That the π and σ complexes with, e.g. methylbenzene and HCl, really are different from each other is confirmed by their differing behaviour. Thus formation of the former leads to a solution that is a non-conductor of electricity, to no colour change, and to but little difference in u.v. spectrum, indicating that there has been little disturbance of electron distribution in the original methylbenzene; while if $AlCl_3$ is present the solution becomes green, will conduct electricity and the u.v. spectrum of the original methylbenzene is modified, indicating the formation of a complex such as (2) as there is no evidence that aluminium chloride forms complexes of the type, $H^{\oplus}AlCl_4^{\ominus}$.

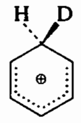
The reaction may be completed by $AlCl_4^{\ominus}$ removing a proton from the σ complex (2)⟶(4). This can lead only to exchange of hydrogen atoms when HCl is employed but to some substitution of hydrogen by deuterium with DCl, i.e. the overall process is electrophilic *substitution*. In theory, (2) could, as an alternative, react by removing $Cl^{\ominus}$ from $AlCl_4^{\ominus}$ resulting in an overall electrophilic *addition* reaction (2)⟶(3) as happens with a simple carbon–carbon double bond (p. 181); but this would result in permanent loss of the stabilisation conferred on the molecule by the presence of delocalised π orbitals involving all six carbon atoms of the nucleus, so that the product, an addition compound, would no longer be aromatic with all that implies. By expelling $H^{\oplus}$, i.e. by undergoing overall substitution rather than addition, the completely filled, delocalised π orbitals are reattained in the product (4) and characteristic aromatic stability recovered:



(3) Addition (2) (4) Substitution

The gain in stabilisation in going from (2)⟶(4) helps to provide the energy required to break the strong C—H bond that expulsion of $H^{\oplus}$ necessitates; in the reaction of, for example, HCl with alkenes (p. 184) there is no such factor promoting substitution and addition reactions are therefore the rule.

It might perhaps be expected that conversion of benzene into the σ complex (2), which has forfeited its aromatic stabilisation, would involve the expenditure of a considerable amount of energy, i.e. that the activation energy for the process would be high and the reaction rate correspondingly low: in fact, many aromatic electrophilic substitutions are found to proceed quite rapidly at room temperature. This is because there are two factors operating in (2) that serve to reduce the energy barrier that has to be surmounted in order to effect its formation: first, the energy liberated by the complete formation of the new bond to the attacking electrophile, and, second, the fact that the positively charged σ complex can stabilise itself, i.e. lower its energy level, by delocalisation



(2)

as has indeed been implied by writing its structure as (2). The use of (2) should not, however, be taken to imply a uniform distribution of electron density in the ion—that this could not be so is plain when the separate canonical structures (2*a*, 2*b* and 2*c*, p. 132) contributing to (2) are written out.

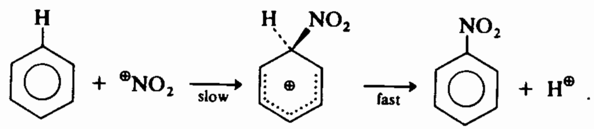
If we are correct in our assumption that the electrophilic substitution of aromatic species involves such σ complexes as intermediates—and it has proved possible actually to isolate them in the course of some such substitutions (p. 136)—then what we commonly refer to as aromatic 'substitution' really involves initial *addition* followed by subsequent *elimination*. How this basic theory is borne out in the common electrophilic substitution reactions of benzene will now be considered.

6.2 NITRATION

The aromatic substitution reaction that has received by far the closest study is nitration and, as a result, it is the one that probably provides the most detailed mechanistic picture. Preparative nitration is most frequently carried out with a mixture of concentrated nitric and sulphuric acids, the so-called nitrating mixture. The 'classical' explanation for the presence of the sulphuric acid is that it absorbs the water formed in the nitration proper

$$C_6H_6 + HNO_3 \rightarrow C_6H_5NO_2 + H_2O$$

isotope effect (*cf.* p. 46) if C_6H_6 is replaced by C_6D_6. The comparison was in fact (for experimental reasons) made on $C_6H_5NO_2$ and $C_6D_5NO_2$—this makes no difference to the argument—and it was found that k_H/k_D at 25° ≈ 1·00, i.e. that there is *no* primary kinetic isotope effect. The C—H bond is thus *not* being broken in the rate-limiting step of the reaction: pathways [1] and [2*b*] are therefore ruled out. This does not of course *prove* that nitration proceeds by pathway [2*a*]: slow, rate-limiting formation of the C—NO_2 bond, followed by fast, *non* rate-limiting breaking of the C—H bond;

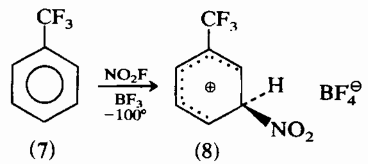


(6)

...... [2*a*]

but this is the only pathway, of those considered, that is compatible with our experimental data.

That the cleavage of the C—H bond—a strong one—should be fast seems less surprising when we realise that by loss of $H^{\oplus}$ the intermediate (6) is able to reattain the highly stabilised aromatic condition in the product nitrobenzene. The incipient proton is removed from (6) by the attack of bases, e.g. probably $HSO_4^{\ominus}$ in nitrating mixture, but sometimes by solvent molecules. The credibility of species such as (6) as intermediates is enhanced by the actual isolation of analogous species, e.g. (8) in the nitration of trifluoromethylbenzene (7) with NO_2F/BF_3:



(7) (8)

(8) is quite stable below −50°, but is converted into the normal nitration product of (7) on warming. The relative stability of (8) is due in part to the $BF_4^{\ominus}$ anion in the ion pair (*cf.* p. 102). The isolation of (8) does not, of course *prove* that similar intermediates are necessarily formed in nitration reactions with nitrating mixture but, coupled with the kinetic and other evidence, it does make the involvement of such species seem very much more plausible.

In discussing rates of aromatic substitution reactions it is, of course, the formation of the transition state (T.S.$_1$) immediately preceding (6) that exerts the controlling influence (Fig. 6.1):

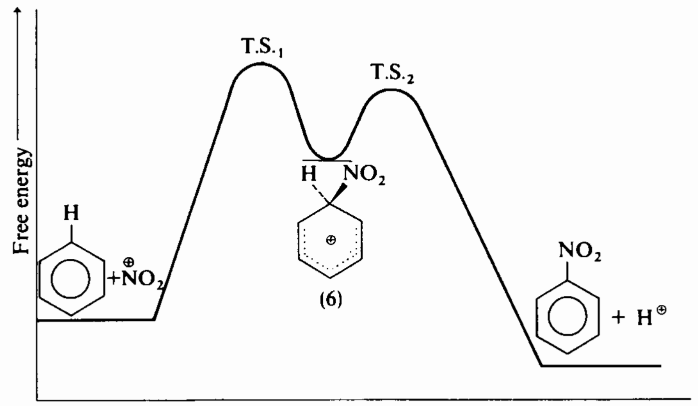
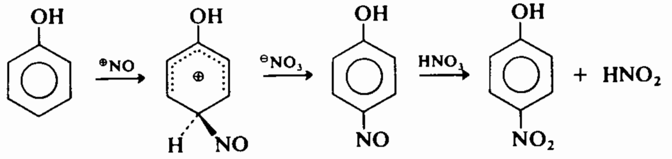


Fig. 6.1

It is often very difficult to obtain detailed information about such species, and the intermediates, of which the transition states are the immediate predecessors, are thus often taken as models for them, because detailed information about such intermediates is much more readily come by. This may be justified on the basis of *Hammond's principle* that in a sequence, immediately succeeding species that closely resemble each other in energy level are likely to resemble each other in structure also; certainly the intermediate (6) in the sequence above is likely to be a better model for T.S.$_1$, than is the starting material. We shall see a number of examples subsequently where σ complexes are used in this way as models for the transition states that precede them (*cf.* p. 151).

A further point of preparative significance still requires explanation, however. Highly reactive aromatic compounds, such as phenol, are found to undergo ready nitration even in dilute nitric acid, and at a far more rapid rate than can be explained on the basis of the concentration of $^{\oplus}NO_2$ that is present in the mixture. This has been shown to be due to the presence of nitrous acid in the system which nitrosates the reactive nucleus *via* the *nitrosonium ion*, $^{\oplus}NO$ (or other species capable of effecting nitrosation, *cf.* p. 120):

$$HNO_2 + 2HNO_3 \rightleftarrows H_3O^{\oplus} + 2NO_3^{\ominus} + {}^{\oplus}NO$$



(9) (10) (11)

The nitrosophenol (10), which may be isolated, is oxidised very rapidly by nitric acid to yield the *p*-nitrophenol (11) and nitrous acid; more nitrous acid is produced thereby and the process is progressively speeded up. No nitrous acid need be present initially in the nitric acid for a little of the latter attacks phenol oxidatively to yield HNO_2. The rate-determining step is again believed to be the formation of the intermediate (9). Some direct nitration of such reactive aromatic compounds by $^{\oplus}NO_2$ also takes place simultaneously, the relative amount by the two routes depending on the conditions.

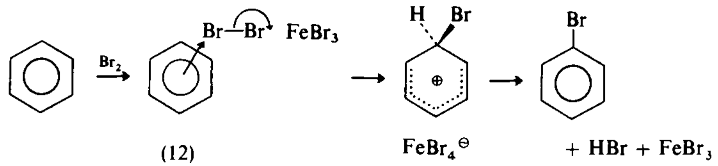
Many other aromatic electrophilic substitution reactions are found to follow the general pathway [2] discussed above, usually corresponding to [2*a*] though a number of [2*b*] examples are known. The major point still requiring elucidation is very often the exact nature of the electrophilic species that is involved in attack on the aromatic nucleus.

6.3 HALOGENATION

In contrast to nitration, halogenation can involve a variety of different electrophiles in attack on the aromatic system. The free halogens, e.g. Cl_2 and Br_2, will readily attack an activated nucleus (*cf.* p. 150) such as phenol, but are unable to substitute benzene itself (photochemical activation can lead to *addition*, however, through the agency of free halogen atoms, p. 316): a Lewis acid catalyst such as $AlCl_3$ is required to assist in polarising the attacking halogen molecule, thereby providing it with an 'electrophilic end'; the energy required to form $Cl^{\oplus}$ is prohibitive. The rate equation found is often of the form:

$$\text{Rate} = k[\text{Ar—H}][\text{Hal}_2][\text{Lewis acid}]$$

It seems likely that benzene forms a π complex (12) with, for example, Br_2 (*cf.* p. 131), and that the Lewis acid then interacts with this. The catalyst probably polarises Br—Br, assists in the formation of a σ bond between the bromine molecule's now electrophilic end and a ring carbon atom, and finally helps to remove the incipient bromide ion so as to form a σ complex (13):

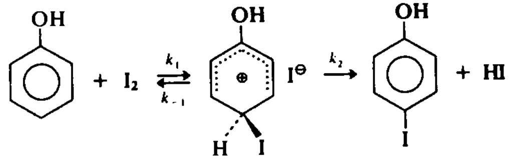


(12)

(13)

The anion $FeBr_4^{\ominus}$ assists in the removal of a proton from the σ complex (13). The classical halogen 'carrier' iron filings does, of course, act only after it has been converted into the Lewis acid, FeX_3.

Kinetic isotope effects have not been observed for chlorination, and only rarely for bromination, i.e. the reactions normally follow pathway [2*a*] like nitration. In iodination, which only takes place with iodine itself on activated species, kinetic isotope effects are the rule. This presumably arises because the reaction is readily reversible (unlike other halogenations), loss of I occurring more often from the σ complex (14) than loss of H, i.e. $k_{-1} \gtrsim k_2$:



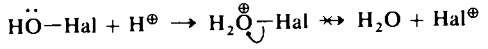
(14)

Thus k_H/k_D for the iodination of phenol and 2,4,6-trideuteriophenol is found to be ≈ 4, i.e. pathway [2*b*]. Iodination is often assisted by the presence of bases or of oxidising agents, which remove HI and thus displace the above equilibrium to the right. Oxidising agents also tend to produce $I^{\oplus}$, or a complex containing positively polarised iodine, from I_2, thus providing a more effective electrophile. Halogenation may also be carried out by use of interhalogen compounds $\overset{\delta+}{\text{Br}}—\overset{\delta-}{\text{Cl}}$, $\overset{\delta+}{\text{I}}—\overset{\delta-}{\text{Cl}}$, etc., attack occurring through the less electronegative halogen as this will constitute the 'electrophilic' end of the molecule. The two species above are thus found to effect bromination and iodination, respectively.

Halogenation may be effected by hypohalous acids, $\overset{\delta-}{\text{HO}}—\overset{\delta+}{\text{Hal}}$, also. This is markedly slower than with molecular halogens as $HO^{\ominus}$ is a poorer leaving group from $\overset{\delta-}{\text{HO}}—\overset{\delta+}{\text{Hal}}$ than $Hal^{\ominus}$ is from $\overset{\delta+}{\text{Hal}}—\overset{\delta-}{\text{Hal}}$. The reaction is speeded in the presence of $Hal^{\ominus}$, however, as HO—Hal is then converted into the more reactive Hal_2, e.g.:

$$^{\ominus}OCl + Cl^{\ominus} + 2H^{\oplus} \rightarrow Cl_2 + H_2O$$

In the presence of strong acid, however, HO—Hal becomes a very powerful halogenating agent due to the formation of a highly polarised complex (15):



$$\text{H}\ddot{\text{O}}\text{—Hal} + \text{H}^{\oplus} \rightarrow \text{H}_2\overset{\oplus}{\text{O}}\text{—Hal} \nrightarrow \text{H}_2\text{O} + \text{Hal}^{\oplus}$$

(15)

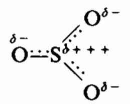
The evidence is that this species is the effective electrophile under these conditions, and does not support the further conversion of (15) into $Hal^{\oplus}$, i.e. unlike the case with $H_2O^{\oplus}—NO_2$ (p. 134); HOCl + acid can still be a more effective chlorinating agent than $Cl_2 + AlCl_3$, however. F_2 reacts vigorously with benzene, but C—C bond-breaking occurs and the reaction is of no preparative significance (*cf.* p. 170).

6.4 SULPHONATION

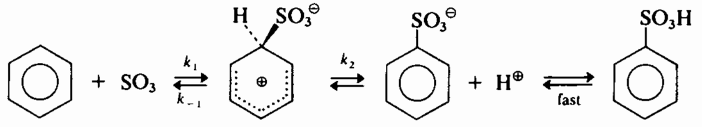
The mechanistic details of sulphonation have been less closely explored than those of nitration or halogenation. Benzene itself is sulphonated fairly slowly by hot concentrated sulphuric acid, but rapidly by oleum (the rate then being related to its SO_3 content) or by SO_3 in inert solvents. The nature of the actual electrophile depends on the conditions, but is probably always SO_3: either free or linked to a 'carrier', e.g. $H_2SO_4{\cdot}SO_3$ ($H_2S_2O_7$) in sulphuric acid. A small concentration of SO_3 is developed in H_2SO_4 itself through the equilibrium:

$$2H_2SO_4 \rightleftarrows SO_3 + H_3O^{\oplus} + HSO_4^{\ominus}$$

Attack takes place through S as this is highly positively polarised, i.e. electron-deficient:



Sulphonation, like iodination, is reversible and is believed to take place in concentrated sulphuric acid *via* the pathway:



(16) (17)

In oleum, the σ complex (16) is believed to undergo protonation of the $SO_3^{\ominus}$ *before* undergoing C—H fission to yield the SO_3H analogue of (17). Like iodination, sulphonation exhibits a kinetic isotope effect, indicating that C—H bond-breaking is involved in the rate-limiting step of the reaction, i.e. that $k_{-1} \gtrsim k_2$.

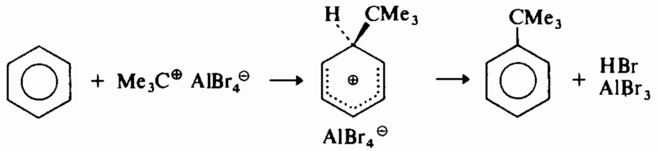
Practical use is made of the reversibility of the reaction in order to replace SO_3H by H on treating sulphonic acids with steam. It may thus be possible to introduce an SO_3H group for its directive influence (*cf.* p. 150), and then eliminate it subsequently. The sulphonation of naphthalene presents some interesting features (p. 164).

6.5 FRIEDEL–CRAFTS REACTIONS

This can be conveniently divided into alkylation and acylation.

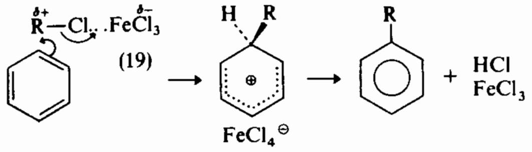
6.5.1 Alkylation

The carbon atom of alkyl halides, $\overset{\delta+}{R}-\overset{\delta-}{Hal}$, is electrophilic, but rarely is it sufficiently so to effect the substitution of aromatic species: the presence of a Lewis acid catalyst, e.g. $AlHal_3$ is also required. That alkyl halides do react with Lewis acids has been demonstrated by the exchange of radioactive bromine into EtBr from $AlBr_3^{*}$ on mixing and re-isolation; also the actual isolation of solid 1:1 complexes, e.g. $CH_3Br{\cdot}AlBr_3$, at low temperatures (−78°). These complexes, though polar, are only faintly conducting. Where R is capable of forming a particularly stable carbocation, e.g. with $Me_3C{-}Br$, it is probable that the attacking electrophile in alkylation is then the actual carbocation, $Me_3C^{\oplus}$, as part of an ion pair:



(18)

In other cases it seems more likely that the attacking electrophile is a polarised complex (19), the degree of polarisation in a particular case depending on R in R—Hal and the Lewis acid employed:



(19)

(20)

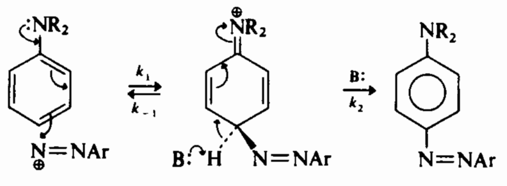
Either pathway is, of course, compatible with the commonly observed rate law:

$$\text{Rate} = k[\text{ArH}][\text{RX}][\text{MX}_3]$$

The order of effectiveness of Lewis acid catalysts has been shown to be:

$$AlCl_3 > FeCl_3 > BF_3 > TiCl_3 > ZnCl_2 > SnCl_4$$

The validity of Wheland intermediates such as (18) and (20) in Friedel–Crafts alkylation has been established by the actual isolation obtained:



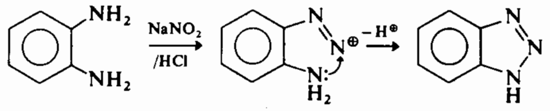
(35) (34)

The reaction is usually found to follow the general rate law:

$$\text{Rate} = k[\text{ArN}_2{}^{\oplus}][\text{PhNR}_2]$$

In some cases the coupling reaction is found to be base-catalysed, and this is found to be accompanied by a kinetic isotope effect, i.e. $k_{-1} \gtrsim k_2$, and the breaking of the C—H bond in (35) is now involved in the rate-limiting step of the reaction.

An interesting example of an internal coupling reaction is provided by the diazotisation of *o*-diaminobenzene (36):

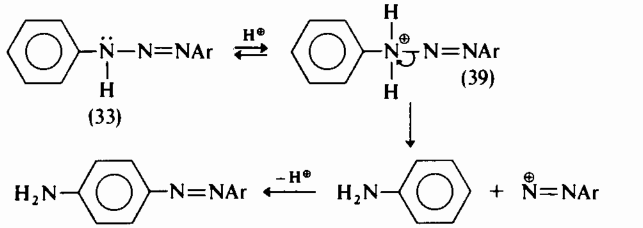


(36) (37)

Benzotriazole (37) may be obtained preparatively (75% yield) in this way.

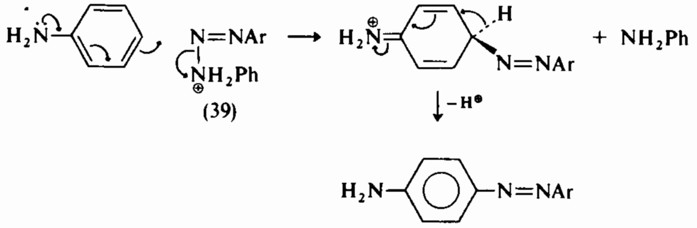
The difference in position of attack on primary and secondary aromatic amines, compared with phenols, probably reflects the relative electron-density of the various positions in the former compounds exerting the controlling influence for, in contrast to a number of other aromatic electrophilic substitution reactions, diazo coupling is sensitive to relatively small differences in electron density (reflecting the rather low ability as an electrophile of $\text{PhN}_2{}^{\oplus}$). Similar differences in electron-density do of course occur in phenols but here control over the position of attack is exerted more by the relative strengths of the bonds formed in the two products: in the two alternative coupled products derivable from amines, this latter difference is much less marked.

The formation of diazoamino compounds, on coupling $\text{ArN}_2{}^{\oplus}$ with primary amines, does not constitute a total preparative bar to obtaining products coupled on the benzene nucleus for diazoamino compounds (33) may be rearranged to the corresponding *amino-azo* compounds (38) by warming in acid:



(33) (39) (38)

The rearrangement has been shown under these conditions to be an *inter*molecular process, i.e. the diazonium cation becomes free, for the latter may be transferred to phenols, aromatic amines or other suitable species added to the solution. It is indeed found that the rearrangement proceeds most readily with an acid catalyst *plus* an excess of the amine that initially underwent coupling to yield the diazoamino compound (33). It may then be that this amine attacks the protonated diazoamino compound (39) directly with expulsion of PhNH_2 and loss of a proton:



(39) (38)

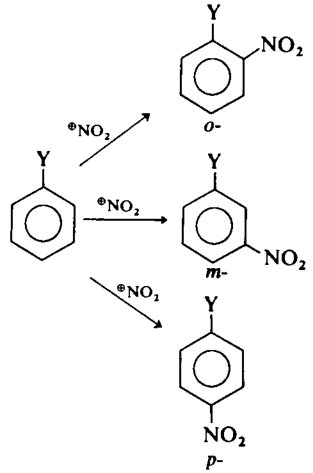
In conclusion, it should be mentioned that though the great majority of aromatic electrophilic substitution reactions involve displacement of hydrogen, other atoms or groups can be involved. Thus we have already seen the displacement of SO_3H in the reversal of sulphonation (p. 140), of alkyl in dealkylation (p. 143), and a further, less common, displacement is that of SiR_3 in *protodesilylation* (*cf.* also p. 161):

$$\text{ArSiR}_3 + \text{H}^{\oplus} \longrightarrow \text{Ar—H} + {}^{\oplus}\text{SiR}_3$$

Displacements such as this show all the usual characteristics of electrophilic aromatic substitution (substituent effects, etc., see below), but they are normally of much less preparative significance than the examples we have already considered. In face of all the foregoing discussion of polar intermediates it is pertinent to point out that homolytic aromatic substitution reactions, i.e. by radicals, are also known (p. 331); as too is attack by nucleophiles (p. 167).

6.7 ELECTROPHILIC ATTACK ON C_6H_5Y

When a mono-substituted benzene derivative, C_6H_5Y, undergoes further electrophilic substitution, e.g. nitration, the incoming substituent may be incorporated at the *o*-, *m*- or *p*-position, and the overall rate at which substitution takes place may be faster or slower than with benzene itself. What is found in practice is that substitution



occurs so as to yield either predominantly the *m*-isomer, or predominantly a mixture of *o*- and *p*-isomers; in the former case the overall rate of attack is always slower than on benzene itself, in the latter case the overall rate of attack is usually faster than on benzene itself. The major controlling influence is found to be exerted by Y, the substituent already present, and this can be explained in detail on the basis of the electronic effects that Y can exert. It can, of course, also exert a steric effect, but the operation of this factor is confined essentially to attack at the *o*-position; this influence will be discussed separately below (p. 159).

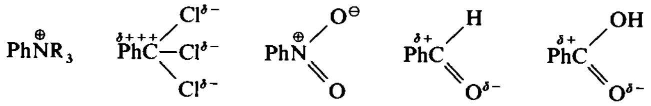
Substituents, Y, are thus classed as being *m*-, or *o*-/*p-directing*; if they induce faster overall attack than on benzene itself they are said to be *activating*, if slower, then *deactivating*. It should be emphasised that these directing effects are relative rather than absolute: some of all three isomers are nearly always formed in a substitution reaction, though the proportion of *m*-product with an *o*-/*p*-directing Y or of *o*-/*p*-products with a *m*-directing Y may well be very small. Thus nitration of nitrobenzene (Y = NO_2) is found to result in a mixture of 93% *m*-, 6% *o*- and 1% *p*-isomers, i.e. NO_2 is classed as a *m*-directing (deactivating) substituent. By contrast nitration of methoxybenzene (anisole, Y = OMe) yields 56% *p*-, 43% *o*- and 1% *m*-isomers, i.e. OMe is an *o*-/*p*-directing (activating) substituent.

6.7.1 Electronic effects of Y

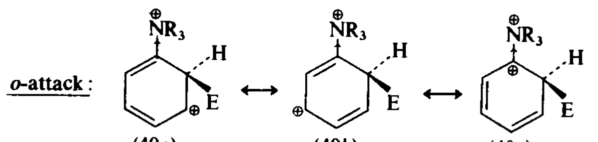
What we shall be doing in the discussion that follows is comparing the effect that a particular Y would be expected to have on the rate of attack on positions *o*-/*p*- and *m*-, respectively, to the substituent Y. This assumes that the proportions of isomers formed are determined entirely by their relative rates of formation, i.e. that the control is wholly *kinetic* (*cf*. p. 163). Strictly we should seek to compare the effect of Y on the different transition states for *o*-, *m*- and *p*-attack, but this is not usually possible. Instead we shall use Wheland intermediates as models for the transition states that immediately precede them in the rate-limiting step, just as we have done already in discussing the individual electrophilic substitution reactions (*cf*. p. 136). It will be convenient to discuss several different types of Y in turn.

6.7.1.1 Y = $^{\oplus}NR_3$, CCl_3, NO_2, CHO, CO_2H, etc.

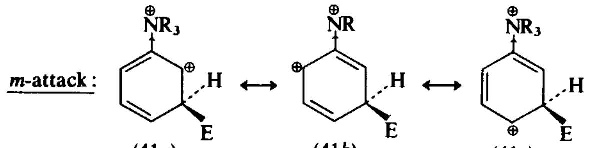
These groups, and other such as SO_3H, CN, COR, etc., all have in common a positively charged, or positively polarised, atom adjacent to a carbon atom of the benzene ring:



They are thus all electron-withdrawing with respect to the benzene ring, i.e. aromatic species containing them all have a dipole with the positive end located on the benzene nucleus. Taking Y = $^{\oplus}NR_3$ as exemplar of the rest, we can write the σ complexes for attack by an electrophile, $E^{\oplus}$ (e.g. $^{\oplus}NO_2$), *o*-, *m*- and *p*- to the original $^{\oplus}NR_3$ substituent:

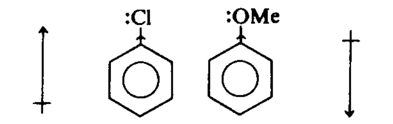


(40*a*) (40*b*) (40*c*)



(41*a*) (41*b*) (41*c*)

i.e. the halogens are *o-/p*-directing. The electron-withdrawing inductive effects of the halogens are such that attack is *slower* than on benzene itself, i.e. they are *deactivating* substituents ($k_{C_6H_5Cl}/k_{C_6H_6} = 3 \times 10^{-2}$ for nitration). This net electron-withdrawal by the halogens is reflected in the *ground state* by a dipole in chlorobenzene (53) with its +ve end on the nucleus, compared with anisole (54) in which the dipole is in the opposite direction:



$\mu = 1{\cdot}6$ D (53) (54) $\mu = 1{\cdot}2$ D

The overall effect exerted by a substituent is, of course, made up from inductive/field and mesomeric contributions. With OMe (p. 154), the balance is such that the selective stabilisation of the positively charged intermediates for *o*- and *p*-attack (48 and 49, respectively) is much greater than stabilisation of the corresponding intermediate [(2), p. 132] for attack on benzene itself: *o*/*p*-attack on C_6H_5OMe is thus much faster than attack on C_6H_6. With a halogen substituent, e.g. Cl, however, the balance—because of a powerful electron-withdrawing inductive/field effect—is such that the selective stabilisation of the intermediates for *o*- and *p*-attack (51 and 52, respectively) is slightly *less* than stabilisation of the corresponding intermediate for attack on benzene itself: *o*-/*p*-attack on C_6H_5Cl is thus slightly slower than attack on C_6H_6.

A very similar situation is encountered in the electrophilic *addition* of unsymmetrical adducts (e.g. HBr) to vinyl halides (e.g. $CH_2{=}CHBr$), where the inductive effect of halogen controls the *rate*, but relative mesomeric stabilisation of the carbocationic intermediate controls the *orientation*, of addition (p. 185).

6.7.2 Partial rate factors and selectivity

More refined kinetic methods, and the ability to determine very precisely the relative proportions of *o*-, *m*- and *p*-isomers formed—by, for example, spectroscopic methods rather than by isolation as in the past—now allow of a much more quantitative approach to aromatic substitution. One very useful concept here is that of *partial rate factors*: the rate at which one position, e.g. the *p*-, in C_6H_5Y is attacked compared with the rate of attack on one position in benzene; it is written as $f_{p\text{-}}$.

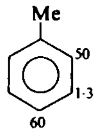
Partial rate factors may be obtained by separate kinetic measurements of the overall rate constants $k_{C_6H_5Y}$ and $k_{C_6H_6}$ under analogous conditions (or by a *competition experiment* in which equimolar quantities of C_6H_5Y and C_6H_6 compete for an inadequate supply of an electrophile, thus giving the ratio $k_{C_6H_5Y}/k_{C_6H_6}$), and analysis of the relative amounts of *o*-, *m*-, and *p*-products obtained from C_6H_5Y—the *isomer distribution* (generally quoted as percentages of the total substitution product obtained). Then, remembering that there are **6** positions available for attack in C_6H_6 compared with **2***o*- **2***m*- and **1***p*-positions in C_6H_5Y, we have:

$$f_{o\text{-}} = \frac{k_{o\text{-}}}{k_H} = \frac{k_{C_6H_5Y/2}}{k_{C_6H_6/6}} \times \frac{\%\,o\text{-isomer}}{100} \qquad (\text{2 } o\text{-positions } v.\ \text{6 H positions})$$

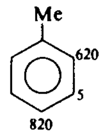
$$f_{m\text{-}} = \frac{k_{m\text{-}}}{k_H} = \frac{k_{C_6H_5Y/2}}{k_{C_6H_6/6}} \times \frac{\%\,m\text{-isomer}}{100} \qquad (\text{2 } m\text{-positions } v.\ \text{6 H positions})$$

$$f_{p\text{-}} = \frac{k_{p\text{-}}}{k_H} = \frac{k_{C_6H_5Y/1}}{k_{C_6H_6/6}} \times \frac{\%\,p\text{-isomer}}{100} \qquad (\text{1 } p\text{-position } v.\ \text{6 H positions})$$

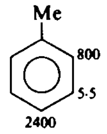
Thus for the nitration of toluene by nitric acid in acetic anhydride at 0° $k_{C_6H_5Me}/k_{C_6H_6}$ was found to be 27, and the isomer distribution (%): *o*-, 61·5; *m*-, 1·5; *p*-, 37·0; the partial rate factors for nitration, under these conditions, are thus:



Nitration



Chlorination



Bromination

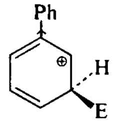
Comparison of the partial rate factors for nitration of toluene with those for chlorination and bromination (above) show that these differ, both absolutely and relatively, with the attacking electrophile: in other words relative directive effects in C_6H_5Y *do* depend on $E^{\oplus}$ as well as on Y. We notice above that the absolute values of the partial rate factors, i.e. k_Y/k_H, increase in the order,

Nitration < Chlorination < Bromination

i.e. as the reactivity of the attacking electrophile decreases. This apparent paradox is seen on reflection to be reasonable enough: if $E^{\oplus}$ was reactive enough every collision would lead to substitution, the attacking reagent would thus be quite undiscriminating, and each partial rate factor would be unity. As the reactivity of $E^{\oplus}$ decreases, however, every collision will no longer lead to reaction, which will increasingly depend on the relative ability of *o*-, *m*- and *p*-positions in C_6H_5Y, and positions in C_6H_6, to supply an electron pair to bond with $E^{\oplus}$. The reagent will thus become increasingly more discriminating—

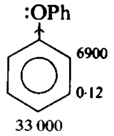
its *selectivity* will rise—the absolute values of the partial rate factors will increase, as will the relative difference between these values: exactly what is seen in the figures quoted above. This relative selectivity is best considered by comparing $f_{p\text{-}}$ and $f_{m\text{-}}$, only, as $f_{o\text{-}}$, will be influenced by steric effects (size of Y, and relative size of attacking reagent, *cf.* p. 159) in addition to the electronic effects that influence all three.

The use of partial rate factors allows of a more precise investigation of directive effects than has been possible to date. Thus all the partial rate factors for toluene above are >1, indicating that the CH_3 group (p. 153) activates all positions in the nucleus compared with benzene. The same is true for Y = CMe_3 but here $f_{m\text{-}}$ for nitration is 3·0, compared with 1·3 for toluene, indicating that CMe_3 exerts a larger electron-donating inductive (polar) effect than does CH_3. By contrast, when Y = C_6H_5 in biphenyl (p. 153), $f_{m\text{-}}$ for chlorination is found to be 0·7, i.e. attack on this position is slower than on benzene (although $k_{C_6H_5Y}/k_{C_6H_6} = 4{\cdot}2 \times 10^2$), because the sp^2 carbon atom by which the C_6H_5 substituent is attached to the benzene ring exerts an electron-withdrawing inductive (polar) effect (55):



(55)

A similar effect is also seen with *o-/p*-directing, activating substituents when a reaction can be investigated that produces enough *m*-product to measure, e.g. deuteration (deuterium exchange) with the strong acid, CF_3CO_2D, on C_6H_5OPh(56):



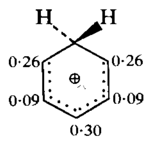
(56)

The enormous $f_{o\text{-}}$ and $f_{p\text{-}}$ values reflect the ability of the electron pair on O to stabilise, selectively, the transition states for *o*- and *p*-attack (*cf.* p. 154), while the $f_{m\text{-}}$ value of <1 reflects the destabilisation (compared with attack on benzene) of the transition state for *m*-attack by the electron-withdrawing inductive (polar) effect of the oxygen atom.

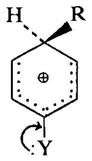
Partial rate factors, and hence the isomer distribution in a particular substitution reaction, are also affected by temperature. Increasing temperature has the greatest relative effect on the substitution reaction of highest $\Delta G^{\neq}$ (out of the three possible, alternative attacks on C_6H_5Y), i.e. on the slowest. The effect of a rise in temperature is thus, like the effect of an increase in the reactivity of $E^{\oplus}$, to 'iron out' differences between partial rate factors, and to make the isomer distribution in the product move a little more towards the statistical.

6.7.3 *o*-/*p*-Ratios

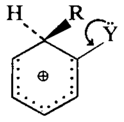
After what we have seen to date, it surely comes as no great surprise to find that the ratio of *o*- to *p*-product obtained from substitution of C_6H_5Y, where Y is *o-/p*-directing, is seldom, if ever, the statistical ratio of 2:1. There is found to be very close agreement between calculation and n.m.r. data for the distribution of +ve charge—*p*- > *o*- ≫ *m*-—around the ring in the cyclohexadienyl cation (57), which is the Wheland intermediate for proton exchange in benzene (*cf.* p. 133):



(57)



(57*a*)



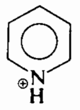
(57*b*)

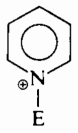
On this basis an electron-donating substituent, Y, should be somewhat better at promoting attack by $H^{\oplus}$ *p*-(57*a*, R = H), rather than *o*-(57*b*, R = H), to Y because of the slightly more effective delocalisation of +ve charge that thereby results. The figures quoted in (57) would point to an expected value for the log partial rate ratio, $\log f_{o\text{-}}/\log f_{p\text{-}}$, of $\approx 0{\cdot}87$, and values very close to this have indeed been observed for protonation of a number of different C_6H_5Y species.

The steric demand of $H^{\oplus}$ is, however, extremely small, and when attack on C_6H_5Y is by any other electrophile, $E^{\oplus}$, which will necessarily be larger, there will be increasing interaction between E and Y in the transition state for attack at the position *o*- to Y (57*b*, R = E) as attacking electrophile and substituent increase in *size*; there can be no such interaction in the transition state for *p*-attack (57*a*, R = E). This will be reflected in an increasing $\Delta G^{\neq}$ for *o*-attack, a consequently slower reaction, and the relative proportion of *o*-product will thus fall as the size of E and/or Y increase. This is illustrated by the falling $f_{o\text{-}}/f_{p\text{-}}$ ratios which are observed for the nitration of alkylbenzenes (Y = $CH_3 \rightarrow CMe_3$) under comparable conditions;

	Y	% *o*-	% *p*-	$f_{o\text{-}}/f_{p\text{-}}$
Increase in size of Y ↓	CH_3	58	37	0·78
	CH_2Me	45	49	0·46
	$CHMe_2$	30	62	0·24
	CMe_3	16	73	0·11

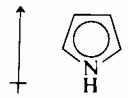
There are certain formal analogies here to *m*- attack on nitrobenzene (*cf.* p. 152), but pyridine is *very* much more difficult to substitute than the former. Thus nitration, chlorination, bromination and Friedel–Crafts reactions cannot really be made to take place usefully, and sulphonation only occurs on heating with oleum for 24 hours at 230°, with an $Hg^{2\oplus}$ catalyst. This difficulty of attack is due partly to the fact that pyridine has an available electron pair on nitrogen, and can thus protonate (66), or interact with an electrophile (67):


(66)

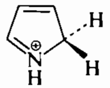

(67)

The positive charge will clearly further destabilise any of the σ complexes for electrophilic substitution, as did a substituent such as $^{\oplus}NR_3$ on the benzene nucleus (p. 152), but the destabilisation will be much more marked than with $^{\oplus}NR_3$ as the ⊕ charge is now on an atom of the ring itself and not merely on a substituent.

Pyrrole (68) also has 6π electrons in delocalised π orbitals, but here the nitrogen atom has to contribute two electrons to make up the six (thus becoming essentially non-basic in the process, *cf.* p. 73), and the dipole of pyrrole is found to be in the opposite direction to that of pyridine, i.e. with the positive end on nitrogen and the negative end on the nucleus:

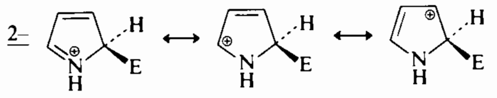

μ = 1·8 D (68)

Pyrrole is thus referred to as a *π-excessive* heterocycle and behaves rather like a reactive benzene derivative, e.g. aniline (p. 153), undergoing very ready electrophilic attack. This may be complicated by the fact that in strongly acid solution protonation (69) is forced even on the weakly basic pyrrole (it takes place on the 2-carbon atom rather than on N, *cf.* p. 73):

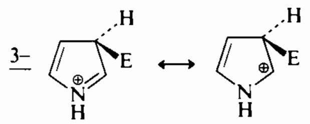

(69)

Aromatic character is thus lost, and the cation behaves like a conjugated diene in undergoing very ready polymerisation.

Electrophilic substitution of pyrrole can, however, be carried out under specialised conditions (e.g. acylation with $(MeCO)_2O/BF_3$, sulphonation with a pyridine/SO_3 complex, $C_5H_5N{\cdot}SO_3$, *cf.* (67)) leading to preferential attack at the 2-, rather than the 3-, position. This reflects the slightly greater stabilisation of the Wheland intermediate for the former (70) compared with that for the latter (71):



(70*a*) (70*b*) (70*c*)



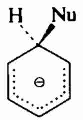
(71*a*) (71*b*)

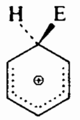
The difference in stability between the two is not very marked, however, reflecting the highly activated state of the nucleus, and ready substitution will take place at the 3-position if the 2- is blocked. It is, indeed, not uncommon to get substitution on all four carbon atoms, e.g. on bromination with bromine in ethanoic acid.

6.10 NUCLEOPHILIC ATTACK ON AROMATIC SPECIES

6.10.1 Substitution of hydrogen

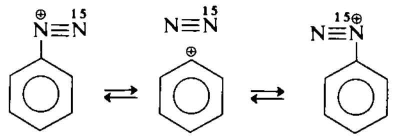
It is to be expected that attack by nucleophiles on an unsubstituted benzene nucleus will be much more difficult than attack by electrophiles. This is so (*a*) because the π electron cloud of the nucleus (p. 130) is likely to repel an approaching nucleophile, and (*b*) because its π orbital system is much less capable of delocalising (and so stabilising) the two extra electrons in the negatively charged (72), than the positively charged Wheland intermediate (73):


(72)


(73)

Both (*a*) and (*b*) would be overcome to some extent if a sufficiently powerful electron-withdrawing substituent was present, and nucleophilic attack might then become possible (*cf.* the *addition* of nucleophiles to alkenes carrying electron-withdrawing substituents, p. 198).

(79):



(79*a*) (79*b*)

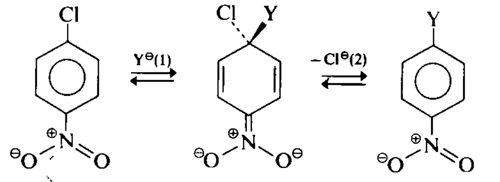
A particularly useful displacement reaction on $ArN_2^{\oplus}$ is the introduction of F into the benzene nucleus (not possible by direct reaction with F_2, *cf.* p. 140):

$$ArN_2^{\oplus}BF_4^{\ominus} \xrightarrow{\Delta} Ar{-}F + N_2\uparrow + BF_3\uparrow$$

The fluoroborates are unusual among diazonium salts in being relatively stable. They may be isolated, and then heated in the dry state to yield pure ArF; the other products being lost as gases.

A number of the reactions of diazonium salts, particularly in less polar solvents, may proceed *via* the initial generation of an aryl radical, however (*cf.* p. 334).

Probably the most common aromatic nucleophilic displacement reactions involve the displacement of $Hal^{\ominus}$ from a halide activated by electron-withdrawing groups, e.g. (80):



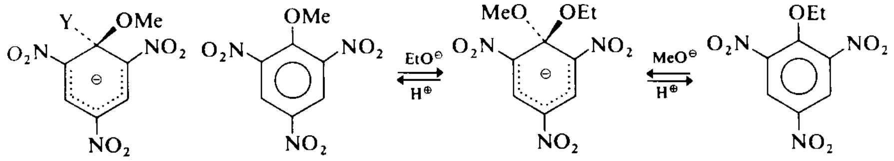
(80) (81)

These reactions are generally found to follow the rate law.

$$\text{Rate} = k[\text{ArX}][\text{Y}^{\ominus}]$$

so that there is some formal resemblance to S_N2. The above pathway must, however, differ in that attack by $Y^{\ominus}$ cannot take place from the back of the carbon atom carrying the leaving group (*cf.* S_N2, p. 78), but must occur from the side; it is thus often referred to as S_N2(*aromatic*). Further, on the basis of the above rate law the reaction could be concerted (like S_N2)—in which case (81) is a transition state—or it could proceed by a stepwise pathway with either step (1) or step (2) as the slow, rate-limiting one—in which case (81) is an intermediate.

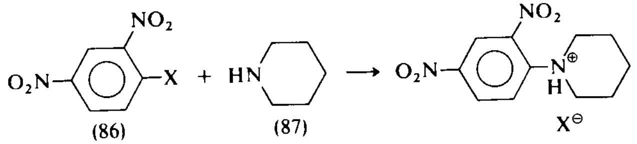
In support of the latter interpretation it has proved possible to isolate, and to characterise by n.m.r. spectroscopy and by X-ray diffraction, a number of species closely analogous to (81), e.g. (82);



(Y = H, MeO)
(82) (84) (83) (85)

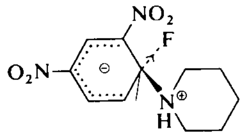
and including the so-called Meisenheimer complex (83), a red crystalline solid obtainable by the action of $EtO^{\ominus}$ on the methyl ether (84) or of $MeO^{\ominus}$ on the ethyl ether (85). Acidification of the reaction mixture from *either* substrate results in the formation of exactly the same equilibrium mixture of (84) + (85). This does not, of course, prove that the normal displacement reactions of, for example, aromatic halides proceed *via* intermediates but it does make is seem more likely.

Direct support for a stepwise pathway is, however, provided by comparison of the rates of reaction of a series of substrates, having different leaving groups, with the same nucleophile, e.g. 2,4-dinitrohalogenobenzenes (86) with piperidine (87):



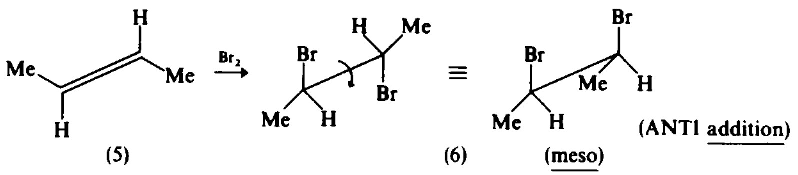
(86) (87)

The relative rates for X = Cl, Br and I were found to be 4·3, 4·3 and 1·0, respectively; breaking of the C—X bond thus cannot be involved in the rate-limiting step of the reaction, or we should expect significantly bigger rate differences and in the sequence I > Br > Cl. The reaction, in this case, cannot therefore be one-step, i.e. concerted (*cf.* S_N2), and in the two-step pathway suggested above, step (1)—attack by the nucleophile—would have to be rate-limiting. It is interesting too, to observe that the rate of the above reaction when X = F is 3300. This results from the very powerfully electron-withdrawing F speeding up step (1): (*a*) by making the nuclear carbon to which it is attached more positive and hence more readily attacked by a nucleophile, and (*b*) by helping to stabilise the anionic intermediate (88):



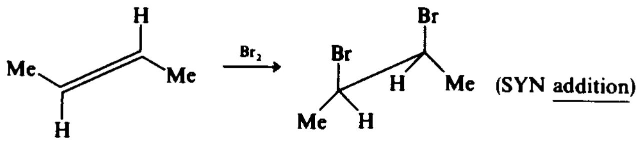
(88)

on from opposite sides of the planar alkene, i.e. ANTI addition:



(5) (6) (meso)

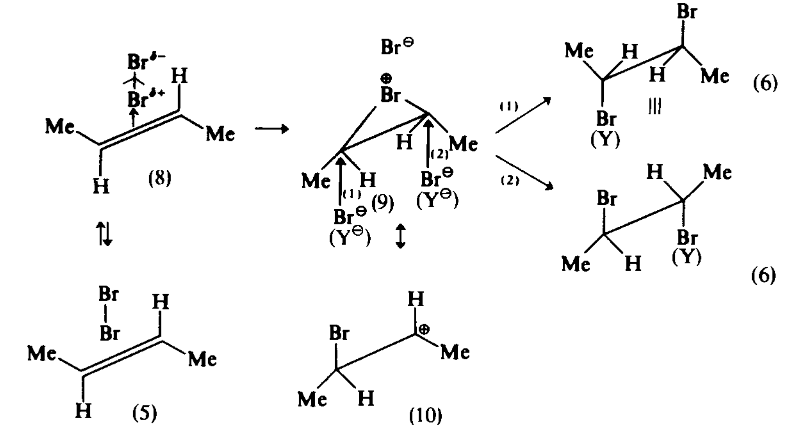
The product is the symmetrical *meso* dibromide (6), whereas if addition had been SYN (both bromine atoms adding from the same side) it would have been the unsymmetrical (±) dibromide (7):



(5) (7) (±)

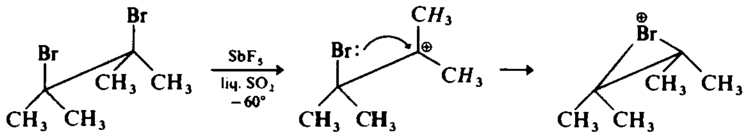
It is found in practice with (5), and with other simple acyclic alkenes, that the addition is almost completely *stereoselective*, i.e. ≈100% ANTI addition. This result also is incompatible with a one-step pathway, as the atoms in a bromine molecule are too close to each other to be able to add, simultaneously, ANTI.

These observations are explainable by a pathway in which one end of a bromine molecule becomes positively polarised through electron repulsion by the π electrons of the alkene, thereby forming a π complex with it (8; *cf.* Br$_2$ + benzene, p. 131). This then breaks down to form a *cyclic bromonium ion* (9)—an alternative canonical form of the carbocation (10). Addition is completed through nucleophilic attack by the residual Br$^\ominus$ (or added Y$^\ominus$) on either of the original double bond carbon atoms, from the side opposite to the large bromonium ion Br$^\oplus$, to yield the *meso* dibromide (6):



Enough mutual polarisation can apparently result, in (8), for (9) to form, but polarisation of the bromine molecule may be greatly increased by the addition of Lewis acids, e.g. AlBr$_3$ (*cf.* bromination of benzene, p. 138), with consequent rise in the rate of reaction. Formation of (9) usually appears to be the rate-limiting step of the reaction.

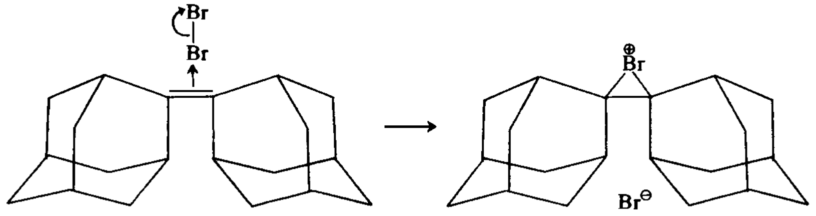
The suggestion of cyclic bromonium ions as intermediates, to account for the highly stereoselective (ANTI) addition often observed with simple acyclic alkenes, was made as long ago as 1938. Evidence supporting the existence of such intermediates has come from a number of different fields: thus it has proved possible to detect one by physical methods using the 'super' acids of Olah (p. 102) and n.m.r. spectroscopy. Thus reaction of the 1,2-dibromide (11) with SbF$_5$ in liquid SO$_2$ at −60° led to the formation of an ion pair, but this exhibited not the two signal (one from each of two different groups of six equivalent protons) n.m.r. spectrum expected of (12). Instead one signal only (δ2·9) was observed, indicating that all twelve protons were equivalent, i.e. what is being observed is almost certainly the bromonium ion (9*a*):



(11) δ 2·0 (12) (9*a*) δ 2·9

This neighbouring group participation by bromine (*cf.* p. 93) does not of course prove that addition to alkenes proceeds *via* cyclic bromonium ions, but it does mean that such species are no longer merely *ad hoc* assumptions, and to that extent are correspondingly more plausible as intermediates.

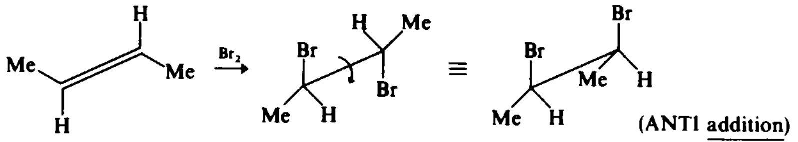
In attempting to add Br$_2$ to the highly unusual alkene (13), it has proved possible actually to isolate the cyclic bromonium ion (14):



(13) (14)

This is possible only because further attack by Br$^\ominus$, on the first-formed intermediate (14), is prevented completely by the extremely bulky, cage-like structures at each end of the original double bond: completion of normal, overall addition of Br$_2$ thus cannot occur.

on from opposite sides of the planar alkene, i.e. ANTI addition:



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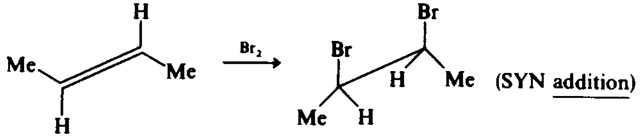

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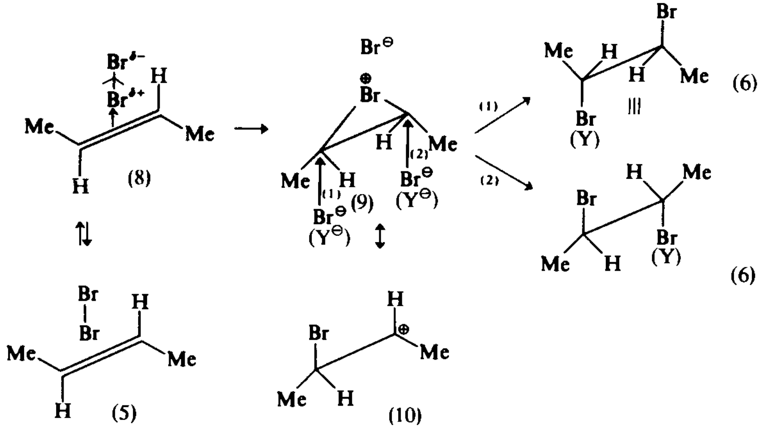
These observations are explainable by a pathway in which one end of a bromine molecule becomes positively polarised through electron repulsion by the π electrons of the alkene, thereby forming a π complex with it (8; *cf.* Br_2 + benzene, p. 131). This then breaks down to form a *cyclic bromonium ion* (9)—an alternative canonical form of the carbocation (10). Addition is completed through nucleophilic attack by the residual $Br^{\ominus}$ (or added $Y^{\ominus}$) on either of the original double bond carbon atoms, from the side opposite to the large bromonium ion $Br^{\oplus}$, to yield the *meso* dibromide (6):



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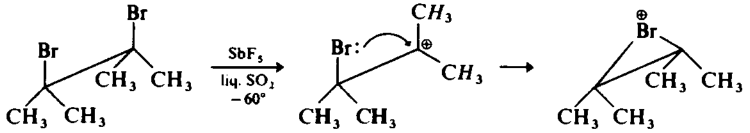

(11) (12) (9*a*)
δ 2·0 δ 2·9

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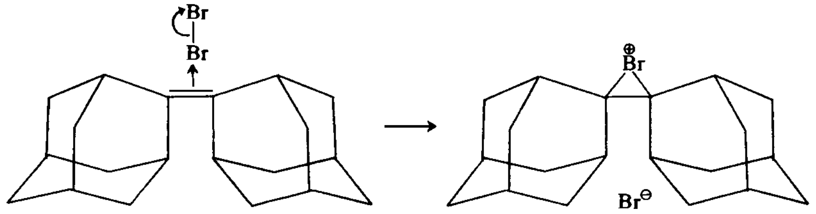


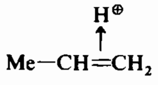
(13) (14)

This is possible only because further attack by $Br^{\ominus}$, on the first-formed intermediate (14), is prevented completely by the extremely bulky, cage-like structures at each end of the original double bond: completion of normal, overall addition of Br_2 thus cannot occur.

7.3 ORIENTATION OF ADDITION

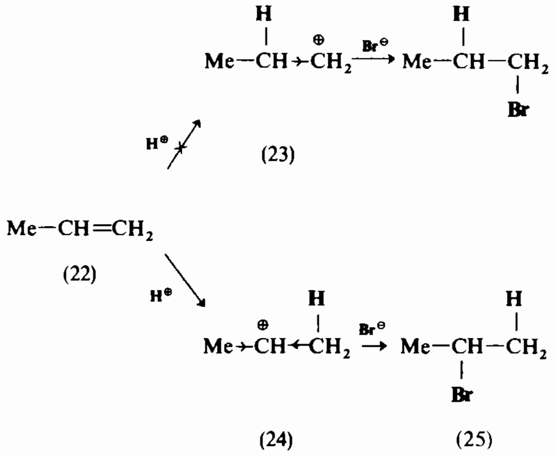
When the electrophile being added is, unlike the halogens, non-symmetrical then with a non-symmetrical alkene, e.g. propene, the problem of *orientation* of addition arises: this will be the case with the hydrogen halides. These are found to add to a given alkene in the rate order: $HI > HBr > HCl \gg HF$, i.e. in order of their acid strengths. This suggests rate-limiting addition of proton to the alkene, followed by rapid nucleophilic attack by $Hal^{\ominus}$ to complete the addition. In non-polar solvents the proton is no doubt provided by HHal, but in polar, and especially in hydroxylic solvents, more likely by its conjugate acid, e.g. by $H_3O^{\oplus}$ in H_2O.

A bridged intermediate exactly analogous to a bromonium ion cannot be formed as H has no electron pair available, but it may be that in some cases a π complex (21) is the intermediate. We shall, however, normally write the intermediate as a carbocation, and it is the relative stability of possible, alternative, carbocations (e.g. 23 and 24) that determines the overall orientation of addition, e.g. in the addition of HBr to propene (22) under polar conditions:



$\mathrm{Me{-}}\overset{\mathrm{H}^{\oplus}\uparrow}{\mathrm{CH{=}CH_2}}$

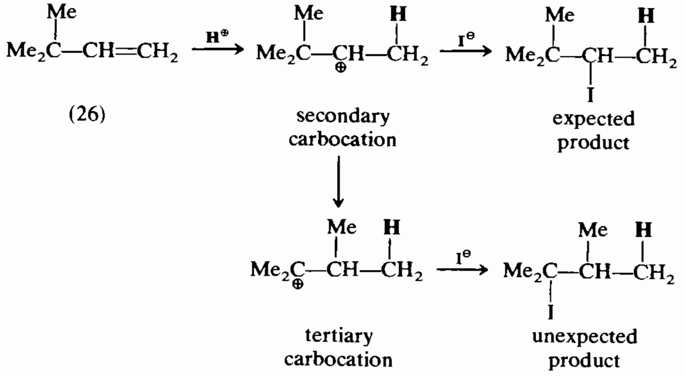
(21)



(22) (23) (24) (25)

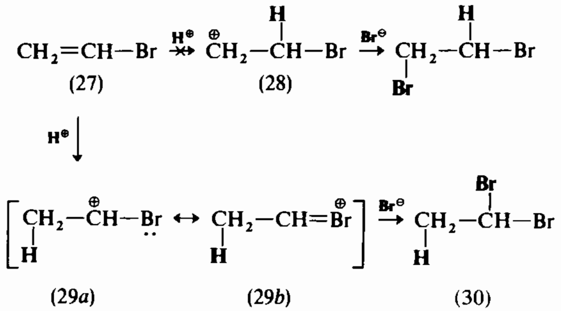
As we have seen already (p. 104) secondary carbocations are more stable than primary, and in so far as this also applies to the transition states that precede them, (24) will be formed in preference to (23). In fact it appears to be formed exclusively, as the only addition product obtained is 2-bromopropane (25). Addition, as here, in which halogen (or the more negative moiety of any other unsymmetrical adduct) becomes attached to the more highly substituted of the two alkene carbon atoms is known as *Markownikov* addition.

Support for the suggestion that addition of HHal does normally proceed *via* carbocation intermediates is provided by the formation, from some alkenes, of abnormal (i.e. unexpected) addition products that could only have arisen through rearrangement of a carbocation (*cf.* p. 112), e.g. with 3,3-dimethylbutene (26) and HI:



Other preparative snags also occur in the addition of HHal to alkenes. Thus in solution in H_2O, or in other hydroxylic solvents, acid-catalysed hydration (p. 187) or solvation may constitute a competing reaction; while in less polar solvents radical formation may be encouraged, resulting in *anti*-Markownikov addition to give 1-bromopropane ($MeCH_2CH_2Br$), *via* the preferentially formed radical intermediate, $Me\dot{C}HCH_2Br$. This is discussed in detail below (p. 316).

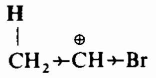
Electrophilic addition to 1-haloalkenes (e.g. 27), presents a number of parallels to the electrophilic substitution of halobenzenes (p. 155). Thus it is the involvement of the electron pairs on Br that controls the orientation of addition (*cf. o-*/*p*-direction in C_6H_5Br);



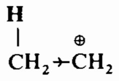
(27) (28) (29*a*) (29*b*) (30)

(29) is stabilised compared with (28), is therefore formed preferentially, and 1,1-dibromoethane (30) is in fact the only product obtained. The rate of addition is, however, controlled by the electron-withdrawing inductive effect of the halogen atom, and (27) is found to add HBr about

30 times more slowly than does ethene (*cf.* bromobenzene is attacked more slowly by electrophiles than is benzene), i.e. (29) is less stable, and is formed more slowly, than (31):



(29)



(31)

The addition of halogen hydracids to simple alkenes is found to be somewhat less stereoselective than was the addition of halogens, being rather more dependent on the particular alkene, and on the reaction conditions.

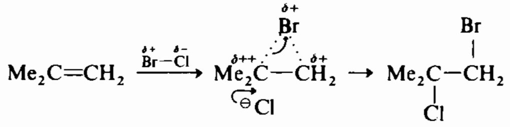
7.4 OTHER ADDITION REACTIONS

7.4.1 Further halogen derivatives

Interhalogen compounds, hardly surprisingly, add to alkenes very much as do the halogens themselves, and the following order of reactivity has been observed:

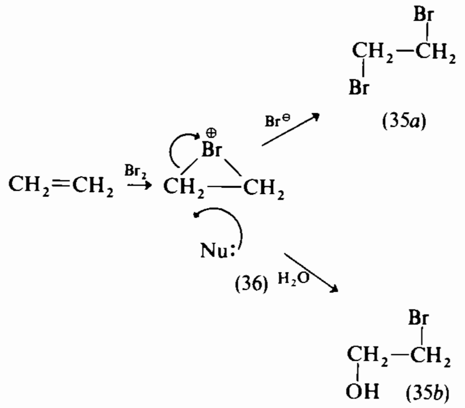
$$BrCl > Br_2 > ICl > IBr > I_2$$

Addition is initiated by the positively polarised end (the less electronegative halogen atom) of the unsymmetrical molecule, and a cyclic halonium ion intermediate probably results. Addition of I—Cl is particularly stereoselective (ANTI) because of the ease of formation (and relative stability compared with carbocations) of cyclic iodonium ions. With an unsymmetrical alkene, e.g. 2-methylpropene (32), the more heavily alkyl-substituted carbon will be the more carbocationic (i.e. the less bonded to Br in 33), and will therefore be attacked preferentially by the residual nucleophile, $Cl^{\ominus}$. The overall orientation of addition will thus be Markownikov to yield (34):



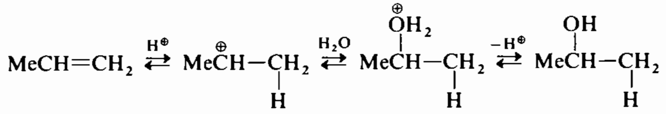
(32) (33) (34)

Hypohalous acids, e.g. $HO^{\delta-}—Br^{\delta+}$ (bromine water), were thought to add on in very much the same way, but there is some evidence that the actual electrophile may well be the halogen itself, e.g. Br_2, and that both 1,2-dibromide (35*a*) and 1,2-bromhydrin (35*b*) are then obtained by competition of $Br^{\ominus}$ and H_2O: for the initial bromonium ion intermediate (36):



7.4.2 Hydration

Acid-catalysed hydration of an alkene is the reversal of the similarly acid-catalysed dehydration (by the E1 pathway, *cf.* p. 248) of alcohols to alkenes:

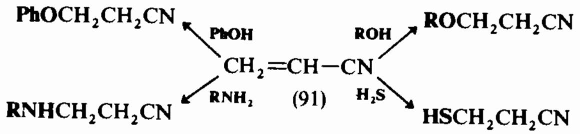


(37)

The formation of the carbocationic intermediate (37), either directly or *via* an initial π complex, appears to be rate-limiting, and the overall orientation of addition is Markownikov. There is evidence of some ANTI stereoselectivity, but this is not very marked and is dependent on the alkene and on the reaction conditions.

Acids that have weakly nucleophilic anions, e.g. $HSO_4^{\ominus}$ from dilute aqueous H_2SO_4, are chosen as catalysts, so that their anions will offer little competition to H_2O; any $ROSO_3H$ formed will in any case be hydrolysed to ROH under the conditions of the reaction. Rearrangement of the carbocationic intermediate may take place, and electrophilic addition of it to as yet unprotonated alkene is also known (p. 185). The reaction is used on the large scale to convert 'cracked' petroleum alkene fractions to alcohols by vapour phase hydration with steam over heterogeneous acid catalysts. Also under acid catalysis, ROH may be added to alkenes to yield ethers, and RCO_2H to yield esters.

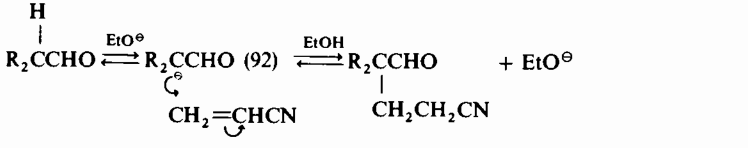
Anti-Markownikov hydration of alkenes may be effected indirectly by addition of B_2H_6 (*hydroboration*), followed by oxidation of the by abstraction of a proton from the solvent, leads overall to the attachment of a 2-cyanoethyl group to the original nucleophile;



the procedure is thus referred to as *cyanoethylation*. It is often carried out in the presence of base in order to convert HY into the more powerfully nucleophilic $Y^{\ominus}$. The synthetic utility of cyanoethylation resides in the incorporation of a three carbon unit, in which the terminal cyano group may be modified by reduction, hydrolysis, etc., preparatory to further synthetic operations. Addition of $Y^{\ominus}$, e.g. $^{\ominus}NH_2$, will of course, form a carbanion, $YCH_2—^{\ominus}CHCN$, and, in the absence of a proton donor, this can add to a further molecule of $CH_2{=}CHCN$ resulting, on subsequent repetition, in *anionic* polymerisation (*cf.* p. 226).

7.6.2 Michael reaction

Where the nucleophile attacking the substituted alkene is a carbanion (*cf.* p. 284) the process is referred to as a *Michael* reaction; its particular synthetic utility resides in its being a general method of carbon–carbon bond formation; e.g. with (91):



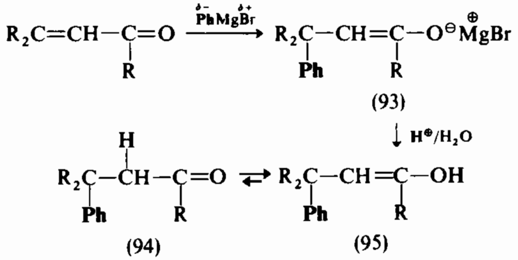
(91)

The reaction is promoted by a variety of bases, usually in catalytic quantities only, which generate an equilibrium concentration of carbanion (92); it is reversible, and the rate-limiting step is believed to be carbon–carbon bond formation, i.e. the reaction of the carbanion (92) with the substituted alkene (91). Its general synthetic utility stems from the wide variety both of substituted alkenes and of carbanions that may be employed; the most common carbanions are probably those from $CH_2(CO_2Et)_2$—see below, $MeCOCH_2CO_2Et$, $NCCH_2CO_2Et$, RCH_2NO_2, etc. Many Michael reactions involve $C{=}C—C{=}O$ as the substituted alkene.

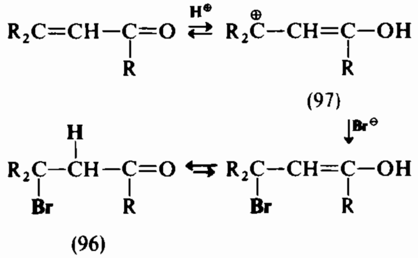
7.6.3 Addition to C=C—C=O

Among the commonest substituents 'activating' an alkene to nucleophilic attack is the C=O group, in such *αβ*-unsaturated compounds

as $RCH{=}CHCHO$, $RCH{=}CHCOR'$, $RCH{=}CHCO_2Et$, etc. As the carbonyl group in such compounds can itself undergo nucleophilic attack (*cf.* p. 204), the question arises as to whether addition is predominantly to C=C, to C=O, or *conjugate* (1,4-) to the overall C=C—C=O system. In fact, the last type of addition (93) normally yields the same product (94) as would be obtained from addition to C=C, owing to tautomerisation of the first formed enol (95), e.g. with the Grignard reagent PhMgBr followed by acidification:

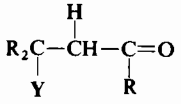


Incidentally, 1,4-*electrophilic* addition (e.g. HBr) also yields the C=C adduct (96) for the same reason, and can be looked upon formally as acid-catalysed (97) addition of the nucleophile $Br^{\ominus}$:

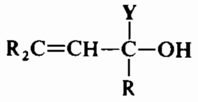


Less powerful nucleophiles such as ROH can also be made to add (1,4-) under acid catalysis.

Whether nucleophilic addition is predominantly conjugate (1,4-) or to C=O may depend on whether the reaction is reversible or not; if it is reversible, then the control of product can be thermodynamic (equilibrium *cf.* p. 43), and this will favour 1,4-addition. This is so because the C=C adduct (98) obtained from 1,4-addition will tend to be thermodynamically more stable than the C=O adduct (99), because the former contains a residual C=O *π* bond, and this is stronger than the residual C=C *π* bond in the latter:

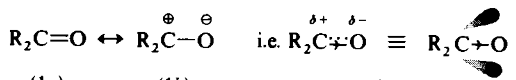


(98)



(99)

Steric hindrance at one site can, however, be very potent at promoting structure (1):

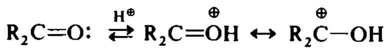


$R_2C{=}O \leftrightarrow R_2\overset{\oplus}{C}{-}\overset{\ominus}{O}$ i.e. $R_2\overset{\delta+}{C}{\cdots}\overset{\delta-}{O} \equiv R_2C{-}O$

(1*a*) (1*b*) (1*ab*)

We would expect the C=O linkage, by analogy with C=C (p. 178), to undergo addition reactions; but whereas polar attack on the latter is normally initiated only by electrophiles, attack on the former—because of its bipolar nature—could be initiated either by electrophilic attack of $X^{\oplus}$ or X on oxygen or by nucleophilic attack of $Y^{\ominus}$ or Y: on carbon (radical-induced addition reactions of carbonyl compounds are rare). In practice, initial electrophilic attack on oxygen is of little significance except where the electrophile is an acid (or a Lewis acid), when rapid, reversible protonation may be a prelude to slow, rate-limiting attack by a nucleophile on carbon, to complete the addition, i.e. the addition is then acid-catalysed.

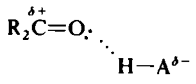
Protonation will clearly increase the positive character of the carbonyl carbon atom (2),



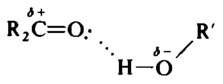
$$R_2C{=}O: \overset{H^{\oplus}}{\rightleftarrows} R_2C{=}\overset{\oplus}{O}H \leftrightarrow R_2\overset{\oplus}{C}{-}OH$$

(2)

and thereby facilitate nucleophilic attack upon it. Similar activation, though to a lesser extent, can also arise through hydrogen-bonding of an acid (3), or even of a hydroxylic solvent (4), to the carbonyl oxygen atom:



(3)

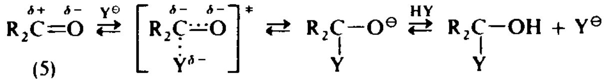


(4)

In the absence of such activation, weak nucleophiles, e.g. H_2O:, may react only very slowly, but strong ones, e.g. $^{\ominus}CN$, do not require such aid. Additions may also be base-catalysed, the base acting by converting the weak nucleophile HY into the stronger one, $Y^{\ominus}$, e.g. HCN + base ⟶ $^{\ominus}CN$. Further, while acids may activate the carbonyl carbon atom to nucleophilic attack, they may simultaneously reduce the effective concentration of the nucleophile, e.g. $^{\ominus}CN + HA \longrightarrow HCN + A^{\ominus}$, $RNH_2 + HA \longrightarrow RNH_3^{\oplus} + A^{\ominus}$. Many simple addition reactions of carbonyl compounds are thus found to have an optimum pH; this can be of great importance for preparative purposes.

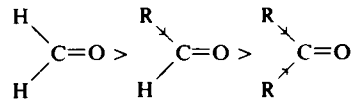
8.1 STRUCTURE AND REACTIVITY

In simple nucleophilic additions where the rate-limiting step is attack by $Y^{\ominus}$, the positive character of the carbonyl carbon atom is reduced on going from the starting material (5) to the transition state (6):

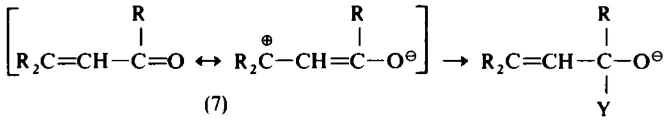


(5) (6)

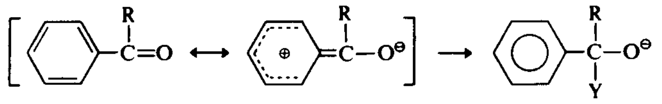
We should thus expect the rate of addition to be reduced by electron-donating R groups and enhanced by electron-withdrawing ones; this is borne out by the observed sequence:



R groups in which the C=O group is conjugated with C=C (1,4-addition can also compete here, *cf.* p. 200), or with a benzene ring, also exhibit slower addition reactions than their saturated analogues. This is because the stabilisation, through delocalisation, in the initial carbonyl compounds (7 and 8) is lost on proceeding to the adducts (9 and 10), and to the transition states that precede them:

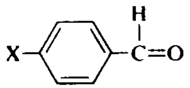


(7) (9)



(8) (10)

In the above examples steric, as well as electronic, effects could be influencing relative rates of reaction, but the influence of electronic effects alone may be seen in the series of compounds (11):



Relative rates: X=NO_2 > H > OMe

(11)

(31) on treatment with D_2O, followed by hydrolysis, results in conversion of the original aldehyde, RCHO, into its deuterio-labelled analogue, RCDO, selectively and in high yield. Alternatively, the anion (31) may be alkylated (e.g. with R′I), and the original aldehyde, RCHO, then converted into a ketone RR′CO.

Thioacetals and thioketals can also be made to undergo *desulphurisation* with Raney nickel catalyst, thus effecting, overall, the indirect conversion of $C{=}O \rightsquigarrow CH_2$:

$$R_2C{=}O \xrightarrow{R'SH} R_2C(SR')_2 \xrightarrow{H_2/Ni} R_2CH_2$$

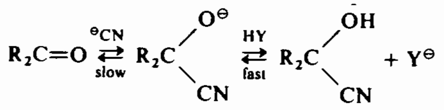
This is a conversion that is usually difficult to effect directly for preparative purposes.

8.2.4 Hydrogen cyanide

Although addition of HCN could be looked upon as a carbanion reaction, it is commonly regarded as involving a simple anion. It is of unusual interest in that it was almost certainly the first organic reaction to have its mechanistic pathway established (Lapworth 1903). HCN is not itself a powerful enough nucleophile to attack C═O, and the reaction requires base-catalysis in order to convert HCN into the more nucleophilic $^{\ominus}CN$; the reaction then obeys the rate law:

$$\text{Rate} = k[R_2C{=}O][^{\ominus}CN]$$

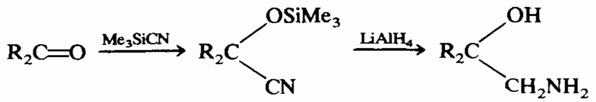
The addition of $^{\ominus}CN$ is reversible, and tends to lie over in favour of starting materials unless a proton donor is present; this pulls the reaction over to the right, as the equilibrium involving the cyanohydrin is more favourable than that involving the intermediate anion (32):



(32)

Attack by $^{\ominus}CN$ is slow (rate-limiting), while proton transfer from HCN or a protic solvent, e.g. H_2O, is rapid. The effect of the structure of the carbonyl compound on the position of equilibrium in cyanohydrin formation has already been referred to (p. 206): it is a preparative proposition with aldehydes, and with simple aliphatic and cyclic ketones, but is poor for ArCOR, and does not take place at all with ArCOAr. With ArCHO the benzoin reaction (p. 231) may compete with cyanohydrin formation; with C═C—C═O, 1,4-addition may compete (*cf.* p. 200).

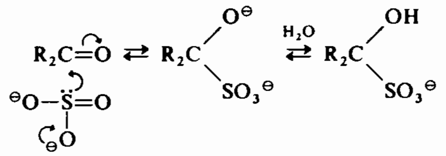
Those carbonyl compounds for which the equilibrium with HCN does not lie over in favour of cyanohydrin formation may often be converted satisfactorily into a derivative of the cyanohydrin through reaction with Me_3SiCN;



this possibility stems from the large amount of energy that is evolved by formation of the very strong O—Si bond. The preparative intent of initial cyanohydrin formation is usually the further transformation of the CN group (e.g. by reduction, hydrolysis, etc.), and this can still be achieved—in high yield—on the Me_3Si derivative. This further transformation must, however, be carried out under conditions (as shown above) such that any backward reaction to the initial carbonyl compound is prevented from taking place. An added advantage of Me_3SiCN, over HCN itself, is that reaction with C═C—C═O is strictly 1,2-(*cf.* p. 200), and with ArCHO no benzoin reaction (p. 231) can take place.

8.2.5 Bisulphite and other anions

Another classic anion reaction is that with bisulphite ion to yield crystalline adducts. The structure of these was long a matter of dispute before it was established that they were indeed salts of sulphonic acids (33), reflecting the greater nucleophilicity of sulphur rather than oxygen in the attacking anion. The effective nucleophile is almost certainly $SO_3{}^{2\ominus}$ (34) rather than $HSO_3{}^{\ominus}$ ($HO^{\ominus} + HSO_3{}^{\ominus} \rightleftharpoons H_2O + SO_3{}^{2\ominus}$), as though the latter will be present in higher relative concentration the former is a much more effective nucleophile:



(34) (33)

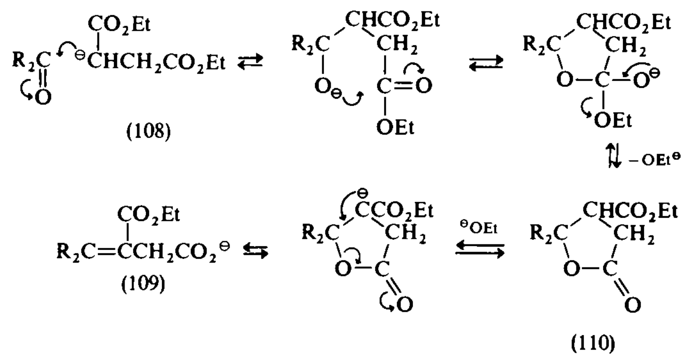
The attacking anion is already present in solution as such so no base catalysis is required, and $SO_3{}^{2\ominus}$ is a sufficiently powerful nucleophile not to require activation (by protonation) of the carbonyl group, so no acid catalysis is required either. This nucleophile is a large one, however, and the *K* values for product formation are normally

The carbanion (103) attacks the carbonyl carbon of the aldehyde in the usual way to yield the alkoxide anion (106*a*). Internal transfer of the acetyl group in this anion is believed to take place: from the carboxyl oxygen atom (in 106*a*) to the alkoxy oxygen atom (in 106*b*), *via* the cyclic intermediate (107); thereby forming a more stable species. Removal of an α-H from this anion by $MeCO_2^{\ominus}$ results in loss of the good leaving group $MeCO_2^{\ominus}$ from the adjacent β-position to yield the anion (105*a*) of the $\alpha\beta$-unsaturated acid. Work up of the reaction mixture with dilute acid leads to the product (105).

Some support for this mechanism is provided by the observation that on reaction with anhydrides of the form $(R_2CHCO)_2O$—where there would be no α-H to remove in the intermediate corresponding to (106*b*)—it is possible to isolate the analogue of (106*b*) as the actual end-product of the reaction.

8.4.7 Knoevenagel and Stobbe reactions

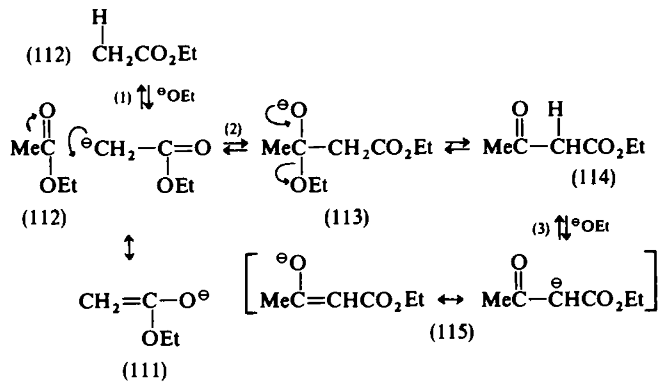
This addition involves carbanions from a wide variety of CH_2XY types but particularly where X and/or Y are CO_2R groups, e.g. $CH_2(CO_2Et)_2$; organic bases are often used as catalysts. In most cases the intermediate aldol is dehydrated to the $\alpha\beta$-unsaturated product (ester). An interesting example is with carbanions, e.g. (108), derived from esters of 1,4-butandioic(succinic) acid, e.g. $(CH_2CO_2Et)_2$, and aldehydes or ketones, employing alkoxide ions as base catalysts: the *Stobbe* condensation. These esters react a great deal more readily than might, *a priori*, have been expected, and one of the CO_2R groups is always, and unexpectedly, converted to $CO_2^{\ominus}$ in the course of the reaction; the product is always the $\alpha\beta$-unsaturated derivative (109), never the aldol. A pathway that will account for all these facts involves a cyclic (*lactone*) intermediate (110):



It has, in a few cases, proved possible actually to isolate cyclic intermediates such as (110).

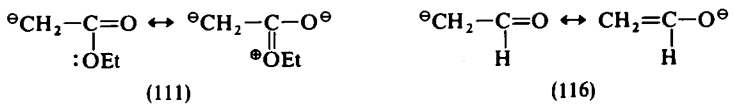
8.4.8 Claisen ester condensation

This is another reaction that involves carbanions derived from esters, e.g. (111), but this time adding to the carbonyl carbon atom of another ester molecule. The reason for considering it here rather than under carboxylic derivatives (p. 237) is that it can, in its initiation, be regarded as something of an analogue, for esters, of the aldol condensation on aldehydes (*cf.* p. 224), e.g. with ethyl ethanoate (acetate, 112):



One significant difference from the simple aldol reaction, however, is that the original adduct (113) now possesses a good leaving group (OEt); thus instead of adding a proton, as in the aldol reaction proper (p. 224), $^{\ominus}OEt$ is lost to yield a β-ketoester, ethyl 3-ketobutanoate (ethyl acetoacetate, 114). This is finally converted by base ($^{\ominus}OEt$) into its stabilised (delocalised) carbanion, (115).

Classically the base catalyst, $^{\ominus}OEt$, is introduced by adding just over one mole of sodium (as wire, or in other finely divided form) plus just a little EtOH to generate an initial small concentration of $Na^{\oplus\ominus}OEt$. Further EtOH is generated in step (1), which yields further $Na^{\oplus\ominus}OEt$ with sodium, and the concentration of $^{\ominus}OEt$ is thereby maintained. A whole mole is required as it is essential for the β-keto ester (114) to be converted (step 3) into its anion (115)—$MeCOCH_2CO_2Et$ is more acidic than EtOH (*cf.* p. 272)—if the overall succession of equilibria is to be displaced to the right. This is necessary because the carbanion-formation equilibrium—step (1)—lies even further over to the left than that with, for example, CH_3CHO; this reflects the less effective stabilisation through delocalisation in the ester carbanion (111) than in that from the aldehyde (116):



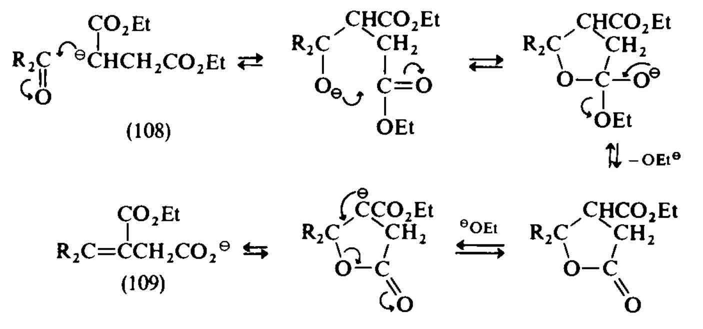
This requirement to pull the equilibrium of step (1) over to the right is reflected in the fact that no reaction occurs with R_2CHCO_2Et

The carbanion (103) attacks the carbonyl carbon of the aldehyde in the usual way to yield the alkoxide anion (106*a*). Internal transfer of the acetyl group in this anion is believed to take place: from the carboxyl oxygen atom (in 106*a*) to the alkoxy oxygen atom (in 106*b*), *via* the cyclic intermediate (107); thereby forming a more stable species. Removal of an α-H from this anion by $MeCO_2^{\ominus}$ results in loss of the good leaving group $MeCO_2^{\ominus}$ from the adjacent β-position to yield the anion (105*a*) of the αβ-unsaturated acid. Work up of the reaction mixture with dilute acid leads to the product (105).

Some support for this mechanism is provided by the observation that on reaction with anhydrides of the form $(R_2CHCO)_2O$—where there would be no α-H to remove in the intermediate corresponding to (106*b*)—it is possible to isolate the analogue of (106*b*) as the actual end-product of the reaction.

8.4.7 Knoevenagel and Stobbe reactions

This addition involves carbanions from a wide variety of CH_2XY types but particularly where X and/or Y are CO_2R groups, e.g. $CH_2(CO_2Et)_2$; organic bases are often used as catalysts. In most cases the intermediate aldol is dehydrated to the αβ-unsaturated product (ester). An interesting example is with carbanions, e.g. (108), derived from esters of 1,4-butandioic(succinic) acid, e.g. $(CH_2CO_2Et)_2$, and aldehydes or ketones, employing alkoxide ions as base catalysts: the *Stobbe* condensation. These esters react a great deal more readily than might, *a priori*, have been expected, and one of the CO_2R groups is always, and unexpectedly, converted to $CO_2^{\ominus}$ in the course of the reaction; the product is always the αβ-unsaturated derivative (109), never the aldol. A pathway that will account for all these facts involves a cyclic (*lactone*) intermediate (110):

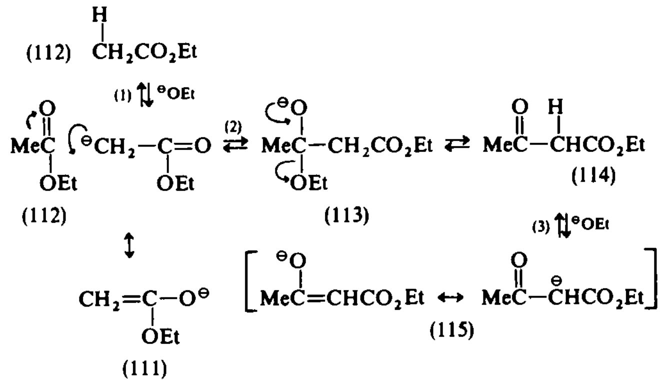


(110)

It has, in a few cases, proved possible actually to isolate cyclic intermediates such as (110).

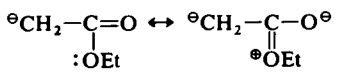
8.4.8 Claisen ester condensation

This is another reaction that involves carbanions derived from esters, e.g. (111), but this time adding to the carbonyl carbon atom of another ester molecule. The reason for considering it here rather than under carboxylic derivatives (p. 237) is that it can, in its initiation, be regarded as something of an analogue, for esters, of the aldol condensation on aldehydes (*cf.* p. 224), e.g. with ethyl ethanoate (acetate, 112):



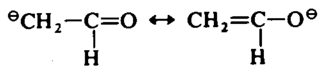
One significant difference from the simple aldol reaction, however, is that the original adduct (113) now possesses a good leaving group (OEt); thus instead of adding a proton, as in the aldol reaction proper (p. 224), $^{\ominus}OEt$ is lost to yield a β-ketoester, ethyl 3-ketobutanoate (ethyl acetoacetate, 114). This is finally converted by base ($^{\ominus}OEt$) into its stabilised (delocalised) carbanion, (115).

Classically the base catalyst, $^{\ominus}OEt$, is introduced by adding just over one mole of sodium (as wire, or in other finely divided form) plus just a little EtOH to generate an initial small concentration of $Na^{\oplus}{}^{\ominus}OEt$. Further EtOH is generated in step (1), which yields further $Na^{\oplus}{}^{\ominus}OEt$ with sodium, and the concentration of $^{\ominus}OEt$ is thereby maintained. A whole mole is required as it is essential for the β-keto ester (114) to be converted (step 3) into its anion (115)—$MeCOCH_2$-CO_2Et is more acidic than EtOH (*cf.* p. 272)—if the overall succession of equilibria is to be displaced to the right. This is necessary because the carbanion-formation equilibrium—step (1)—lies even further over to the left than that with, for example, CH_3CHO; this reflects the less effective stabilisation through delocalisation in the ester carbanion (111) than in that from the aldehyde (116):



$$^{\ominus}CH_2{-}\underset{:OEt}{\underset{|}{C}}{=}O \leftrightarrow {}^{\ominus}CH_2{-}\underset{^{\oplus}OEt}{\underset{\|}{C}}{-}O^{\ominus}$$

(111)



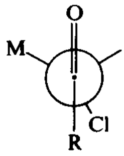
$$^{\ominus}CH_2{-}\underset{H}{\underset{|}{C}}{=}O \leftrightarrow CH_2{=}\underset{H}{\underset{|}{C}}{-}O^{\ominus}$$

(116)

This requirement to pull the equilibrium of step (1) over to the right is reflected in the fact that no reaction occurs with R_2CHCO_2Et

expect the ratio x/y to increase: (i) as the difference in size between M and S increases, and (ii) as the size of R′ in R′MgBr increases. In practice, it is found that for attack of MeMgI on the aldehyde C_6H_5-(Me)CHCHO (152, L = C_6H_5, M = Me, S = H, R = H) $x/y = 2{:}1$, while replacing Me by the rather bulkier Et raises x/y to 2·5 : 1. Similarly, replacing MeMgI by the much bulkier C_6H_5MgBr for attack on the Me compound (152, M=Me) is found to raise the x/y ratio to $>4{:}1$.

The operation of Cram's rule has been investigated very largely for Grignard additions, and some hydride additions, to C=O; in general it works quite well at forecasting which will be the more favoured product, but there are a number of exceptions. This is hardly surprising for the rule assumes that product control depends only on steric interactions, whereas complex formation—between groups in the substrate, e.g. hydrogen bonding, or between substrate and attacking nucleophile, e.g. RMgX and carbonyl oxygen atom—and dipole/dipole interaction may also play a part. As an example of the latter effect α-chloro-aldehydes and -ketones are found to react (because of electrostatic repulsion) in that conformation, e.g. (155), in which Cl and carbonyl oxygen atom are *anti* to each other,

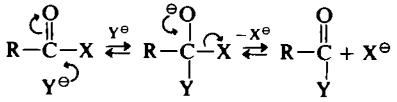


(155)

irrespective of the size, relative to Cl, of the other groups attached to that α-carbon atom. Either of these types of effect may outweigh purely steric considerations in determining the geometry of the preferred T.S.

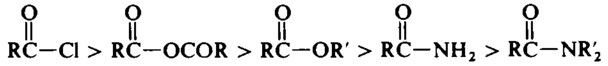
8.6 ADDITION/ELIMINATION REACTIONS OF CARBOXYLIC DERIVATIVES

The general reactions of this series are of the form:



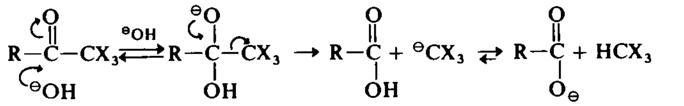
(156) (157)

The reaction pathway is normally nucleophilic addition/elimination, *via* a so-called *tetrahedral intermediate* (157), leading to overall substitution. The difference between the reactions of carboxylic derivatives (156) and those of simple carbonyl compounds (aldehydes and ketones) stems from the fact that in carboxylic derivatives there is, attached to the carbonyl carbon atom, a group X which is a good potential leaving group (as $X^{\ominus}$); whereas in simple carbonyl compounds the potential leaving group ($R^{\ominus}$ or $H^{\ominus}$) is very poor indeed. The relative reactivity of the series (156, with differing X) towards a particular nucleophile $Y^{\ominus}$ (e.g. $^{\ominus}OH$) depends on: (*a*) the relative electron-donating or -withdrawing power of X towards the carbonyl carbon atom, and (*b*) the relative ability of X as a leaving group. The reactivity series is not necessarily exactly the same for every $Y^{\ominus}$, but in general it follows the order:



$$\overset{O}{\overset{\|}{R C}}{-}Cl > \overset{O}{\overset{\|}{R C}}{-}OCOR > \overset{O}{\overset{\|}{R C}}{-}OR' > \overset{O}{\overset{\|}{R C}}{-}NH_2 > \overset{O}{\overset{\|}{R C}}{-}NR'_2$$

Thus acid chlorides and anhydrides react readily with ROH and NH_3 to yield esters and amides, respectively, while esters react with NH_3 or amines to give amides, but the simple reversal of any of these reactions on an amide, though not impossible, is usually pretty difficult. The relative reactivity will also depend on both the electronic and, more particularly, the steric effect of R. A slightly unusual leaving group is $^{\ominus}CX_3$ (e.g. $^{\ominus}CI_3$) in the *haloform* (158) *reaction* (*cf.* p. 297):

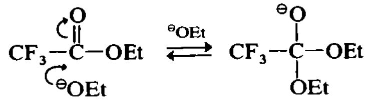


(158)

The rate law followed by these reactions is generally of the form,

$$\text{Rate} = k[\text{RCOX}][\text{Y}^{\ominus}]$$

and the question arises whether they might perhaps proceed by a direct, one step (*cf.* S_N2) displacement on the carbonyl carbon atom. It is not normally possible to isolate tetrahedral intermediates such as (157), but it has proved possible to obtain evidence of the formation of one where R carries strongly electron-withdrawing atoms or groups (*cf.* Cl_3CCHO, p. 208), i.e. (159) from the addition of $^{\ominus}OEt$ (in dibutyl ether) to CF_3CO_2Et (160):



(160) (159)

This adduct (≈100% yield) may be isolated and characterised; the less nucleophilic H_2O or EtOH does not add on. On going from the original carboxylic derivative (156) to the tetrahedral intermediate

The slow, rate-limiting step seems to be loss of the leaving group from (170), and this normally needs the assistance of a proton donor BH, e.g. H_2O.

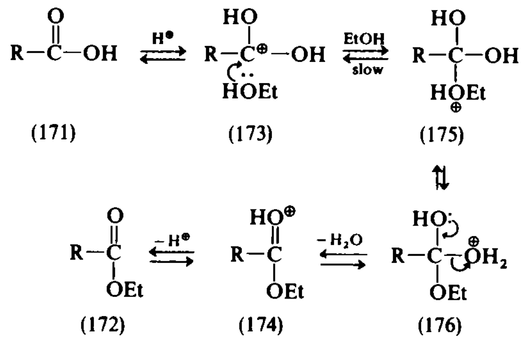
Acid chlorides, RCOCl, undergo ready attack by weaker nucleophiles, e.g. H_2O, ROH. The question then arises whether, with the better potential leaving group $Cl^{\ominus}$, the reactions of acid chlorides could proceed either *via* a single step 'S_N2 type' pathway (*cf.* p. 78) involving a T.S., in which attack by $Y^{\ominus}$ and loss of $Cl^{\ominus}$ are essentially synchronous; or *via* an 'S_N1 type' pathway (*cf.* p. 79) in which the slow step is $RCOCl \rightarrow RCO^{\oplus}Cl^{\ominus}$, followed by fast attack by $Y^{\ominus}$ on the acyl cation, $RCO^{\oplus}$. In fact, most reactions of acid chlorides probably proceed *via* the now familiar 'tetrahedral intermediate' pathway, though there may be some exceptions.

Acid anhydrides, $(RCO)_2O$, will also often react with weaker nucleophiles, though more slowly than acid chlorides; neither 'S_N1 nor S_N2 types' of reaction pathway normally occurs. Anhydrides are essentially intermediate in reactivity—towards a particular nucleophile—between acid chlorides and esters, reflecting the leaving group ability sequence:

$$Cl^{\ominus} > RCO_2^{\ominus} > RO^{\ominus}$$

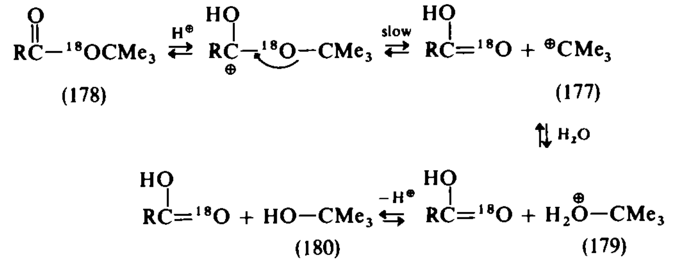
8.6.3 Acid-catalysed reactions

It is difficult to effect attack on the carbonyl carbon atom of RCO_2H, (171), with nucleophiles of the general type $Y^{\ominus}$, as they commonly remove proton instead, and the resultant $RCO_2^{\ominus}$ is then insusceptible to nucleophilic attack. Weaker nucleophiles of the form YH, e.g. ROH, do not suffer this inability, but their reactions with the relatively unreactive carbonyl carbon atom of RCO_2H are slow. The carbonyl character may be enhanced by protonation, however, i.e. by acid catalysis in, for example, esterification [(171) ⟶ (172)]:



N.m.r. spectra support preferential protonation of the carbonyl oxygen of the acid (173) in the forward reaction (esterification), and of the ester (174) in the reverse reaction (hydrolysis). Acid catalysis also has the effect of promoting the loss of the leaving group, i.e. it is easier to lose H_2O from (176)—esterification—or EtOH from (175)—hydrolysis—than it is, for example, to lose $^{\ominus}OEt$ from (165) above. The formation of a tetrahedral intermediate (an associative process) in the rate-limiting step (174 → 176, for hydrolysis) is borne out by the activation parameters observed for acid-catalysed hydrolysis of a simple ethanoate ester: $\Delta H^{\ddagger} = 75\ \mathrm{kJ\ mol^{-1}}$; $\Delta S^{\ddagger} = -105\ \mathrm{J\ K^{-1}\ mol^{-1}}$ (*cf.* p. 239). The equilibrium is normally displaced in the desired direction by using an excess of ROH (or of H_2O for hydrolysis). This mechanism is generally referred to as $A_{AC}2$ (Acid-catalysed, *acyl*-oxygen cleavage, *bimolecular*). Reaction of R′OH with RCO_2R'', under these conditions, results in transesterification, the position of equilibrium being determined by the relative proportions of R′OH and R″OH. Acid anhydrides and amides undergo acid-catalysed hydrolysis in very much the same way as esters.

Esters, RCO_2R', where the alkyl group R′ can form a relatively stable carbocation, e.g. (177) from (178), have been shown—by ^{18}O labelling experiments—to undergo *alkyl-oxygen* cleavage:

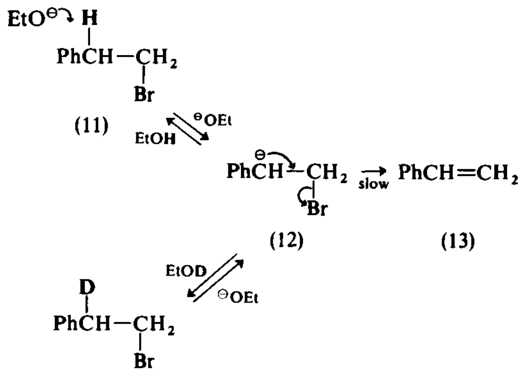


The activation parameters for the acid-catalysed hydrolysis of $MeCO_2CMe_3$ are found to be: $\Delta H^{\ddagger} = 112\ \mathrm{kJ\ mol^{-1}}$; $\Delta S^{\ddagger} = +55\ \mathrm{J\ K^{-1}\ mol^{-1}}$. The now +ve value of $\Delta S^{\ddagger}$ (indicating an *increase* in translational entropy in forming the T.S. for the rate-limiting step) suggests that this step is a *dissociative* process: as exemplified in the reaction pathway above by breakdown of the protonated ester into *two* separate species, the carboxylic acid and the carbocation (177). This mechanism is generally referred to as $A_{AL}1$ (*Acid*-catalysed, *alkyl*-oxygen cleavage, *unimolecular*), it also occurs with ester alkyl groups such as Ph_2CH, etc. When attempts are made to transesterify (178) with R′OH, the product is not now the expected ester, RCO_2R', but RCO_2H plus, the ether $R'OCMe_3$; the latter arises from attack of R′OH on the carbocationic intermediate (177), *cf.* the conversion of (177) to (179) by H_2O above.

Where the acid alkyl group, R in RCO_2R', is sufficiently bulky, e.g. R_3C (181), that bimolecular hydrolysis *via* a tetrahedral intermediate is inhibited (because of the degree of crowding there would be leaving group, $Y^{\ominus}$, is slow and rate-limiting, i.e. $k_{-1} > k_2$, then this reaction will follow the rate law,

$$\text{Rate} = k[\text{RY}][\text{B}]$$

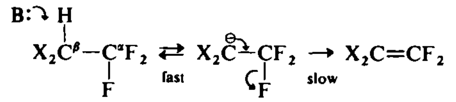
and will be kinetically indistinguishable from the concerted (E2) pathway. It should be possible to distinguish between them, however, by observing exchange of isotopic label, between as yet unchanged substrate and solvent, arising during fast, reversible carbanion (6) formation—something that clearly could not happen in the one-step, concerted (E2) pathway. A good example to test would be $PhCH_2CH_2Br$ (11), as the Ph group on the β-carbon would be expected to promote acidity in the β-H atoms, and also to stabilise the resultant carbanion (12) by delocalisation:



(11) (12) (13) (14)

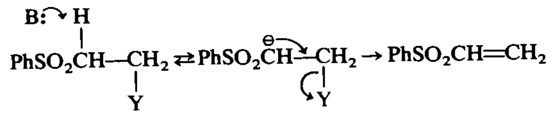
The reaction was carried out with $^{\ominus}$OEt in EtOD, and (11) re-isolated after ≈ half-conversion to (13): it was found to contain no deuterium, i.e. no (14); nor did the alkene (13) contain any deuterium, as might have been expected by elimination from any (14) formed. This potentially favourable case thus does not proceed by an E1cB pathway of the form described above; though we have not ruled out the case where $k_2 \gg k_{-1}$, i.e. essentially irreversible carbanion formation.

In fact reactions proceeding by this carbanion pathway are exceedingly rare; this is not altogether surprising as calculations suggest that the energy of activation for E2 is generally more favourable than that for E1cB, in most cases by ≈30–60 kJ (7–14 kcal) mol^{-1} (the reverse of step 2 would require addition of $Y^{\ominus}$ to C=C, which certainly doesn't happen at all easily). One example that almost certainly involves the latter pathway, however, is X_2CHCF_3 (15, X = Hal):



(15) (16) (17)

This has all the right attributes in the substrate: (*a*) electronegative halogen atoms on the β-carbon to make the β-H more acid, (*b*) stabilisation of the carbanion (16) through electron-withdrawal by the halogen atoms on the carbanion carbon atom, and (*c*) a poor leaving group in F. An attempt has been made to correlate the relative leaving group ability of a series of different Y groups in the E1cB reaction:

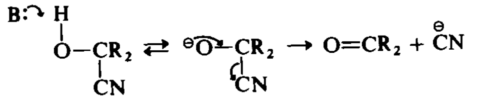


(18) (19)

$$\text{Y: PhSe} > \text{PhO} > \text{PhS} \approx \text{PhSO}_2 > \text{PhSO} > \text{MeO} \gg \text{CN}$$

The observed order of ability did not, however, correlate with the pK_a of YH, with the strength of the C—Y bond, or with the polar effect of Y! Clearly, leaving group ability even in this simple reaction is a highly complex attribute.

Other examples of the E1cB pathway are benzyne formation from C_6H_5F (*cf.* p. 174), reversal of simple nucleophilic addition to C=O, e.g. base-induced elimination of HCN from cyanohydrins (20; *cf.* p. 212),



(20)

and base-induced dehydration of aldols to $\alpha\beta$-unsaturated carbonyl compounds (*cf.* p. 225).

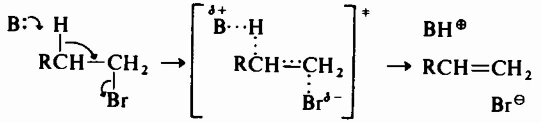
9.4 E2 MECHANISM

By far the commonest elimination mechanism is the one-step concerted (E2) pathway exhibiting, e.g. for the base-induced elimination of HBr from the halide RCH_2CH_2Br (21), the rate law:

$$\text{Rate} = k[\text{RCH}_2\text{CH}_2\text{Br}][\text{B}]$$

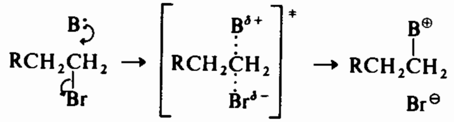
As B is often a nucleophile as well as a base, elimination is frequently accompanied by one-step, concerted (S_N2) nucleophilic substitution (*cf.* p. 78):

E2:



(21) (22)

S_N2:



(21) (23)

The factors that influence elimination *v.* substitution are discussed subsequently (p. 260). Evidence for the involvement of C—H bond fission in the rate-limiting step—as a concerted pathway requires—is provided by the observation of a primary kinetic isotope effect (*cf.* p. 46) when H is replaced by D on the β-carbon.

One of the factors that affects the rate of E2 reactions is, hardly surprisingly, the strength of the base employed; thus we find:

$$^{\ominus}NH_2 > {}^{\ominus}OR > {}^{\ominus}OH$$

Some studies have been made with bases of the type $ArO^{\ominus}$, as this allows study of the effects of variation in basic strength (by introduction of *p*-substituents in $C_6H_5O^{\ominus}$) without concomitant change in the steric requirements of the base. With a given base, transfer from a hydroxylic solvent, e.g. H_2O or EtOH, to a bipolar aprotic one, e.g. $HCONMe_2$ (DMF) or $Me_2S^{\oplus}—O^{\ominus}$ (DMSO), can have a very pronounced effect as the strength of the base, e.g. $^{\ominus}OH$, $^{\ominus}OR$, is enormously increased thereby. This arises because the base has, in the latter solvents, no envelope of hydrogen-bonded solvent molecules that have to be stripped away before it can act as a base (*cf.* effect on nucleophilicity in S_N2, p. 81). Such change of solvent may result in a shift of mechanistic pathway from E1 to E2 for some substrate/base pairs.

To explain the effect change of Y may have on the rate of reaction of R—Y (in which R remains the same) we need to consider: (*a*) any effect Y may have on C—H bond-breaking (E2 is a *concerted* reaction), (*b*) the strength of the C—Y bond, and (*c*) the stability of $Y^{\ominus}$, as reflected in the pK_a of H—Y. It thus comes as no surprise to find that forecasting the relative ability of Y as a leaving group is far from easy! If the atom in Y that is directly bonded to C in R—Y (and to H in H—Y) remains the same, e.g. oxygen, then the rate of reaction of R—Y may correlate not too badly with the *inverse* of the pK_a of H—Y: the stronger the oxy-acid, the better is its oxy-anion as a leaving group. Thus *p*-$MeC_6H_4SO_3^{\ominus}$ ('tosylate', Ts) is a very much better leaving group than $^{\ominus}OH$, reflecting *p*-$MeC_6H_4SO_3H$ being a very much stronger acid (lower pK_a value) than H_2O. Where the atom through which Y is bonded to C in R—Y does not stay the same, however, this inverse correlation with pK_a often breaks down. Thus the importance of the strength of the C—Y bond (rather than the pK_a of H—Y) is borne out by the relative rate sequence observed for $PhCH_2CH_2Hal$ with $^{\ominus}OEt/EtOH$:

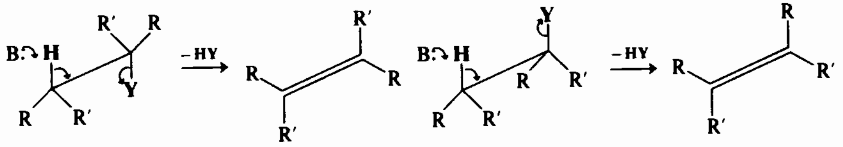
	$PhCH_2CH_2F$	$PhCH_2CH_2Cl$	$PhCH_2CH_2Br$	$PhCH_2CH_2I$
Rel. rate:	1	70	$4{\cdot}2 \times 10^3$	$2{\cdot}7 \times 10^4$

Incipient solvation of the developing $Y^{\ominus}$ in the transition state (e.g. 22), through hydrogen-bonding or other means, can also play its part in determining relative leaving group ability, and this may or may not follow the same general sequence as acid strength of HY and/or C—Y bond strength. Change of solvent thus can, and does, change the sequence of relative leaving group ability in a series of different $Y^{\ominus}$s.

Finally, the major structural features in the substrate promoting E2 elimination are those that serve to stabilise the resultant alkene or, more particularly, the T.S. that precedes it. Such features include increasing alkyl substitution at both α- and β-carbon atoms (leading to alkenes of increasing thermodynamic stability), or introduction of a phenyl group that can become conjugated with the developing double bond.

9.4.1 Stereoselectivity in E2

With acyclic molecules elimination could be envisaged as taking place from one or other of two limiting conformations—the *anti-periplanar* (24*a*) or the *syn-periplanar* (24*b*):

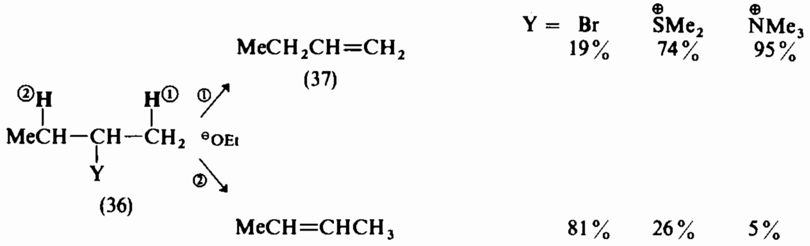


(24*a*) (25) (24*b*) (26)

There is an obvious advantage in elimination taking place from a conformation in which H, C^{β}, C^{α} and Y are in the same plane as the *p* orbitals that are developing on C^{β} and C^{α}, as $H^{\oplus}$ and $Y^{\ominus}$ are departing, will then be parallel to each other, and thus capable of maximum overlap in the forming π bond. It will be energetically advantageous for the attacking atom of the base B to lie in this common plane also.

9.4.2 Orientation in E2: Saytzev *v.* Hofmann

In substrates which have alternative β-hydrogen atoms available, it is possible to obtain more than one alkene on elimination, e.g. (36) where there are two possibilities:



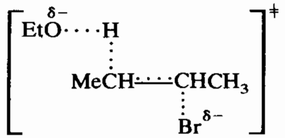
(37)

(36)

(38)

To help in forecasting which alkene is the more likely to be produced there have long been two empirical rules that can be summarised as follows: (*a*) Hofmann (1851; working on $R\overset{\oplus}{N}Me_3$ compounds, i.e. Y = $\overset{\oplus}{N}Me_3$) stated 'that alkene will predominate which has least alkyl substituents on the double bond carbons', i.e. (37) above; (*b*) Saytzev (1875; working on RBr compounds, i.e. Y = Br) stated 'that alkene will predominate which has most alkyl substituents on the double bond carbons', i.e. (38) above. Both generalisations are valid as the figures quoted above indicate. It is thus clear that the composition of the alkene mixture obtained on elimination is influenced by Y, the nature of the leaving group, and an explanation is required about how this influence may be exerted.

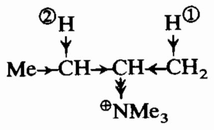
Saytzev elimination, which appears to occur when Y is neutral (e.g. with Y = OTs, etc., as well as Br), leads to the more stable (i.e. more heavily substituted, *cf.* p. 26) alkene. It seems reasonable to suppose, therefore, that reaction here proceeds *via* a T.S. in which a not inconsiderable degree of 'alkene character' has already been developed; the alkyl substituents thereby being able to begin exerting their stabilising (energy lowering) effect quite early in the single step of the E2 pathway, e.g. (38*a*):



(38*a*)

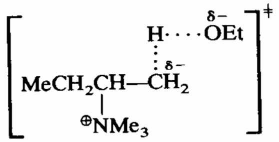
The preference for Saytzev elimination in the E1 pathway has already been referred to (p. 249).

This appears to be wholly logical—just what we would have expected from an E2 pathway—so the real question is why a +vely charged Y should prompt a divergence from this apparent norm? A Y group such as $^{\oplus}NMe_3$ will exert a powerful, electron-withdrawing, inductive/field effect on both the β-carbon atoms, and thus on the H atoms attached to them,



(36*a*)

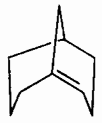
thus making these hydrogens markedly more acidic. They will thus be much more readily removed by base than when Y was Br, and the powerful electron-withdrawal by $^{\oplus}NMe_3$ will also stabilise the incipient carbanion forming as either H is being removed. This effect will, in the case of ②H, be reduced to some extent through electron-donation by the Me substituent on this β-carbon; such an acid-weakening effect does not occur with ①H, which is thus more acidic than ②H, and hence the proton that is more easily removed by base. This effect of $^{\oplus}NMe_3$ is apparently sufficient to make relative proton acidity, rather than potential alkene stabilisation, the controlling factor. The reaction now proceeds through a T.S. (37*a*)



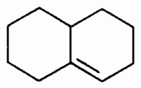
(37*a*)

possessing some degree of 'carbanion character', but in which little or no 'alkene character' has yet developed. E2 eliminations can thus involve transition states along a whole spectrum of 'character', whose nature is determined in considerable part by Y.

It is interesting in this respect that when Y is F, despite this not being +vely charged, there is a marked tendency towards the Hofmann product: thus $EtCH_2CH(F)CH_3$ leads to no less than 85% of $EtCH_2CH{=}CH_2$. This 'unexpected' result stems from the extremely powerful electron-withdrawing effect of F (*cf.* $^{\oplus}NMe_3$); and also that $F^{\ominus}$ is an extremely poor leaving group, thereby delaying C—F bond-breaking in the T.S. 'spectrum'. Support for the importance of proton acidity, and the development of 'carbanion character' in the T.S., for Hofmann elimination is provided by the observation that increase in the strength of the base attacking RY (whether Y is +vely charged or not) also leads to increasing formation of the Hofmann product. β-Substituents that would help stabilise a developing −ve charge promote formation of the Hofmann product, This is presumably the case because the developing p orbitals in an E2 reaction, far from being coplanar (*cf.* p. 253), would be virtually at right angles to each other (49), and so could not overlap significantly to allow development of a double bond. The relatively small ring system is rigid enough to make the distortion required for effective p orbital overlap energetically unattainable; there seems no reason why an E1 or E1cB pathway would be any more successful: the bicycloheptene (48) has, indeed, never been prepared. With bigger rings, e.g. the bicyclononene (50), or a more flexible system (51), sufficient distortion is now possible to allow the introduction of a double bond by an elimination reaction:



(50)



(51)

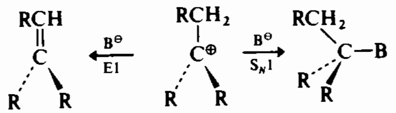
9.5 ELIMINATION *v.* SUBSTITUTION

E1 elimination reactions are normally accompanied by S_N1 substitution, as both have a common—carbocationic—intermediate; though this is converted into *either* elimination *or* substitution products *via* different T.S.s in a fast, non rate-limiting step. Similarly, E2 elimination is often accompanied by S_N2 substitution, though in this case the parallel, concerted processes involve entirely separate pathways throughout. Thus considering elimination *v.* substitution there are really three main issues: (*a*) factors influencing E1/S_N1 product ratios, (*b*) factors influencing E2/S_N2 product ratios, and (*c*) factors influencing change of pathway, i.e. E1/$S_N1 \rightarrow$ E2/S_N2 (or *vice versa*), as such a shift often changes the proportion of elimination to substitution.

The last of these, (*c*), may well be the most potent. Thus E1/S_N1 solvolysis of Me_3CBr, and of $EtMe_2CBr$, in EtOH (at 25°) was found to yield 19% and 36%, respectively, of alkene; while introduction of 2M $EtO^{\ominus}$—which shifts the mechanism in part at least to E2/S_N2—resulted in the alkene yields rising to 93% and 99%, respectively. It is indeed found generally, for a given substrate, that the E2/S_N2 ratio is substantially higher than the E1/S_N1 ratio. A point that is worth bearing in mind when contemplating preparative, synthetic operations is the use of a less polar solvent (the E1/S_N1 process is favoured by polar, ion-solvating media)—the classical alcoholic, rather than aqueous, potash for elimination of HBr from alkyl bromides. A shift in mechanism may also be induced by increasing the concentration of the base employed, e.g. $^{\ominus}OH$; hence the classical use of concentrated, rather than dilute, potash for elimination.

In either (*a*) or (*b*), the carbon structure of the substrate is of considerable importance, the proportion of elimination rising on going: primary < secondary < tertiary. In electronic terms this stems from increasing relative stabilisation of the T.S. for elimination as the number of alkyl groups on the carbon atoms of the developing double bond increases (*cf.* p. 256). Thus with $EtO^{\ominus}$ in EtOH on alkyl bromides, we find: primary → *ca.* 10% alkene, secondary → *ca.* 60%, and tertiary → >90%. This stems not only from an increasing rate of elimination, but also from a decreasing rate of substitution. Similarly, substituents such as C=C and Ar that can stabilise the developing double bond through conjugation (*cf.* p. 253) also strongly favour elimination: under comparable conditions, CH_3CH_2Br yielded ≈1% alkene, while $PhCH_2CH_2Br$ yielded ≈99%.

In E1/S_N1 increasing branching in R—Y leads to an increase in the proportion of elimination. This arises from increasing stability of the progressively more highly substituted alkene product and, more importantly, of the T.S. leading to it from the carbocation intermediate. A steric factor may also operate to favour elimination in that the sp^2 hybridised carbon atom in the carbocation (52) remains sp^2 hybridised (≈120° bond angles) on elimination (53), but becomes sp^3 hybridised (≈109° bond angles) on substitution (54):



(53) (52) (54)

Crowding strain is thus re-introduced in the T.S. for substitution, but much less so, if at all, in the T.S. for elimination, and the differential between them will become greater—increasingly favouring elimination—as the size and degree of branching in the R groups increases; but only becoming significant when larger/more branched than Me_3C—Y. A related, but slightly different, point is that the peripheral H will be much more accessible than the relatively hindered carbocationic carbon; we should thus expect the proportion of elimination to rise as the size of the attacking base/nucleophile increases: as is indeed observed, i.e. $Me_3CO^{\ominus}$ is usually better than $EtO^{\ominus}$ for carrying out elimination reactions with. This discussion has tended to centre on the E1/S_N1 case, but essentially analogous steric effects are involved in the differential stabilisation of the T.S. for E2 with respect to the T.S. for S_N2.

The E1/S_N1 ratio is, of course, substantially independent of the leaving group Y, but this is not the case with E2/S_N2, where breaking of the C—Y bond is involved in each alternative T.S. The following rough sequence, in order of increasing promotion of elimination, is observed:

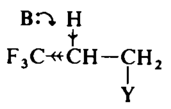
$$\text{Tosylate} < \text{Br} < \overset{\oplus}{\text{S}}\text{Me}_2 < \overset{\oplus}{\text{N}}\text{Me}_3$$

The attacking base/nucleophile is obviously of importance also; we require, ideally, a species that is a strong base but a poor nucleophile. Preparatively, tertiary amines, e.g. Et_3N, pyridine, are often used to promote elimination. Though these are not particularly strong bases, they are poor nucleophiles because of steric effects, e.g. branching in Et_3N, impeding nucleophilic attack on carbon, but not basic attack on a peripheral hydrogen. The use of a base of relatively high b.p. is also advantageous (see below).

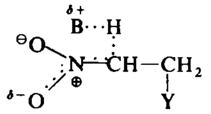
Finally, elimination—whether E1 or E2—is favoured with respect to substitution by rise in temperature. This is probably due to elimination leading to an increase in the number of particles, whereas substitution does not. Elimination thus has a more +ve entropy term (*cf.* p. 241), and because this ($\Delta S^{\ddagger}$) is multiplied by T in the relation for the free energy of activation, $\Delta G^{\ddagger}$ ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, *cf.* p. 38), it will increasingly outweigh a less favourable $\Delta H^{\ddagger}$ term as the temperature rises.

9.6 EFFECT OF ACTIVATING GROUPS

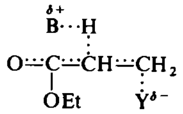
We have to date considered the effect of alkyl substituents in promoting elimination reactions in suitable substrates, and also, in passing, that of Ar and C=C. Elimination is, in general, promoted by most electron-withdrawing substituents, e.g. CF_3, NO_2, $ArSO_2$, CN, C=O, CO_2Et, etc. Their effect can be exerted: (*a*) through making the β-H atoms more acidic (55), and hence more easily removable by a base, (*b*) through stabilisation of a developing carbanion by electron-withdrawal (56), or in some cases, (*c*) through stabilisation of the developing double bond by conjugation with it (57):



(55)



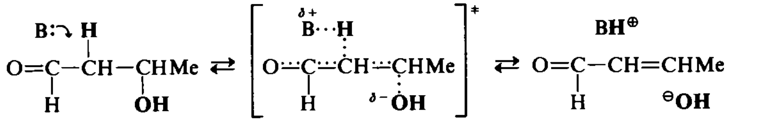
(56)



(57)

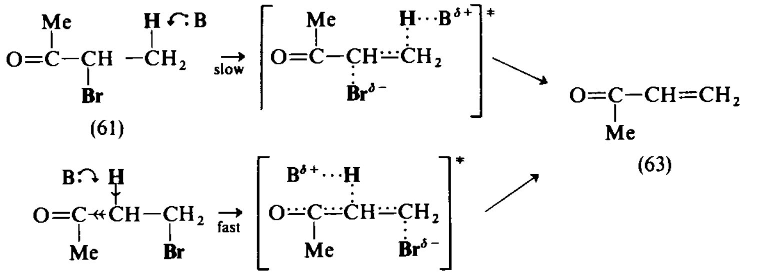
The more powerfully electron-withdrawing the substituent the greater the chance that the T.S. in an E2 elimination will be 'carbanion-like' (*cf.* p. 257), or even that the reaction pathway may be shifted to the E1cB mode (*cf.* p. 249), e.g. possibly with NO_2 or $ArSO_2$, especially if the leaving group, Y, is a poor one.

A good example of elimination promotion is by the CHO group in aldol (58) making possible a base-catalysed dehydration to an $\alpha\beta$-unsaturated aldehyde (59, *cf.* p. 225):



(58) (60) (59)

Dehydrations are normally acid-catalysed (protonation of $\ddot{O}H$ turning it into $^{\oplus}OH_2$, H_2O being a better leaving group than $^{\ominus}OH$), and a base-catalysed elimination is here made possible by the CHO group making the β-H atoms more acidic, and stabilising the resultant carbanion, i.e. (*a*)/(*b*) on p. 262. Stabilisation, by conjugation, of the developing double bond [(*c*) above] has been included in the T.S. (60) above, but how large a part this plays is not wholly clear. It is, however, significant that electron-withdrawing substituents are usually very much more effective in promoting elimination when they are on the β-, rather than the α-, carbon atom: they could conjugate with a developing double bond equally well from either position, but can only increase acidity of β-H, and stabilise a carbanion from the β-position. This is clearly seen in base-induced elimination of HBr from 1- and 2-bromoketones, (61) and (62), respectively,



(61) (63) (62)

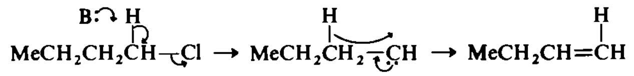
where both give the same $\alpha\beta$-unsaturated (i.e. conjugated) ketone (63), but (62) is found to eliminate HBr very much faster than (61), under analogous conditions. Such β-substituents are often effective enough to promote loss of more unusual—and poor—leaving groups such as OR, NH_2, etc. (OH above).

9.7 OTHER 1,2-ELIMINATIONS

Attention has to-date been devoted almost entirely to eliminations in which it has been H that has been lost, as a proton, from the β-carbon atom. These are certainly the most important eliminations, but examples are known that involve the departure of an atom or group other than

9.8 1,1-(α-)ELIMINATION

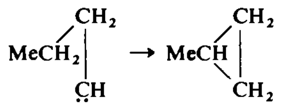
A relatively small number of examples are known of 1,1-eliminations in which both H and the leaving group, Y, are lost from the same (α-) carbon atom, e.g. (73) ⟶ (74). They tend to be favoured: (*a*) by powerfully electron-withdrawing Y groups—these increase the acidity of the α-H atoms, and stabilise a developing -ve charge on the α-carbon atom, (*b*) by using very strong bases, B, and (*c*) by the absence of β-H atoms—though this is not a requirement (*cf.* 73):



(73) (75) (74)

In some, though not necessarily all, cases loss of $H^{\oplus}$ and $Cl^{\ominus}$ is thought to be concerted, leading directly to the *carbene* (*cf.* p. 50) intermediate (75); formation of the product alkene from (75) then requires migration of H, with its electron pair, from the β-carbon atom. A 1,1-elimination (Eα) will be indistinguishable kinetically from 1,2-(E2), and evidence for its occurrence rests on isotopic labelling, and on inferential evidence for the formation of carbenes, e.g. (75).

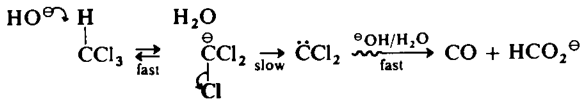
Thus introduction of 2D atoms at the α-position in (73) is found to result in one of them being lost in going to (74)—both would be retained in E2; while introduction of 2D at the β-position in (73) results in both being still present in (74), though one is now on the terminal (α- in 73) carbon atom—one would have been lost in E2. From such isotopic labelling data it is possible to determine how much of a given elimination proceeds by the 1,1-, and how much by the 1,2-pathway. Use of $C_6H_5^{\ominus}Na^{\oplus}$—an enormously strong base—in decane solution is found to result in 94% 1,1-elimination from (73), while $Na^{\oplus}NH_2^{\ominus}$ caused much less, and $Na^{\oplus}OMe^{\ominus}$ hardly any at all, i.e. the operation of factor (*b*) above. It was also found that, for a given base, alkyl bromides and iodides underwent much less 1,1-elimination than the corresponding chlorides, i.e. operation of factor (*a*), above. Inferential evidence for the formation of the carbene intermediate (75) is provided by the isolation from the reaction mixture of the cyclopropane (76),



(75) (76)

such intramolecular 'insertions' to form cyclopropanes being a common reaction of suitable carbenes; it is an example of 'internal trapping' (*cf.* p. 50). Only 4% of (76) was isolated from the reaction of (73), but no less than 32% of (76) was isolated from the 1,1-elimination of the isomeric chloride, $MeCH(Cl)CH_2CH_3$.

The most familiar, and most studied, example of 1,1-elimination occurs where no β-H atoms are available—the operation of factor (*c*) above—in the hydrolysis of haloforms, e.g. $CHCl_3$ (77), with strong bases. This involves an initial 1,1-elimination, probably *via* a two-step, i.e. 1,1-E1cB, pathway, to yield a dichlorocarbene intermediate (78);

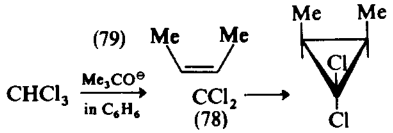


(77) (78)

The hydrolysis, as expected, follows the rate law,

$$\text{Rate} = k[\mathrm{CHCl_3}][^{\ominus}\mathrm{OH}]$$

and the fast, reversible first step is supported by the fact that deuterated chloroform, $CDCl_3$, is found to undergo base-catalysed exchange with H_2O (loss of D) much faster than it undergoes hydrolysis. Further support for the above mechanism comes from the observation that $HCCl_3$ is relatively inert towards $PhS^{\ominus}$ alone; but will, if $^{\ominus}OH$ is added, then react very rapidly to form $HC(SPh)_3$, i.e. $PhS^{\ominus}$ while not nucleophilic enough to attack $HCCl_3$ will attack the highly reactive CCl_2. This dichlorocarbene is a highly electron-deficient species and (if generated in a non-protic solvent) will add to the double bond of (electron-rich) alkenes, e.g. *cis* 2-butene (79), to form cyclopropanes, e.g. (80), a 'trapping' reaction (*cf.* p. 50):



(79) (78) (80)

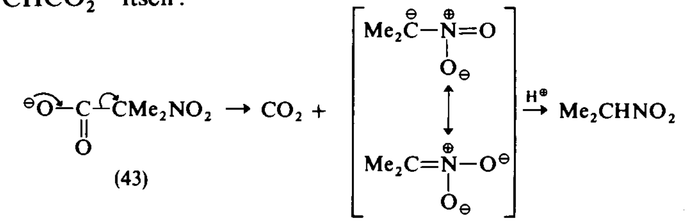
Under suitable conditions, this can be a useful preparative method for cyclopropanes; another preparative 'trapping' reaction of CCl_2 is its electrophilic attack on phenols in the Reimer–Tiemann reaction (p. 290).

It should however, be emphasised that in protic solvents, with the common bases, and with substrates containing β-H atoms 1,1-elimination occurs to only a small extent if at all.

9.9 PYROLYTIC SYN ELIMINATION

There are a number of organic compounds including esters—especially acetates, xanthates (see below)—amine oxides, and halides that undergo

$Me_2CHCO_2^{\ominus}$ itself:

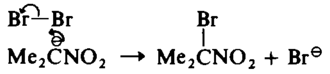


(43)

(44)

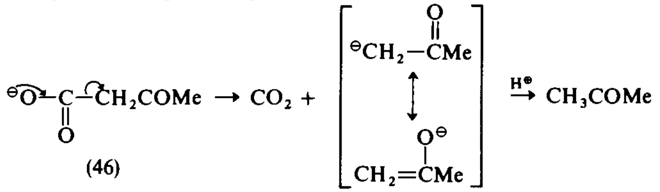
Similar ease of decarboxylation is seen in $Hal_3CCH_2CO_2^{\ominus}$, 2,4,6-$(NO_2)_3C_6H_2CO_2^{\ominus}$, etc., but the reaction is not normally of preparative value with the anions of simple aliphatic acids other than $MeCO_2^{\ominus}$.

Evidence that carbanion intermediates, e.g. (44), are involved is provided by carrying out the decarboxylation in the presence of bromine. This is without effect on the overall rate of the reaction but the end-product is now Me_2CBrNO_2 rather than Me_2CHNO_2—under conditions where neither $Me_2C(NO_2)CO_2^{\ominus}$ nor Me_2CHNO_2 undergoes bromination. The bromo product (45) arises from rapid attack of Br_2 on the carbanion intermediate (44), which is thereby 'trapped' (*cf.* the base-catalysed bromination of ketones, p. 295):



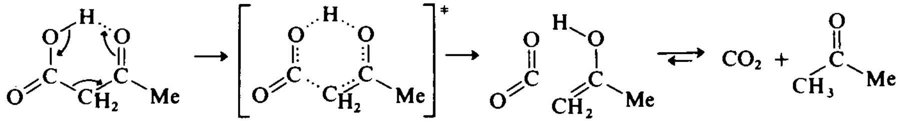
(44) (45)

C=O can also act like NO_2, and the anions of β-ketoacids (46) are decarboxylated very readily:



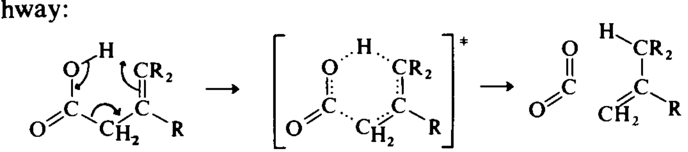
(46)

The overall rate law is, however, found to contain a term involving [ketoacid] (47) as well as the term involving [ketoacid anion]. The ready decarboxylation of the β-ketoacid itself is probably due to incipient proton transfer to C=O through hydrogen-bonding in (47):



(47) (48)

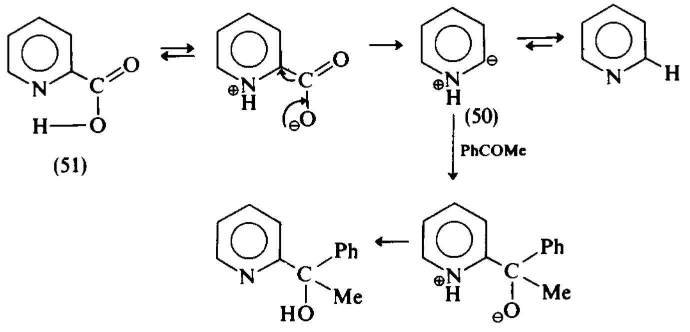
Some evidence for this mode of decarboxylation of the free acid has been obtained by 'trapping' the enol intermediate (48). $\beta\gamma$-Unsaturated acids (49) probably also decarboxylate by an analogous pathway:



(49)

$\alpha\beta$-unsaturated acids, $R_2CHCR{=}CHCO_2H$, probably decarboxylate by this pathway also, as it has been shown that they isomerise to the corresponding $\beta\gamma$-unsaturated acid prior to decarboxylation.

Another example in which the free acid undergoes ready decarboxylation, but this time *via* a carbanion intermediate (50, actually an *ylid*), is pyridine-2-carboxylic acid (51), which is decarboxylated very much more readily that its 3- or 4-isomers:



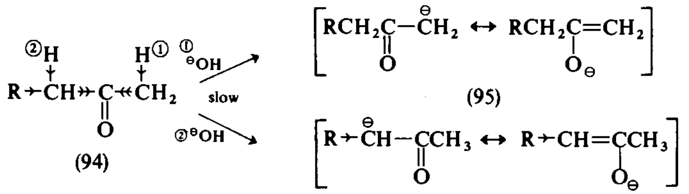
(51) (50) (52)

The ylid intermediate (50) can be 'trapped' by carrying out the decarboxylation in the presence of carbonyl compounds, e.g. PhCOMe, to yield the carbanion addition product, e.g. (52); this process can indeed be used preparatively. The reason for the much easier decarboxylation of (51), than of its 3-, and 4-isomers, is the stabilisation that the $N^{\oplus}$ can effect on the adjacent carbanion carbon atom in the intermediate ylid (50).

10.5.3 Displacement

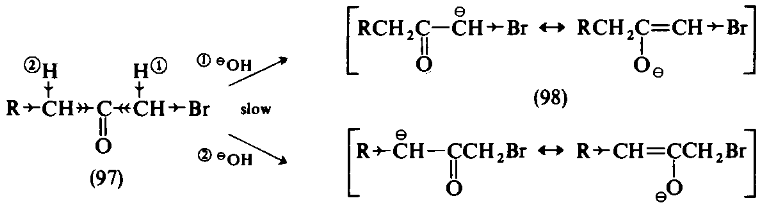
Carbanions, or similar species, are involved in a variety of displacement reactions, either as intermediates or as attacking nucleophiles.

stability of the resultant carbanion/enolate anion, (96):



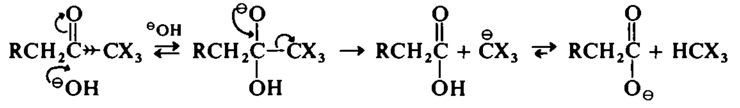
(94) (95) (96)

So far as (*b*) is concerned, an introduced halogen substituent, e.g. Br in (97), is found to exert very considerable influence on the position at which further halogenation occurs:



(97) (98) (99)

The powerful electron-withdrawing inductive/field effect exerted by Br makes the α-H atoms of the CH_2Br group more acidic than those of the RCH_2 group, and may also help stabilise the resultant carbanion (98), compared with (99). The former will thus be formed preferentially, and further bromination will thus be expected on $C\underline{H_2}Br$ rather than on $RC\underline{H_2}$. Further, because of this electron-withdrawal by the Br atom, (98) will be formed more rapidly than was, for example, (95), i.e. the second bromination will be faster than the first; and the third bromination of CH_3 will be correspondingly faster still. We might thus expect the end-product of this base-catalysed halogenation to be RCH_2COCX_3(100). Reversible addition of ${}^{\ominus}OH$ to the C=O group of the ketone can, however, take place at any time, and in CX_3 we now have an excellent leaving group; the result is thus C—C bond fission (*cf.* p. 237):



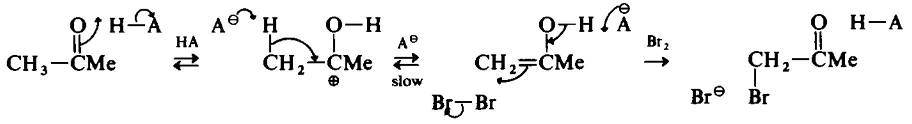
(100) (101) (102) (103)

CX_3 is a good leaving group because of the electron-withdrawing inductive effect of the three halogen atoms; this activates the carbonyl carbon atom in (100) to nucleophilic attack, and also stabilises the departing carbanion (101). The end-product, apart from the carboxylate anion (102), is the haloform (103), and the overall process—$RCH_2COCH_3 \rightarrow RCH_2CO_2^{\ominus} + HCX_3$—is known as the *haloform reaction*. It has been employed as a diagnostic test for methyl ketones, using I_2 and aqueous base as the resultant CHI_3 ('iodoform') is yellow, has a highly characteristic smell, and is insoluble in the reaction medium.

The halogenation of ketones is also catalysed by acids (general acid catalysis, *cf.* p. 74), the rate law observed is,

$$\text{Rate} = k[\text{ketone}][\text{acid}]$$

and, as with the base-catalysed reaction, the rates of bromination, iodination, deuterium exchange and racemisation are identical. This time the common intermediate, whose formation is slow and rate-limiting, is the enol (104):



(104)

This then undergoes rapid, non rate-limiting attack by Br_2 or any other electrophile present.

To discover which of the groups of α-H atoms would be expected to undergo preferential substitution in RCH_2COCH_3 requires comparison of the formation of the relevant enols, (105) and (106):

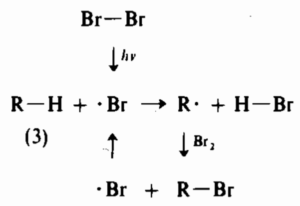
(105) (107) (106) (108)

Of these (105) is likely to be more stable than (106) as it has the more heavily substituted double bond of the two (*cf.* p. 26); the favoured bromination product is thus expected to be (107). In fact, the acid-catalysed bromination of $MeCH_2COCH_3$ is indeed found to yield about three times as much 3- as 1-bromobutanone.

It is also found, in contrast to bromination under base-catalysed conditions, that introduction of a further bromine into a monobromoketone is more difficult than was introduction of the initial one. It is thus normally possible, under acid conditions, to stop bromination so as to obtain the mono-bromo product, e.g. (107), preparatively. This is, of course, in contrast to under base conditions, where further bromination cannot be prevented and is followed, in suitable cases, by haloform cleavage (p. 296).

tion engines is the largest scale, and most widespread, chemical reaction of all! Radical reactions also occur in solution, particularly if carried out in non-polar solvents, and if catalysed by light or the simultaneous decomposition of substances known to produce radicals themselves, e.g. organic peroxides. Radicals, once formed in solution, are generally found to be less selective in their attack on other species, or on alternative positions within the same species, than are carbocations or carbanions.

Another characteristic of many radical reactions is that, once initiated, they often proceed with great rapidity owing to the establishment of fast chain reactions of low energy requirement, e.g. in the halogenation of alkanes (3, *cf.* p. 323):



(3)

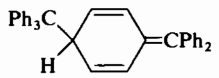
In this case, the radical obtained photochemically, a bromine atom Br·, generates another, R·, on reaction with the neutral substrate, R—H (3). This radical reacts in turn with a further neutral molecule, Br_2, generating Br· once again: the cycle thus proceeds without the need for further photochemical generation of Br·, i.e. it is self-perpetuating. It is also characteristic of such radical reactions that they can be inhibited by the introduction of substances that themselves react particularly readily with radicals (*inhibitors*, or radical 'scavengers'), e.g. phenols, quinones, diphenylamine, iodine, etc. These and similar substances can also be used to bring a radical reaction, already in progress, to a stop (*terminators*).

The first radicals to be studied were, hardly surprisingly, those that were somewhat less reactive, and thus capable of rather longer independent existence. The first such radical to be detected unequivocally was $Ph_3C\cdot$ (4), obtained in 1900 on reacting Ph_3CCl with finely divided silver (*cf.* p. 43). The radical reacted with halogens to reform the triphenylmethyl halide (5), or with oxygen from the air to form (6), a peroxide (all radicals react readily with O_2 from the air):

$$\underset{(4)}{Ph_3C\cdot} + X{-}X \rightarrow \underset{(5)}{Ph_3C{-}X} + X\cdot \xrightarrow{Ph_3C\cdot} \underset{(5)}{2Ph_3C{-}X}$$

$$\underset{(4)}{Ph_3C\cdot} + O_2 \rightarrow Ph_3COO\cdot \xrightarrow{Ph_3C\cdot} \underset{(6)}{Ph_3COOCPh_3}$$

The yellow radical (4) was in equilibrium in solution in inert solvents with a colourless dimer, the proportion of radical increasing on dilution, and with rise of temperature. Thus a dilute solution of the dimer in benzene contains ≈2% of $Ph_3C\cdot$ at 20° and ≈10% at 80°; on removal of the solvent only the dimer was obtained. This was, not unnaturally, assumed to be hexaphenylethane, $Ph_3C{-}CPh_3$, and, as mentioned previously (p. 44), it was only 70 years later that the dimer was shown (by proton n.m.r. spectroscopy) not to be this, but to have the structure (7):



(7)

Hexaphenylethane has not, indeed, ever been prepared, and may well be not capable of existing under normal conditions due to the enormous steric crowding that would be present. The reasons for the relatively high stability of $Ph_3C\cdot$ are discussed below (p. 311).

Simple alkyl radicals are very much more reactive, and were first studied systematically only in 1929. The radicals were generated by the thermal decomposition of organometallic compounds, such as $PbMe_4$,

$$PbMe_4 \rightleftarrows Pb + 4Me\cdot$$

and conveyed along a glass tube in a stream of an inert carrier gas, e.g. nitrogen. It was found that thin lead mirrors deposited at various distances along the inner wall of the tube were attacked by the stream of radicals. By measurements of how far along the tube mirrors continued to be attacked, coupled with a known rate of flow of carrier gas, it was possible to make accurate estimates of the half-life of alkyl radicals; for Me this was found to be 8×10^{-3} sec. The fate of such alkyl radicals, in the absence of metal mirrors to attack, is very largely dimerisation:

$$CH_3\cdot + \cdot CH_3 \rightarrow CH_3{-}CH_3$$

Once recognised in this way, alkyl radicals were invoked as intermediates in a number of reactions (see below).

Radicals, of varying degrees of stability, involving atoms other than carbon—*heteroradicals*—were also recognised. Thus it was discovered in 1911 that on warming N,N,N′,N′-tetraarylhydrazines, e.g. (8), in non-polar solvents resulted in the development of a green colour due to the radical (9):

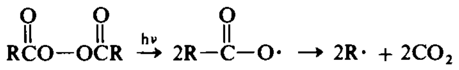
$$2Ph_2NH \xrightarrow{MnO_4^{\ominus}} \underset{(8)}{Ph_2N{-}NPh_2} \rightleftarrows \underset{(9)}{Ph_2N\cdot + \cdot NPh_2}$$

Another nitrogen radical, of considerable importance, is 1,1-diphenyl-2-picrylhydrazyl (10) obtained by PbO_2 oxidation of the triaryle.g. azoalkanes (21),

$$R{-}N{=}N{-}R \xrightarrow{h\nu} R\cdot + N{\equiv}N + \cdot R$$

(21)

and (*b*) energy at only one particular level is transferred to a molecule, so that it is a more specific method of effecting homolysis than is pyrolysis. Thus the cleavage of diacyl peroxides, e.g. (22), occurs cleanly on photolysis,



$$R\overset{O}{\overset{\|}{C}}O{-}O\overset{O}{\overset{\|}{C}}R \xrightarrow{h\nu} 2R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot \longrightarrow 2R\cdot + 2CO_2$$

(22)

whereas in a number of cases thermolysis gives rise to other side reactions.

A very interesting technique for radical generation is *flash photolysis*, which employs a very intense pulse of radiation (visible or u.v.) of very short duration. This produces a very high immediate concentration of radicals, which may be detected—and whose fate may be followed—by spectroscopy through one or more subsequent pulses of lower intensity radiation of suitable wavelength. This is, of course, primarily a technique for the study of radicals rather than for their use in preparative procedures. Radicals may also be generated, in suitable cases, by irradiation of neutral molecules with X-rays or with γ-rays: *radiolysis*.

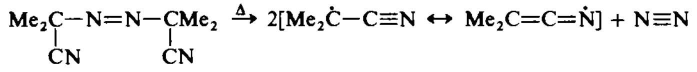
11.2.2 Thermolysis

Much of the early work on alkyl radicals of short life was, as we have seen (p. 301), carried out in the vapour phase through decomposition of metal alkyls, e.g. (23):

$$PbR_4 \rightleftarrows Pb + 4R\cdot$$

(23)

This stems from the weakness, i.e. ease of thermal fission, of the Pb—R bond, and radicals may be generated in solution in inert solvents, as well as in the vapour phase, through such thermolysis of weak enough bonds, e.g. those with a bond dissociation energy of < ≈165 kJ (40 kcal) mol^{-1}. Such bonds very often involve elements other than carbon, and the major sources of radicals in solution are the thermolysis of suitable peroxides (O$\nmid$O) and azo compounds (C$\nmid$N). Relatively vigorous conditions may, however, be necessary if the substrate does not contain substituents capable of stabilising the product radical, or promoting initial decomposition of the peroxide. Thus $(Me_3CCOO)_2$ has a half-life of ≈200 hr at 100°, while $(PhCOO)_2$ has one of only ≈0·5 hr at the same temperature. As was mentioned above, simple alkyl azo compounds, e.g. (21), are too stable to undergo thermolysis at reasonable temperatures, but can be made useful sources of radicals by the introduction of suitable substituents, e.g. (24):



$$\underset{CN}{\underset{|}{Me_2C}}{-}N{=}N{-}\underset{CN}{\underset{|}{CMe_2}} \xrightarrow{\Delta} 2[Me_2\dot{C}{-}C{\equiv}N \leftrightarrow Me_2C{=}C{=}\dot{N}] + N{\equiv}N$$

(24)

Thus MeN=NMe, despite the driving force supplied by N≡N as among the best of all leaving groups, is stable up to ≈200°, while (24) has a half-life of only ≈5 min at 100°.

In the absence of other species with which a radical can react (e.g. abstraction of H from a suitable solvent), their life is terminated largely by dimerisation,

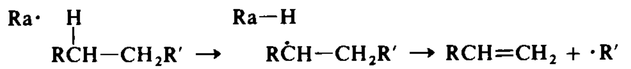
$$CH_3CH_2\cdot + \cdot CH_2CH_3 \longrightarrow CH_3CH_2{-}CH_2CH_3$$

but also by disproportionation:

$$CH_3CH_2\cdot + H{-}CH_2CH_2\cdot \longrightarrow CH_3CH_3 + CH_2{=}CH_2$$

The use of $PbEt_4$ as an anti-knock agent in petrol depends in part on the ability of the ethyl radicals, generated on its thermal decomposition, to combine with radicals produced in the over-rapid combustion of petroleum hydrocarbons; chain reactions which are building up to explosion (*knocking*) are thus terminated short of this. The complete details of how $PbEt_4$ operates are not known, but there is some evidence that minute PbO_2 particles derived from it can also act as 'chain-stoppers'.

Radical formation through carbon–carbon bond-fission is seen in the radical-induced 'cracking' at ≈600° of long-chain alkanes. The radicals introduced initially into the system probably act by abstracting a hydrogen atom from a CH_2 group of the chain; the resultant long chain, non-terminal radical (25) then undergoes fission β- to the radical carbon atom to yield a lower molecular weight alkene (26) plus a further radical (27) to maintain a chain reaction:



$$\overset{Ra\cdot\quad H}{\overset{|}{R\dot{}CH}}{-}CH_2R' \longrightarrow \overset{Ra{-}H}{R\dot{C}H{-}CH_2R'} \longrightarrow RCH{=}CH_2 + \cdot R'$$

(25) (26) (27)

Termination of the reaction by radical/radical interaction is unlikely to occur to any significant extent, until the concentration of long-chain alkane has dropped to a very low level.

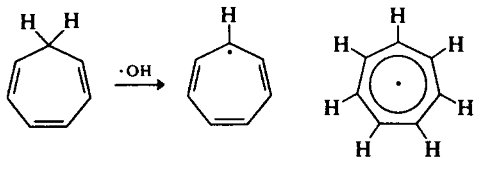
11.3 RADICAL DETECTION

We have already seen how the high chemical reactivity of short-lived radicals can be enlisted to aid in their detection through their ability to etch metal mirrors (p. 301). The fact that the transition of an unpaired electron between the energy levels of a radical involves less energy than the transition of the paired electrons in the stable parent molecule means that the radical tends to absorb at longer wavelength. A number of radicals are thus coloured—where their precursors are not—and may readily be detected in this way, e.g. (11, p. 302) and (15, p. 302). Radicals may also be detected by their rapid discharge of the colour of solutions containing species such as 1,1-diphenyl-2-picrylhydrazyl (11).

Another useful, and quite sensitive, test is the initiation of polymerisation (*cf.* p. 320). Polymerisation can be initiated, in suitable substrates, by cations and anions as well as by radicals, but the effect of these several species can be differentiated by using a 50/50 mixture of phenylethene (styrene), $PhCH{=}CH_2$, and methyl 2-methylpropenoate (methyl methacrylate), $CH_2{=}C(Me)CO_2Me$, as substrate: cationic initiators are found to produce polystyrene only, anions polymethyl methacrylate only, while radicals produce a copolymer containing equal amounts of the two monomers.

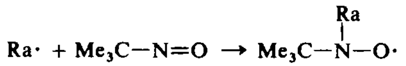
By far the most useful method for detecting radicals is, however, electron spin resonance (e.s.r.) spectroscopy, which utilises the permanent magnetic moment conferred on a radical by virtue of the spin of its unpaired electron (radicals are *paramagnetic*, species containing only electron pairs are *diamagnetic*). The electron spin can have one of two values ($+\frac{1}{2}$ or $-\frac{1}{2}$, *cf.* p. 2) and, in the presence of an applied magnetic field, these correspond to different energy levels; transitions are possible between them resulting in a characteristic, and detectable, absorption spectrum. E.s.r. spectroscopy of unpaired electrons is thus the analogue of n.m.r. spectroscopy of nuclei that have a permanent magnetic moment, e.g. ^1H, ^{13}C, etc.; hardly surprisingly, they occur in different energy ranges (an unpaired electron has a much larger magnetic moment than a proton—^1H—and more energy is required to reverse its spin).

In e.s.r. spectroscopy, interaction (‘*splitting*’) occurs between the unpaired electron and neighbouring magnetic nuclei—especially ^1H—leading to quite complex patterns of lines; analysis of these can provide a great deal of detailed information about the structure and shape of a radical. Thus hydrogen abstraction from cycloheptatriene (38) by $\cdot OH$ is found to lead to a radical having a very simple e.s.r. spectrum: eight equally spaced lines, indicating interaction of the unpaired electron with seven equivalent ^1H nuclei. The product radical thus cannot have the expected structure (39)—which would have a very much more complex e.s.r. spectrum—but must be the delocalised species (40, *cf.* p. 106):



(38) (39) (40)

Radicals have been detected by e.s.r. spectroscopy, under the best conditions, in concentrations as low as 10^{-8} M. Radicals to be studied may sometimes be generated (by irradiation) actually in the cavity of the spectrometer; failing that, they may be generated just outside, and a continuous flow technique then used to maintain a ‘standing’ concentration in the spectrometer cavity. A disadvantage of this method is that it requires relatively large volumes, and quantities of starting material. The longer the life of the radical the greater the chance of observing its spectrum; thus species such as $Ph_3C\cdot$ are easily observed, but species like $Ph\cdot$, $PhCH_2\cdot$, $C_2H_5\cdot$, etc., are a little more difficult. A technique that has been used to ‘prolong’ the life of short-lived species is to introduce a suitable diamagnetic substance, e.g. (41), which will react with the transient radical, and convert it into a longer-lived radical (42) that can be detected quite readily:



$$Ra\cdot + Me_3C{-}N{=}O \rightarrow Me_3C{-}\overset{\displaystyle Ra}{\overset{|}{N}}{-}O\cdot$$

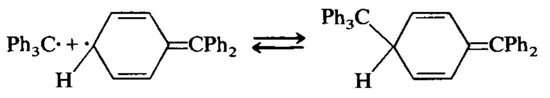
(41) (42)

This is known as ‘*spin trapping*’. Another technique, that has been used to study very short-lived radicals, is to generate them photolytically, from precursors, in a solid inert matrix, e.g. frozen argon. Their life is thus artificially prolonged because they are shielded from collision either with each other, or with other species that could terminate their existence.

Quite apart from such specific physical methods for the detection of radicals, it should be emphasised that more general indications that radical intermediates are involved in a particular reaction are provided by its high susceptibility to the addition of radical initiators (*cf.* p. 314) or inhibitors (*cf.* p. 300), and (compared with polar reactions) its relative insusceptibility to change of solvent.

11.4 RADICAL SHAPE AND STABILISATION

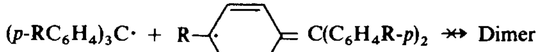
As with carbocations (p. 104) and carbanions (p. 276), the question arises of whether simple radicals—of the type $R_3C\cdot$—accommodate delocalisation) of the other:



(7)

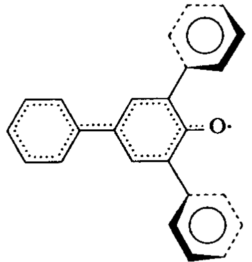
The benzene rings are forced out of the coplanar conformation by steric interaction of the *o*-H atoms of adjacent rings with each other; as would be expected, *o*-substituents bulkier than H are found to increase the out of plane dihedral angle of the aromatic nuclei—to 50° or more. Delocalisation must then be even further decreased, but such radicals with bulky *o*-substituents are nevertheless found to be more stable, i.e. more reluctant to form their dimers than is $Ph_3C\cdot$ itself. This must, of course, be due to a steric effect—the *o*-substituents are very close to the radical carbon atom and are thus capable of preventing its access to other species, or other species access to it [*cf.* (15), p. 302]. It is significant, in the light of what has been said above, that their effectiveness at 'masking' the radical carbon atom will increase the more the benzene rings are angled out of the coplanar conformation, i.e. the greater the dihedral angle.

If each aromatic nucleus in the radical has a bulky *p*-substituent, e.g. (50), then, irrespective of any substitution at the *o*-positions, dimerisation will be greatly inhibited, or even prevented [*cf.* (7), p. 301]:



(50*a*) (50*b*)

The hetero radicals that have already been referred to—(9, p. 301), (10, p. 302), (14, p. 302) and (15, p. 302)—owe their relative stability [with respect to their dimers—apart from 1,1-diphenyl-2-picrylhydrazyl (10)] to a variety of factors: (*a*) the relative weakness of N—N, S—S and O—O bonds, (*b*) the delocalisation through the agency of aromatic nuclei, and (*c*) steric inhibition of access to the atom with the unpaired electron, or to an aryl *p*-position, *cf.* (50). The latter factor bulks large (in addition to the weakness of O—O bonds) in the great stability of (15, *cf.* p. 302); and all three factors operate to stabilise (51), which is wholly dissociated in solution:



(51)

This radical has been shown, from calculations based on e.s.r. spectra, to have the *p*-phenyl group coplanar with the central phenoxy nucleus, but the two *o*-phenyl groups angled at 46° to it. The *p*-group can thus effect maximum delocalisation—(*b*)—and also act as a bulky group to inhibit dimerisation—(*c*), *cf.* (50) above, while the two angled *o*-substituents inhibit access to the O atom, preventing formation of an O—O dimer [dimerisation does occur in the solid state, but it is then through one *p*-position, *cf.* (7, p. 301)].

11.5 RADICAL REACTIONS

It is possible, and logical, to classify the multifarious reactions of radicals from the point of view of the radical itself: (*a*) unimolecular reactions, e.g. fragmentation, rearrangement; (*b*) bimolecular reactions between radicals, e.g. dimerisation, disproportionation; and (*c*) bimolecular reactions between radicals and molecules, e.g. addition, displacement, atom (often H) abstraction. Such a grouping has, for our purpose, the disadvantage of fitting much less well into the general classification of reaction types that has been adopted throughout. We shall therefore discuss the reactions in which radicals are involved, either as reactants or intermediates, under the general heads of addition, displacement and rearrangement.

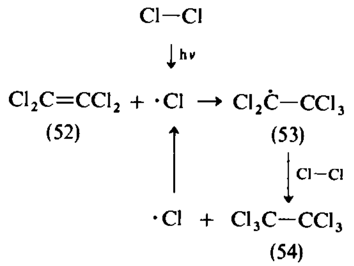
It is important to emphasise that in any reaction of a radical with a neutral molecule a further radical will be formed (*cf.* p. 309), thus establishing a chain reaction that does not require further input of initiator radicals to sustain it. Such a chain reaction is normally terminated by the relatively rare reaction of two radicals with each other (radicals are present in only very low ambient concentration) resulting in dimerisation or disproportionation (*cf.* p. 305), with no new radical now being produced.

11.5.1 Addition

Additions to C=C are almost certainly the most important group of reactions involving radicals. This is due largely to the importance of addition (vinyl) polymerisation (p. 320), and the consequent extent to which its mechanism has been investigated; but addition of halogens and of halogen hydracids is also of significance.

11.5.1.1 Halogens

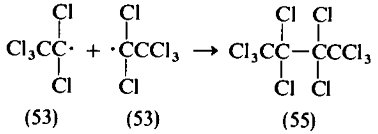
In addition to the polar mechanism already considered (p. 179), halogen addition to alkenes can proceed *via* radical intermediates. The former is favoured by polar solvents and by the presence of Lewis acid catalysts, the latter by non-polar solvents (or in the gas phase), by sunlight or u.v. irradiation, and by the addition of radical precursors (*initiators*) as catalysts. An example is the photochemically catalysed addition of chlorine to tetrachloroethene (52), which involves a chain reaction (*cf.* p. 300):



Each molecule of chlorine, on photochemical fission, will give rise to two chlorine atoms, i.e. radicals, each of which is capable of initiating a continuing reaction chain. That each quantum of energy absorbed does indeed lead to the initiation of two reaction chains is confirmed by the observation that:

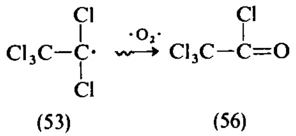
$$\text{Rate} \propto \sqrt{\text{Intensity of absorbed light}}$$

Chlorine atoms are electrophilic (the element is electronegative, and $Cl\cdot$ will readily take up an electron to complete its octet) and thus add readily to the double bond of (52) to yield the radical (53). This, in turn, can abstract a chlorine atom from a second molecule (the process can equally well be regarded as a radical displacement reaction on Cl—Cl) to yield the end-product of addition (54), plus a further atom of chlorine to continue the reaction chain, i.e. a very fast, continuing chain reaction is set up by each chlorine atom initiator generated photochemically. Each quantum of energy absorbed is found to lead to the conversion of several thousand molecules of (52) into (54); the reaction chains are, in this case, said to be long. Until the later stages of the reaction, when nearly all of (52) and Cl_2 have been used up, the concentrations of (53) and of $Cl\cdot$ will be very small compared with those of the starting materials; collision of a radical with a molecule will thus be very much more frequent than collision of a radical with another radical. Chain termination will ultimately take place through radical/radical collision, however, and this is generally found to involve (53) + (53) ⟶ (55):



The reaction is found to be inhibited by the presence of oxygen;

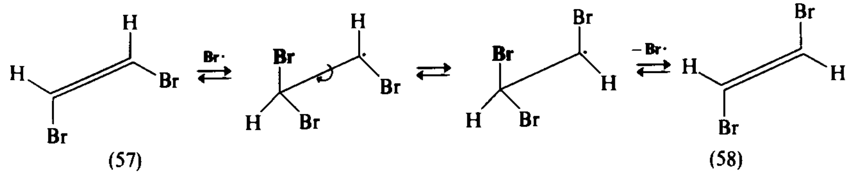
this is because the molecule of oxygen has two unpaired electrons, and behaves as a diradical (*cf.* p. 337), $\cdot O—O\cdot$, albeit a not very reactive one. It can, however, combine with the highly reactive radical intermediates in the above addition, converting them into the very much less reactive peroxy radicals, $RaO—O\cdot$, which are unable to carry on the chain: it is thus a highly efficient inhibitor. That oxygen is reacting largely with the pentachloroethyl radicals (53) is shown by the formation of (56),



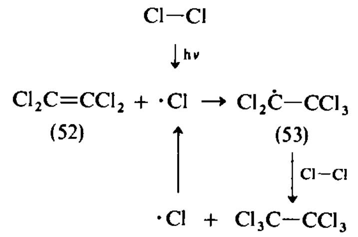
when the normal addition reaction is inhibited by oxygen.

The reactivity sequence for homolytic addition of the different halogens to alkenes is, hardly surprisingly, the same as that for electrophilic addition, i.e. $F_2 > Cl_2 > Br_2 > I_2$. The addition of fluorine—not requiring photochemical or other activation—is too vigorous to be of much use, and side reactions are common. Chlorination is generally rapid, with long reaction chains, and not readily reversible except at temperatures >200°; as the temperature rises, however, there is an increasing tendency to hydrogen abstraction leading to overall substitution by chlorine—rather than addition—in suitable cases (*cf.* p. 325). Bromination occurs readily, but with somewhat shorter reaction chains, and is usually reversible, while iodination takes place with difficulty, if at all, and is very readily reversible. The effect of increasing alkyl substitution at the double bond carbon atoms is found to have relatively little effect on the rate of halogen addition, certainly a good deal less than for addition by the polar mechanism (p. 183). Halogen substitution, e.g. by Cl, on the double bond carbon atoms results in a decreased reaction rate, e.g. $Cl_2C{=}CCl_2$ adds chlorine much more slowly than $CH_2{=}CH_2$.

The reversibility of addition of Br_2 and I_2—particularly the latter—has been made use of in the isomerisation (of the less to the more stable) of a pair of doubly bonded geometrical isomerides: in simple cases the *cis* to the *trans* e.g. (57) ⟶ (58). This may be carried out by u.v. irridation in the presence of catalytic quantities of Br_2 or I_2:



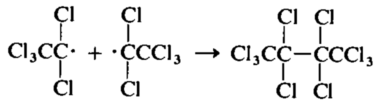
Normally, of course, an equilibrium mixture will be produced with the more stable form preponderating. That the interconversion does by sunlight or u.v. irradiation, and by the addition of radical precursors (*initiators*) as catalysts. An example is the photochemically catalysed addition of chlorine to tetrachloroethene (52), which involves a chain reaction (*cf.* p. 300):



Each molecule of chlorine, on photochemical fission, will give rise to two chlorine atoms, i.e. radicals, each of which is capable of initiating a continuing reaction chain. That each quantum of energy absorbed does indeed lead to the initiation of two reaction chains is confirmed by the observation that:

$$\text{Rate} \propto \sqrt{\text{Intensity of absorbed light}}$$

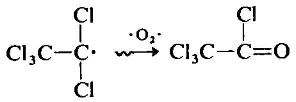
Chlorine atoms are electrophilic (the element is electronegative, and Cl· will readily take up an electron to complete its octet) and thus add readily to the double bond of (52) to yield the radical (53). This, in turn, can abstract a chlorine atom from a second molecule (the process can equally well be regarded as a radical displacement reaction on Cl—Cl) to yield the end-product of addition (54), plus a further atom of chlorine to continue the reaction chain, i.e. a very fast, continuing chain reaction is set up by each chlorine atom initiator generated photochemically. Each quantum of energy absorbed is found to lead to the conversion of several thousand molecules of (52) into (54); the reaction chains are, in this case, said to be long. Until the later stages of the reaction, when nearly all of (52) and Cl_2 have been used up, the concentrations of (53) and of Cl· will be very small compared with those of the starting materials; collision of a radical with a molecule will thus be very much more frequent than collision of a radical with another radical. Chain termination will ultimately take place through radical/radical collision, however, and this is generally found to involve (53) + (53) ⟶ (55):



$$Cl_3C\overset{Cl}{\underset{Cl}{C}}\cdot + \cdot\overset{Cl}{\underset{Cl}{C}}CCl_3 \rightarrow Cl_3C\overset{Cl}{\underset{Cl}{C}}{-}\overset{Cl}{\underset{Cl}{C}}CCl_3$$

(53) (53) (55)

The reaction is found to be inhibited by the presence of oxygen; this is because the molecule of oxygen has two unpaired electrons, and behaves as a diradical (*cf.* p. 337), ·O—O·, albeit a not very reactive one. It can, however, combine with the highly reactive radical intermediates in the above addition, converting them into the very much less reactive peroxy radicals, RaO—O·, which are unable to carry on the chain: it is thus a highly efficient inhibitor. That oxygen is reacting largely with the pentachloroethyl radicals (53) is shown by the formation of (56),



$$Cl_3C{-}\overset{Cl}{\underset{Cl}{C}}\cdot \xrightarrow{\cdot O_2\cdot} Cl_3C{-}\overset{Cl}{C}{=}O$$

(53) (56)

when the normal addition reaction is inhibited by oxygen.

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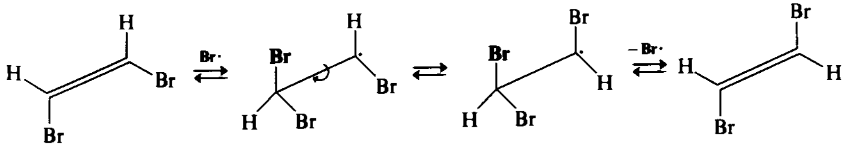
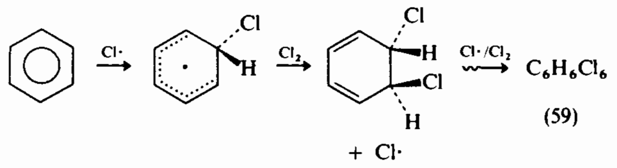


(57) (58)

Normally, of course, an equilibrium mixture will be produced with the more stable form preponderating. That the interconversion does proceed, as above, *via* addition and elimination of Br· has been shown by using radioactive Br_2 as catalyst: both (58) and (57), in the equilibrium mixture obtained, are then found to contain radioactive Br.

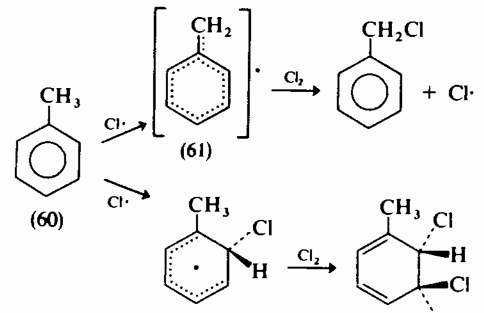
The addition of chlorine or bromine to benzene—one of the few overall addition reactions of a simple benzene nucleus—has also been shown to proceed *via* a radical pathway, i.e. it is catalysed by light and by the addition of peroxides, and is slowed or prevented by the usual inhibitors. With chlorine this presumably proceeds;



(59)

the product is a mixture of several of the eight possible geometrical isomerides of hexachlorocyclohexane (59). In the absence of light or peroxides no reaction takes place, while in the presence of Lewis acids overall electrophilic substitution takes place by an addition/elimination pathway (p. 138). With radicals other than Cl·, e.g. Ph·, overall homolytic substitution can be made to take place on benzene by an addition/elimination pathway too (p. 331).

Radical attack on methylbenzene (toluene, 60) results in preferential hydrogen abstraction by Cl· leading to overall substitution in the CH_3 group, rather than addition to the nucleus. This reflects the greater stability of the first formed (delocalised) benzyl radical, $PhCH_2$· (61), rather than the hexadienyl radical (62), in which the aromatic stabilisation of the starting material has been lost:



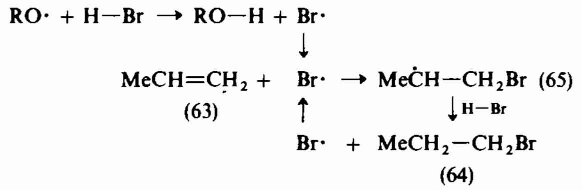
(60)

(61)

(62)

11.5.1.2 Hydrogen bromide

The addition of HBr to propene, MeCH=CH_2 (63), under polar conditions to yield 2-bromopropane, has already been referred to (p. 184). In the presence of peroxides (or under other conditions that promote radical formation), however, the addition proceeds *via* a rapid chain reaction to yield 1-bromopropane (64); this is generally referred to as the *peroxide effect* leading to anti-Markownikov addition. This difference in orientation of HBr addition is due to the fact that in the first (polar) case it is initiated by $H^{\oplus}$ and proceeds *via* the more stable (secondary) carbocation, while in the second (radical) case it is initiated by Br· and proceeds *via* the more stable (secondary) radical (65):



$$\begin{tikzcd}[column sep=small]
& \text{RO}\cdot + \text{H—Br} \arrow[r] & \text{RO—H} + \text{Br}\cdot \arrow[d] & \\
& \underset{(63)}{\text{MeCH=CH}_2} + & \text{Br}\cdot \arrow[r] & \text{Me}\dot{\text{C}}\text{H—CH}_2\text{Br}\ (65) \arrow[d, "\text{H—Br}"] \\
& & \text{Br}\cdot \arrow[u] & + \underset{(64)}{\text{MeCH}_2\text{—CH}_2\text{Br}}
\end{tikzcd}$$

The initiation is by Br·, as hydrogen abstraction by RO· from HBr (as above) is energetically much more favourable than the alternative of bromine abstraction to form ROBr + H·. The alternative addition of Br· to (63) to form MeCH(Br)CH_2· (66) does not occur, as secondary radicals, e.g. (65), are more stable (*cf.* p. 310) than primary, e.g. (66).

HBr is the only one of the four hydrogen halides that will add readily to alkenes *via* a radical pathway. The reason for this is reflected in the ΔH values—in kJ (kcal) mol^{-1}—below for the two steps of the chain reaction for addition of HX to CH_2=CH_2, for example:

	(1) X· + CH_2=CH_2		(2) XCH_2CH_2· + HX	
H—F	−188	(−45)	+155	(+37)
H—Cl	−109	(−26)	+21	(+5)
H—Br	−21	(−5)	−46	(−11)
H—I	+29	(+7)	−113	(−27)

Only for HBr are both chain steps exothermic; for HF the second step is highly endothermic, reflecting the strength of the H—F bond and the difficulty of breaking it; for HCl it is again the second step that is endothermic, though not to so great an extent; while for HI it is the first step that is endothermic, reflecting the fact that the energy gained in forming the weak I—C bond is not as great as that lost in breaking the C=C double bond. Thus a few radical additions of HCl are known, but the reactions are not very rapid, and the reaction chains are short at ordinary temperatures.

Even with HBr addition the reaction chains tend to be rather short—much shorter than those in halogen addition—and more than a trace of peroxide is thus needed to provide sufficient initiator radicals: for preparative purposes up to 0·01 mol peroxide per mol of alkene. In practical terms, however, there may already be sufficient peroxide thereby terminating the chain but generating a new radical, X·, in the process, that is capable of initiating a new chain (77) from monomer. Thiols, RSH, are often used:

$$\mathrm{Ra(CH_2)_nCH_2\cdot + RSH \longrightarrow Ra(CH_2)_nCH_3 + RS\cdot \xrightarrow{n\mathrm{CH_2{=}CH_2}} RS(CH_2)_{2n}\cdot}$$

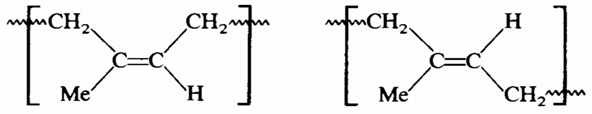
(77)

A new growing chain is thus generated without slowing down the overall process of monomer conversion. In the case of terminators, XH is chosen so that X· is not reactive enough to initiate a new chain from monomer.

Radical-induced polymerisation of simple alkenes, e.g. ethene and propene, requires vigorous conditions including very high pressure, but many other alkene monomers carrying substituents polymerise readily. These include $CH_2{=}CHCl$ → polyvinyl chloride (p.v.c.) for making pipes, etc., $CH_2{=}CMeCO_2Me$ → perspex, $PhCH{=}CH_2$ → polystyrene, the expanded form for insulation, etc., and $CF_2{=}CF_2$ → teflon, which has an extremely low coefficient of friction, high chemical inertness and high m.p. (lining of frying pans, etc.). The properties of a polymer may be varied even further—almost as required—by the *copolymerisation* of two different monomers so that both are incorporated, equally or in other proportions, in the polymer molecules; thus most of the synthetic rubbers are styrene/butadiene copolymers. Reference has already been made (p. 308) to the analytical use of 50:50 copolymerisation of $PhCH{=}CH_2$ and $CH_2{=}CMeCO_2Me$ to distinguish radical-induced polymerisation from that initiated by anions or cations (*cf.* p. 188).

Radical-induced polymerisation has some drawbacks, however; thus branching induced by H-abstraction from the growing chain has already been referred to (p. 321). Another difficulty arises with monomers of the form $CH_2{=}CHX$ (i.e. with all the common monomers except $CH_2{=}CH_2$ and $CF_2{=}CF_2$) over the orientation of the substituent groups, X, with respect to the 'backbone' alkane chain of polymer molecules, whose conformation is 'frozen' in the final rigid solid. In radical polymerisation, the arrangement of the X groups is random, and such *atactic* polymers, e.g. atactic polypropene, are found to be non-crystalline, low density, low melting, and mechanically weak. It has been found, however, that use of a $TiCl_3{\cdot}AlEt_3$ catalyst results not only in polymerisation occurring under very mild conditions, but with, for example, propene, the resultant polymer has all the Me groups oriented, regularly, in the same direction. This *isotactic* polypropene is found to be crystalline, high density (closer packing of chains), high melting, and mechanically strong—all desirable qualities—and branching has been largely avoided. This regular, *coordination* polymerisation is believed to result from groups of atoms in the surface of the heterogeneous catalyst acting as a template, so that each successive monomer molecule can be added to the growing polymer chain only through 'coordination', in one particular orientation, at the catalyst surface.

When the monomers are conjugated dienes, e.g. buta-1,3-diene, $CH_2{=}CH{-}CH{=}CH_2$, or 2-methylbuta-1,3-diene (isoprene), $CH_2{=}C(Me){-}CH{=}CH_2$, the polymer chain obtained from normal (1,4-, *cf.* p. 195) addition polymerisation will still contain one carbon–carbon double bond per monomer unit. The resulting residual reactivity allows of chemical *cross-linking* from one polymer chain to another, e.g. the formation of S—S 'bridges' between the polymer chains by reaction with sulphur in the vulcanisation of rubber. A relatively low degree of cross-linking is found to impart elastic properties to the polymer aggregate, while carrying it further yields a rigid structure through extensive cross-linking in three dimensions. A stereochemical point also arises, in that the relative orientation of the parts of the polymer molecule on each side of a double bond in the chain can be either *cis* or *trans* to each other, e.g. with polyisoprene:



cis *trans*

We might well expect this differing stereochemistry to have a marked effect on the properties of the polymer, and this is borne out by the two naturally occurring polyisoprenes, natural rubber and gutta percha. The former, which before vulcanisation is soft and tacky, has all *cis* junctions in its chains; while the latter, which is hard and brittle, has all *trans* junctions.

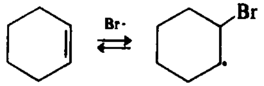
11.5.2 Substitution

Although most of the reactions to be considered under this head are net, i.e. overall, displacements or substitutions, this is not commonly achieved directly, *cf.* S_N2. In some cases a radical is obtained from the substrate by abstraction (usually of H), and this radical then effects displacement on, or addition to, a further species. In some cases, however, the net displacement is achieved by addition/abstraction.

11.5.2.1 Halogenation

Alkanes are attacked extremely readily by halogens, provided the conditions allow the formation of radicals. This is in marked contrast to their extreme resistance to attack by electrophiles or nucleophiles, which stems from the very low polarity of the C—H bond

Control of the bromine concentration is maintained by reaction (*c*) which is fast, though ionic, but can be activated only by HBr produced in the chain reaction (*b*). The alternative reaction of addition of Br· to the double bond to form (89) is reversible,



(86) (89)

while formation of (87) is not; overall substitution is thus favoured over addition so long as $[Br_2]$ is kept low. The radical (87) is also stabilised by delocalisation, while (89) is not (*cf.* p. 311). Support for the above interpretation of the reaction of NBS is provided: (i) by the fact that NBS shows exactly the same selectivity ratios as does Br_2, and (ii) by the fact that cyclohexene (86) is found to undergo largely addition with high concentrations of bromine, but largely allylic substitution with low (it is necessary to remove the HBr produced—as happens with NBS).

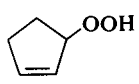
11.5.2.2 Autoxidation

Autoxidation is the low temperature oxidation of organic compounds by O_2, involving a radical chain reaction; as opposed to combustion which happens only at higher temperature. The initial stage is commonly the formation of hydroperoxides, RH → ROOH, so it is a net, overall displacement, though the actual pathway involves H-abstraction and O_2 addition (see below). The first-formed hydroperoxides frequently undergo further reactions. Autoxidation is of importance in the hardening of paints, where unsaturated esters in the oils used form hydroperoxides, whose decomposition to RO· initiates polymerisation in further unsaturated molecules to form a protective, polymeric, surface film. But autoxidation is also responsible for deleterious changes, particularly in materials containing unsaturated linkages, e.g. rancidity in fats, and perishing of rubber. Indeed, the gradual decomposition of most organic compounds exposed to air and sunlight is due to photosensitised autoxidation. Autoxidation may be initiated by trace metal ions (*cf.* below), as well as by light and the usual radical initiators.

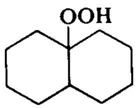
The main reaction pathway is a two-step chain involving H-abstraction:

$$\begin{tikzcd}
\mathrm{Ra}\cdot + \mathrm{H{-}R} \arrow[r] & \mathrm{Ra{-}H} + \mathrm{R}\cdot \arrow[r, "\cdot O_2 \cdot"] & \mathrm{RO{-}O}\cdot \arrow[d, "\mathrm{R{-}H}"] & (91) \\
 & \mathrm{R}\cdot \arrow[u] & + \ \mathrm{RO{-}OH} & (90)
\end{tikzcd}$$

Under certain conditions the hydroperoxide (90) itself breaks down to radicals, RO· + ·OH which can act as initiators, and the autoxidation then becomes autocatalytic. The addition of O_2 to R· is very fast, often diffusion-controlled, but the peroxy radicals (91) are usually of relatively low reactivity (*cf.* ·O—O· itself, p. 315), and are thus highly selective in the positions from which they will abstract H. Thus allylic and benzylic C—H are relatively readily attacked, because the C—H bonds are slightly weaker and the resultant radicals stabilised by delocalisation, e.g. the allylic position in cyclopentene to form (92). In simple alkanes only tertiary ⋟C—H is generally attacked, e.g. as in decalin, which yields the bridgehead peroxide (93):



(92)

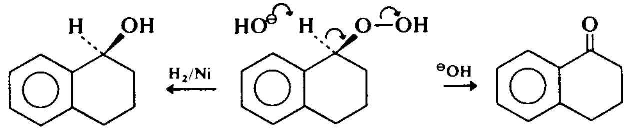


(93)

Relative reactivities towards H-abstraction by $RO_2\cdot$ at 30° are observed as follows: $PhC\underline{H}_3$:1, $Ph_2C\underline{H}_2$:30, and $PhC\underline{H}_2CH{=}CH_2$:63.

With alkenes, rather than alkanes, autoxidation can involve addition of $RO_2\cdot$ to the double bond as well as, or in place of, H-abstraction, particularly where there are no allylic, benzylic or tertiary C—H linkages available. The effect of the presence of such peroxides in alkenes on the orientation of HBr addition to the latter has already been referred to (p. 317). Ethers are particularly prone to autoxidation, initial attack taking place at a C—H linkage α- to the oxygen atom to yield a stabilised radical; the first-formed hydroperoxide reacts further to yield dialkyl peroxides that are highly explosive on heating—not to be forgotten on evaporating ethereal solutions to dryness! Accumulated peroxides, in ether that has been standing, may be safely decomposed before its use by washing with a solution of a reducing agent, e.g. $FeSO_4$.

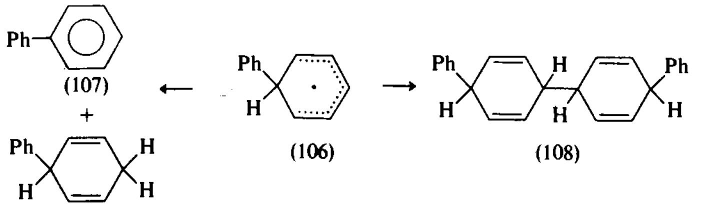
Autoxidation may in some cases be of preparative use; thus reference has already been made to the large-scale production of phenol + acetone by the acid-catalysed rearrangement of the hydroperoxide from 2-phenylpropane (cumene, p. 128). Another example involves the hydroperoxide (94) obtained by the air oxidation at 70° of tetrahydronaphthalene (tetralin); the action of base then yields the ketone (α-tetralone, 95), and reductive fission of the O—O linkage the alcohol (α-tetralol, 96):



(96) (94) (95)

further radical, Ra·, to abstract H·. Reaction between two radicals—(106) and the H-abstractor—is likely to be fast, i.e. non rate-limiting, and no significant k_H/k_D kinetic isotope effect is observed, i.e. attack of Ra· on the original aromatic substrate is rate-limiting. Overall substitution reactions have been investigated in which Ra· is Ar· (especially Ph·), $PhCO_2$· (and some RCO_2·), R· and HO·. Attack by HO·, *hydroxylation*, is of particular importance in biological systems: as the first step in the detoxification of 'foreign' aromatic molecules. There are also a few reactions known in which it is an atom or group other than H, e.g. halogen, MeO, that is displaced. It is, however, the displacement of H by Ar·—*arylation*—that has been studied in by far the greatest detail.

Attack of, for example, Ph· on aromatic species such as benzene is found to lead to products other than the one arising from overall substitution (107, Ra = Ph). This is because the intermediate radical (106), as well as undergoing H-abstraction to (107), can also dimerise to (108) and/or disproportionate to (107) + (109):



For simplicity's sake only the products of *p*-interaction in (106) have been shown above: *o*-interaction can also lead to an *o*-dihydro isomer of (109), and to both *o*-/*o*- and *o*-/*p*-coupled isomers of (108). Product mixtures from arylation of aromatic species can thus be quite complex.

So far as the overall substitution reaction (⟶107) is concerned, marked differences from electrophilic and nucleophilic attack become apparent as soon as the behaviour of substituted benzene derivatives (C_6H_5Y) is considered. Thus homolytic attack on C_6H_5Y is found to be faster than on C_6H_6, no matter whether Y is electron-attracting or -withdrawing, as shown by the relative rate data for attack by Ph·:

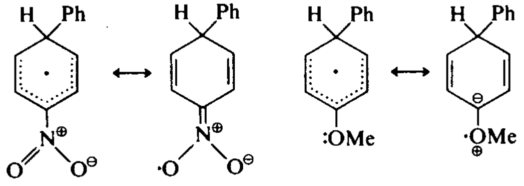
Y:	H	OMe	Br	Me	CN	NO_2	Ph
k_{rel}:	1·0	1·2	1·8	1·9	3·7	4·0	4·0

The very small spread in relative rate, as Y is varied, is in marked contrast to electrophilic substitution, e.g. nitration, on the same substrates where the spread in relative rate would have been $\approx 10^8$. Though it should be remembered that phenylation involves attack by a species of low polarity.

It is also found, as shown by the partial rate factors (*cf.* p. 156),

PhY	f_{o-}	f_{m-}	f_{p-}
PhOMe	5·60	1·23	2·31
$PhNO_2$	5·50	0·86	4·90
PhMe	4·70	1·24	3·55
PhCl	3·90	1·65	2·12
PhBr	3·05	1·70	1·92
$PhCMe_3$	0·70	1·64	1·81

that, irrespective of the nature of Y, the observed preference for position of attack by Ph· is *o*->*p*->*m*- except, as with Y = Me_3C, where the steric effect of Y may impede *o*-attack. This preference for *o*- and *p*-attack can be rationalised on the basis that the electron, brought by the attacking Ph· radical to the intermediate (106), can be delocalised (and the intermediate thereby stabilised) by *either* an electron-withdrawing (110), *or* an electron-donating (111), substituent—as shown here for attack at the *p*-position:

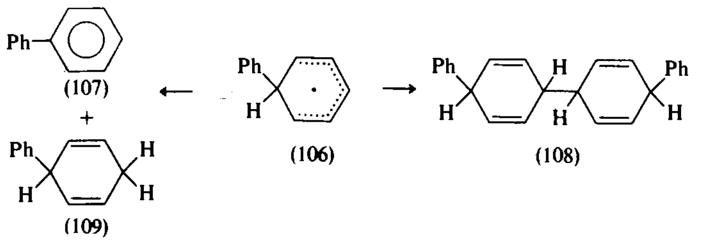


(110*a*) (110*b*) (111*a*) (111*b*)

There is, however, no very satisfactory explanation of why such *m*-attack as does take place on C_6H_5Y should also be faster than attack on C_6H_6; or of why attack on the *o*-position in C_6H_5Y is commonly faster than attack on the *p*-position. The relatively small spread of the partial rate factors for a particular C_6H_5Y means that homolytic aromatic substitution normally leads to a more complex mixture of products than does electrophilic attack on the same species.

The above data all refer to phenylation by Ph· derived from $(PhCO_2)_2$. This, and other, diacylperoxides have been much used for this purpose, but as the Ph· formation involves the step, $PhCO_2\cdot \rightarrow Ph\cdot + CO_2$, it is usually impossible to stop some formation of esters either by Ph· + $PhCO_2$· or, more commonly, by attack of $PhCO_2$· on the aromatic substrate (*acyloxylation*). This particular difficulty may be avoided by generating Ar· from the thermal decomposition of N-nitroso derivatives of acetylated aromatic amines, ArN(NO)COMe, or of diazonium salts, $ArN_2^{\oplus}$, under slightly basic conditions—the latter is the Gomberg reaction for the synthesis of unsymmetrical diaryls, Ar—Ar′. In each case the Ar· precursor is decomposed in the presence of an excess of the aromatic substrate, which is in fact often used as the solvent. The yield from the classical Gomberg reaction may be much improved by diazotising further radical, Ra·, to abstract H·. Reaction between two radicals—(106) and the H-abstractor—is likely to be fast, i.e. non rate-limiting, and no significant k_H/k_D kinetic isotope effect is observed, i.e. attack of Ra· on the original aromatic substrate is rate-limiting. Overall substitution reactions have been investigated in which Ra· is Ar· (especially Ph·), $PhCO_2$· (and some RCO_2·), R· and HO·. Attack by HO·, *hydroxylation*, is of particular importance in biological systems: as the first step in the detoxification of 'foreign' aromatic molecules. There are also a few reactions known in which it is an atom or group other than H, e.g. halogen, MeO, that is displaced. It is, however, the displacement of H by Ar·—*arylation*—that has been studied in by far the greatest detail.

Attack of, for example, Ph· on aromatic species such as benzene is found to lead to products other than the one arising from overall substitution (107, Ra = Ph). This is because the intermediate radical (106), as well as undergoing H-abstraction to (107), can also dimerise to (108) and/or disproportionate to (107) + (109):



For simplicity's sake only the products of *p*-interaction in (106) have been shown above: *o*-interaction can also lead to an *o*-dihydro isomer of (109), and to both *o*-/*o*- and *o*-/*p*-coupled isomers of (108). Product mixtures from arylation of aromatic species can thus be quite complex.

So far as the overall substitution reaction (→107) is concerned, marked differences from electrophilic and nucleophilic attack become apparent as soon as the behaviour of substituted benzene derivatives (C_6H_5Y) is considered. Thus homolytic attack on C_6H_5Y is found to be faster than on C_6H_6, no matter whether Y is electron-attracting or -withdrawing, as shown by the relative rate data for attack by Ph·:

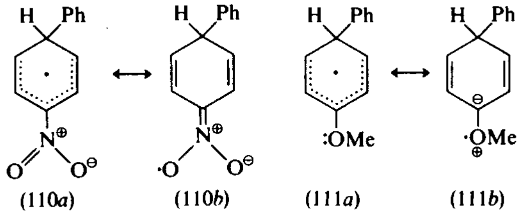
Y:	H	OMe	Br	Me	CN	NO_2	Ph
k_{rel}:	1·0	1·2	1·8	1·9	3·7	4·0	4·0

The very small spread in relative rate, as Y is varied, is in marked contrast to electrophilic substitution, e.g. nitration, on the same substrates where the spread in relative rate would have been $\approx 10^8$. Though it should be remembered that phenylation involves attack by a species of low polarity.

It is also found, as shown by the partial rate factors (*cf.* p. 156),

PhY	f_{o-}	f_{m-}	f_{p-}
PhOMe	5·60	1·23	2·31
$PhNO_2$	5·50	0·86	4·90
PhMe	4·70	1·24	3·55
PhCl	3·90	1·65	2·12
PhBr	3·05	1·70	1·92
$PhCMe_3$	0·70	1·64	1·81

that, irrespective of the nature of Y, the observed preference for position of attack by Ph· is *o*- > *p*- > *m*- except, as with Y = Me_3C, where the steric effect of Y may impede *o*-attack. This preference for *o*- and *p*-attack can be rationalised on the basis that the electron, brought by the attacking Ph· radical to the intermediate (106), can be delocalised (and the intermediate thereby stabilised) by *either* an electron-withdrawing (110), *or* an electron-donating (111), substituent—as shown here for attack at the *p*-position:



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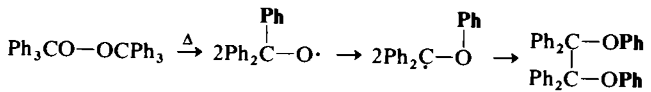
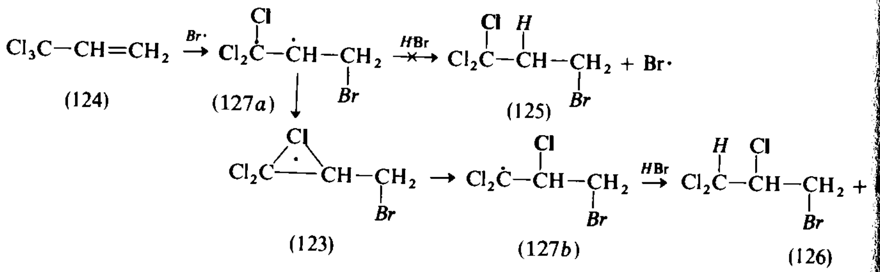
The rearranged radical (119) is more stable than the original one (117) not only because the former is tertiary and the latter primary, but also because (119) is stabilised by delocalisation of the unpaired electron over the π orbital system of a benzene nucleus. It is significant that only Ph migrates in (117), despite the fact that migration of Me would yield the even more stabilised radical, $Ph_2\dot{C}CH_2Me$; this reflects the energetic advantage of migration *via* a bridged, delocalised T.S. such as (114). When no Ph group is present, as in $EtMe_2CCH_2\cdot$ from $EtMe_2CCH_2CHO$, no migration takes place at all and the end-product is $EtMe_2CCH_3$.

Aryl migrations are not confined to carbon/carbon rearrangements, as is seen in the behaviour of $(Ph_3CO)_2$ (120, *cf.* p. 300) on heating:

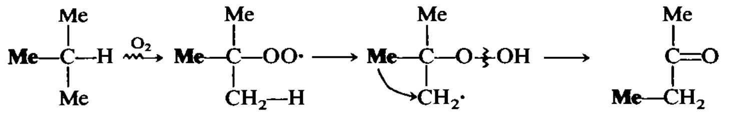

(120) (121) (122)

This too proceeds *via* a bridged T.S.; again the driving force of the rearrangement is the much greater stability of (122) than (121). As well as 1,2-aryl shifts, similar migrations of vinyl, acyl and acyloxy groups are known, occurring *via* bridged transition states or intermediates, and also 1,2-chlorine shifts in which an empty *d* orbital on the halogen atom is used to accommodate the unpaired electron in a bridged intermediate, e.g. (123). Thus photo-catalysed addition of HBr to $CCl_3CH{=}CH_2$ (124) yields none of the expected $CCl_3CH_2CH_2Br$ (125), but 100% of $CHCl_2CHClCH_2Br$ (126):



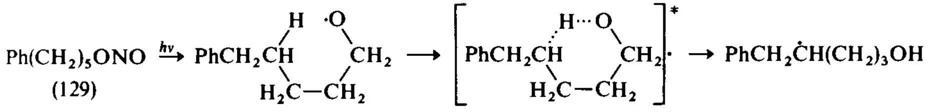
The driving force of the reaction is the formation of a more stable radical, i.e. the unpaired electron is delocalised more effectively by Cl in (127*b*) than by H in (127*a*). Migration of fluorine does not occur as its *d* orbitals are not accessible, and migration of Br only rarely as the intermediate radicals undergo elimination (to alkene) more readily than rearrangement.

While no 1,2-alkyl shifts have been observed in solution, the 'cool flame' oxidation of Me_3CH (in the gas phase at 480°) is found to yield considerable quantities of $MeCH_2COMe$:


(128)

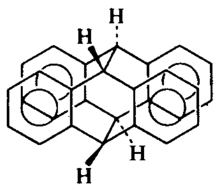
The formation of this ketone is believed to proceed *via* internal abstraction of H in the initial peroxy radical (128; *cf.* p. 328), followed by migration of **Me**·. It may be that the vigorous conditions employed now make a 1,2-alkyl shift feasible, or that the shift of **Me**· may involve fragmentation followed by re-addition, rather than direct migration.

Radical migration of hydrogen is also known, though only over longer distances than 1,2-shifts, e.g. a 1,5-shift to oxygen *via* a 6-membered cyclic T.S. in the photolysis of the nitrite ester (129)—an example of the Barton reaction:



11.6 BIRADICALS

The oxygen molecule, a paramagnetic species with an unpaired electron on each atom, has already been referred to as biradical, albeit an unreactive one. The photochemical excitation of an anthracene to a biradical, or to something rather like one, has also been mentioned (p. 331); if this excitation is carried out in the absence of air or oxygen, instead of the trans-annular peroxide—(104)—a photo-dimer (130) is obtained:


(130)

Biradicals have also been encountered as intermediates in the Mg reduction of ketones to pinacols (p. 218) and, as radical anions, in the acyloin condensation of esters (p. 218). The thermolysis of cyclopropane (131) to propene (132) at ≈500° is also believed to involve intermediate, will be determined by the relative magnitude of $\Delta G^{\ddagger}$ (*cf.* p. 38) for the former compared with that of $\Delta G^{\ddagger}$ for the rate-limiting step of the latter. $\Delta G^{\ddagger}$ is, of course, the resultant of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ terms; it is found in practice that concerted reactions tend to have large −ve values of $\Delta S^{\ddagger}$ and small +ve values of $\Delta H^{\ddagger}$. The former reflects the degree of ordering—of participant molecules or groups—required by a cyclic T.S.; while the latter reflects the extent to which energy derived from bond-formation in the T.S. can assist in necessary bond-breaking. It should, however, be stressed that observation of high −ve $\Delta S^{\ddagger}$, and low +ve $\Delta H^{\ddagger}$, values for a particular reaction cannot necessarily be taken as *establishing* that it proceeds *via* a concerted pathway.

So far as $\Delta H^{\ddagger}$ is concerned, it would seem reasonable to suppose that the favoured pathway for a particular reaction would be that one in which the greatest degree of residual bonding is maintained in the T.S. Maintenance of bonding implies maintenance of orbital overlap, and it is therefore necessary to establish the conditions that ensure the maintenance of such overlap. To do this we have to consider a property of atomic and molecular orbitals not yet referred to, namely *phase*.

12.2 PHASE AND SYMMETRY OF ORBITALS

We have already seen (p. 2) that the individual electrons of an atom can be symbolised by wave functions, ψ, and some physical analogy can be drawn between the behaviour of such a 'wave-like' electron and the standing waves that can be generated in a string fastened at both ends—the 'electron in a (one-dimensional) box' analogy. The first three possible modes of vibration will thus be (Fig. 12.1):

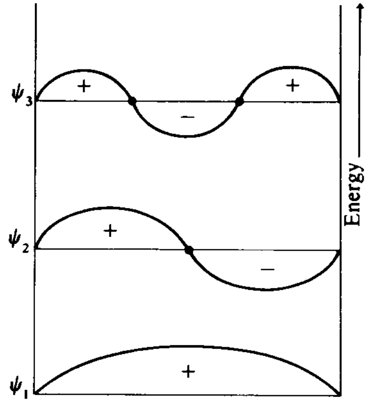
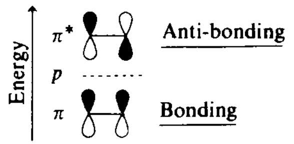


Fig. 12.1

In the first mode, ψ_1, the amplitude of the wave increases from zero to a maximum, and then decreases to zero again; in the second, ψ_2, the amplitude increases to a maximum, decreases through zero (a *node*, marked ● above) to a minimum, and then back to zero again, i.e. the *phase* of the wave changes once; while in the third mode, ψ_3, the amplitude changes from zero to a maximum, through zero to a minimum, through zero to a maximum again, and then finally back to zero, i.e. there are two nodes (marked ● above), and the phase of the wave changes twice. Displacements above the nodal plane are conventionally designated +, and those below −. The lobes of, for example, a 2*p* atomic orbital, which has one nodal plane, thus differ in phase, and are conventionally designated as + and −, i.e. (9); this can, however, lead to confusion because of the usual association of + and − with charge,† and phase differences, which are purely relative, will therefore be designated here by shading and no shading, i.e. (10):

(9) (10)

Molecular orbitals are obtained by the linear combination of atomic orbitals, and the question of phase will, of course, arise with them too. Thus we can write the two MOs (π and π^*, *cf.* p. 12) arising from the two *p* atomic orbitals in ethene,



and the four MOs (ψ_1, ψ_2, ψ_3 and ψ_4) arising from the four *p* AOs in

---

† It is important to emphasise that ψ^2, which represents the probability of finding an electron in a particular element of space, will always be positive, no matter whether ψ is positive or negative.

opposite phases require *conrotatory* movement before bond-making/bond-breaking can occur. This thermal/photochemical antithesis may thus be summarised in the generalisations:

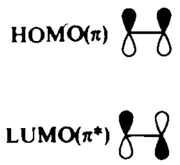
No. of π electrons	Conditions for reaction	Motion for bonding
$4n$	thermal	conrotatory
$4n$	photochemical	disrotatory
$4n + 2$	thermal	disrotatory
$4n + 2$	photochemical	conrotatory

Apart from their intrinsic interest, these electrocyclic reactions have considerable synthetic carbon–carbon bond-forming importance because of their rigid stereospecificity, which is much greater than in the vast majority of other, non-concerted reactions involving biradical or bipolar intermediates.

12.4 CYCLOADDITIONS

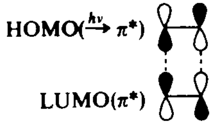
In cycloadditions two components are commonly involved, and the feasibility of a concerted process will be determined by whether overlap can take place between the HOMO of one component and the LUMO of the other. Thus for a diene plus a monoene,

the situation is a bonding one and concerted addition will be feasible, whichever component has the HOMO, or the LUMO: the cycloaddition is said to be *symmetry allowed*. By contrast, for two monoene components,

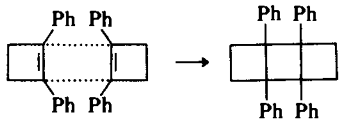


the situation is a non-bonding one and concerted addition will not be feasible: the cycloaddition is said to be *symmetry forbidden*.

This is a general situation for thermal, concerted additions: those involving $4\pi e + 2\pi e$ systems proceed readily, e.g. the Diels–Alder reaction, whereas those involving $2\pi e + 2\pi e$ systems, e.g. the cyclodimerisation of alkenes, do not. We might, however, expect that photochemical cyclodimerisation of alkenes would be symmetry allowed, as irradiation will promote an electron, of one component, into the orbital of next higher energy level, i.e. $\pi \xrightarrow{h\nu} \pi^*$, and the HOMO to be considered now therefore becomes (π^*):



Many such reactions may indeed be carried out preparatively under photochemical conditions, though, for reasons that cannot be gone into here (the detailed mechanism of photochemical changes), they are often not concerted but proceed *via* biradical intermediates. One photochemical ($2\pi + 2\pi$) cycloaddition that does, however, proceed *via* a concerted process is the example we have already referred to:

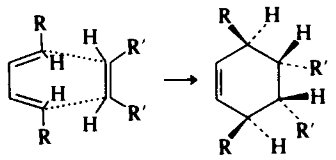


(4) (4) (5)

The importance of ($4\pi + 2\pi$) thermal, concerted cycloadditions is great enough to warrant their separate consideration.

12.4.1 Diels–Alder reaction

By far the best known ($4\pi + 2\pi$) cycloaddition is the Diels–Alder reaction. This has been discussed to some extent already (p. 197), including the fact that it proceeds rigorously, stereospecifically SYN, with respect to both diene (26) and dienophile (27):



(26) (27)

This is confirmatory evidence of a concerted pathway, implying as it does the simultaneous formation of *both* new σ bonds in the T.S. That both new bonds are not necessarily formed to the same extent in the T.S. is, however, suggested by the fact that the reaction is markedly influenced by the electronic effect of substituents. It is found to be promoted by electron-donating substituents in the diene, and by

T.S. such as (43) when $x = 0$ (an overall $4e$ system):

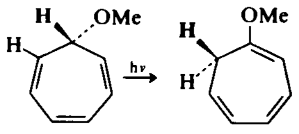

(43)

Such a transition state is likely to be highly strained, however, and no such 1,3-antarafacial shifts have actually been observed. A 1,7-thermal antarafacial shift in (36, $x = 2$), where the T.S. is likely to be much less strained (i.e. able to adopt the required helical geometry) has, however, been observed in the vitamin D series.

1,3-Photochemical shifts should, however, be allowed and suprafacial (44 → 45) as the HOMO of the T.S. (ψ_3, due to $\psi_1^2\psi_2^1 \rightarrow \psi_1^2\psi_3^1$) now has terminal lobes which are of the same phase (46):


(44) (46) (45)

Such 1,3-shifts are, indeed, found to be relatively common. 1,5-Photochemical shifts in (36, $x = 1$) should be antarafacial, but this is likely to involve a strained T.S. and no examples are known. 1,7-Photochemical shifts in (36, $x = 2$) should be allowed and suprafacial, and the example (47 ⟶ 48) has in fact been observed:

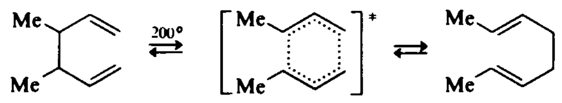


(47) (48)

The occurrence of a 1,7-photochemical shift of H in this compound does not, of itself, establish directly that this shift proceeds *via* a suprafacial pathway. The relatively rigid cyclic structure of (47) must, however, rule out the possibility of the shift having proceeded *via* the antarafacial route.

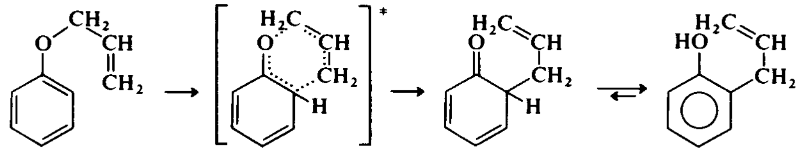
12.5.2 Carbon shifts

Among the best known examples, involving a carbon moiety, is the shift from one carbon atom to another observed in the Cope rearrangement of 1,5-dienes (49 → 50; not to be confused with the Cope *elimination*, p. 268),

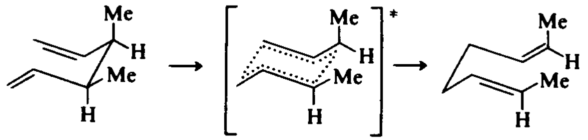


(49) (50)

and a shift from oxygen to carbon in the Claisen rearrangement of allyl aryl ethers (51 ⟶ 52):

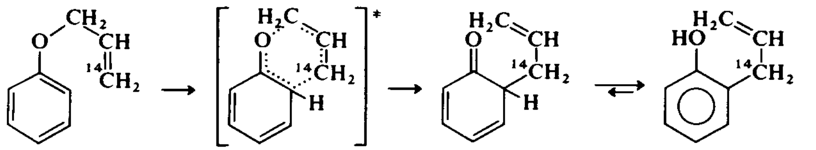

(51) (52)

So far as thermal reactions are concerned, those that can proceed *via* six-membered transition states go most readily, and are by far the commonest. That a six-membered cyclic T.S. in the *chair* conformation is commonly preferred is shown by the fact that the *meso* form of (49) yields *only* (99.7%) the *cis,trans* form (50*a*), out of the three possible geometrical isomerides (*cis,cis*; *cis,trans*; and *trans,trans*) of (50):

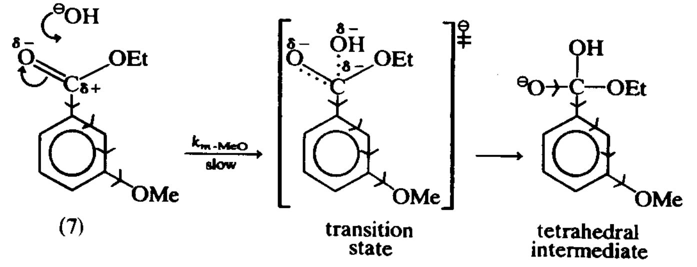

meso *cis, trans*
(49*a*) (50*a*)

This corresponds to a shift which is suprafacial at both 'ends' of the migrating system.

The Claisen rearrangement is strictly intramolecular, and shows the large negative value of $\Delta S^{\ddagger}$ characteristic of the degree of ordering required by a cyclic T.S. This latter requirement is also borne out by ^{14}C labelling, which indicates that the position of the ^{14}C atom in the allyl group is 'inverted' during migration (51*a* ⟶ 52*a*):

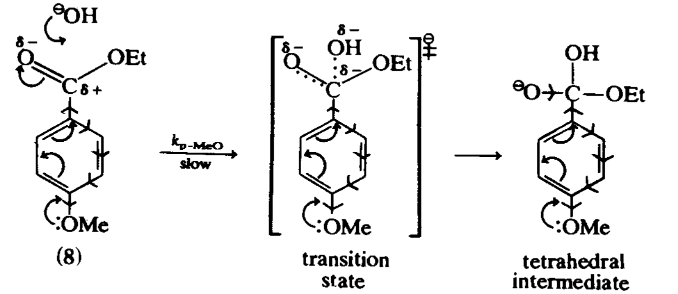

(51*a*) (53*a*) (52*a*)

hydrolysis) makes plain the reason for this change in sign:



(7)

$\sigma_{m\text{-MeO}} = +0{\cdot}12$ $k_{m\text{-MeO}} > k_{\mathrm{H}}$



(8)

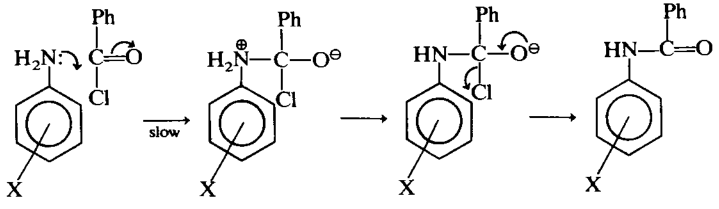
$\sigma_{p\text{-MeO}} = -0{\cdot}27$ $k_{\mathrm{H}} > k_{p\text{-MeO}}$

In the *m*-position, the electronegative oxygen atom of the MeO group exerts an electron-withdrawing inductive effect ($\sigma_{m\text{-MeO}} = +0{\cdot}12$) and hydrolysis is faster than with the unsubstituted ester [*cf.* the *m*-NO_2 ester (5)]. In the *p*-position, MeO will still exert an electron-withdrawing inductive effect, but in addition it can, through its electron pairs, exert an electron-donating mesomeric effect on the ring carbon atom to which the CO_2Et group is attached. The latter effect, because it involves the more readily polarisable π electron system, is the greater of the two, and the overall result is therefore *net* electron-donation ($\sigma_{p\text{-MeO}} = -0{\cdot}27$); as is required by the observation that the *p*-MeO ester is hydrolysed markedly more slowly than the unsubstituted compound (*cf.* p. 154).

Thus σ_X can be regarded as a measure of the *overall polar effect* exerted by a substituent, X, on the reaction centre. Its *sign* indicates the *direction* (−ve = electron-donating; +ve = electron-withdrawing), and its *magnitude* the *extent*, of the effect that X exerts—compared, of course, with the effect exerted by H. Indeed, the assumed constancy of a substituent's σ_X value, over a wide range of different reactions, does not necessarily imply that the *absolute* polar effect of X always remains constant, but only that its effect *relative* to H remains constant.

13.3.5 Physical significance of ρ

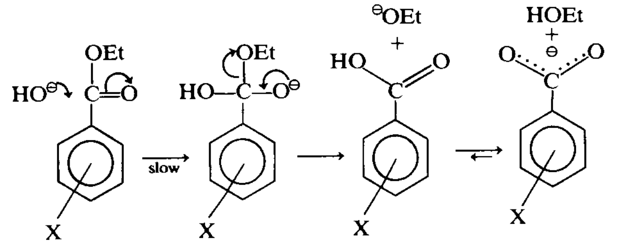
Now let us consider ρ, the reaction constant. Looking at the list of ρ values (p. 364), we can select first a reaction with a sizeable −ve ρ value, say reaction 2—the benzoylation of *m*- and *p*-substituted anilines (9)—with $\rho = -2{\cdot}69$, and look at this reaction rather more closely:



(9) (10)

The slow, rate-limiting step of this reaction is found to be initial attack by the electron pair of the nitrogen atom of the substituted aniline (9) on the carbonyl carbon atom of the acid chloride. This results in the development of +ve charge at the reaction centre—the N atom attached directly to the substituted benzene ring in the forming intermediate (10). The reaction is thus accelerated by electron-donating substituents, which help delocalise this forming +ve charge in the transition state leading to the intermediate (10), and correspondingly retarded by electron-withdrawing substituents; this behaviour is found to hold in general for reactions with −ve ρ values.

We have already had some discussion of a reaction with a +ve ρ value, reaction 13 in the list (p. 364), the base-catalysed hydrolysis of *m*- and *p*-substituted ethyl benzoates (11):



(11) (12)

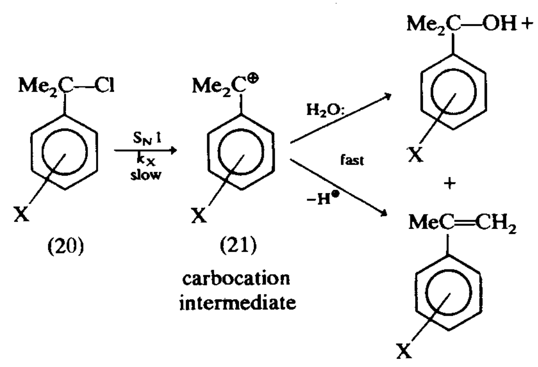
This has ρ value of $+2{\cdot}51$, the known slow, rate-limiting step in this reaction is attended by the development of −ve charge adjacent to the reaction centre in the transition state leading to the intermediate (12), and the overall reaction is, as we have already seen (p. 365), For each species, the inductive effect of the p-NO_2 substituent—which will be essentially similar in each of the sets of species—has been omitted, but the mesomeric or conjugative effect has been included. In (18*a*) $\rightleftarrows$ (18*b*), the standard reaction that was used to evaluate $\sigma_{p\text{-}NO_2}$, the conjugative effect of the p-NO_2 substituent is transmitted ultimately to the reaction centre only through an inductive effect: operating on the CO_2H, or $CO_2^{\ominus}$, group from the ring carbon atom to which it is attached. In (19*a*) $\rightleftarrows$ (19*b*), however, the conjugative effect can be transmitted right through from the p-NO_2 substituent to the electron pairs on the oxygen atom which is now the reaction centre. This effect will be particularly marked in (19*b*), where the anion will be stabilised substantially by delocalisation of its −ve charge, and the ionisation equilibrium for p-NO_2 phenol thereby displaced over towards the right in the anion's favour; thus increasing this phenol's strength as an acid.

The value for $\sigma_{p\text{-}NO_2}$ obtained from the standard reaction (18*a* $\rightleftarrows$ 18*b*) clearly does not take into account the heightened effect of this '*through-conjugation*', which is why the point for p-NO_2—and for p-CN—is off the line in Fig. 13.4. Such through-conjugation can, however, be allowed for by using the aqueous ionisation of phenols to establish a set of new, alternative, σ values, for p-NO_2 and other comparable electron-*withdrawing* substituents: these new values may then be used for reactions in which through-conjugation can occur.

This can be achieved by first plotting $\log K_X/K_H$ against σ_X for m-substituted phenols only (which cannot be involved in through-conjugation), then the slope of the resulting straight line will give the value of ρ, the reaction constant, for this reaction. Using this value in the normal Hammett equation ([6], p. 363), enables us to calculate the new, revised, $\sigma_{p\text{-}}$ value for p-NO_2, and for similar substituents capable of through-conjugation. These revised figures are generally referred to as $\sigma^-_{p\text{-}}$ values, and a number are compared with the normal $\sigma_{p\text{-}}$ values below:

Substituent, X	$\sigma^-_{p\text{-}X}$	$\sigma_{p\text{-}X}$
CO_2Et	0·68	0·45
COMe	0·84	0·50
CN	0·88	0·66
CHO	1·03	0·43
NO_2	1·27	0·78

An exactly analogous situation will arise where there is the possibility of direct through-conjugation between a suitable electron-*donating* p-substituent and a reaction centre at which +ve charge is developing. A good example is solvolysis (S_N1) of the tertiary halides, 2-aryl-2-chloropropanes (20), shown in Fig. 13.5:



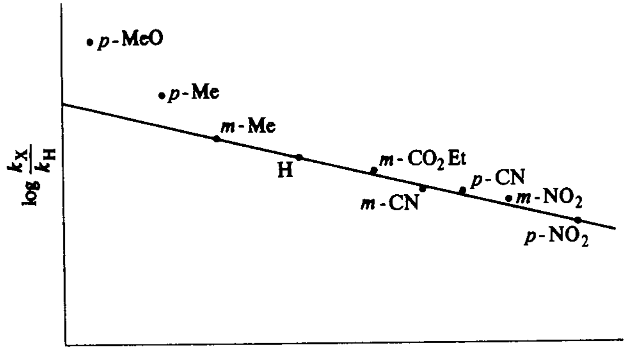
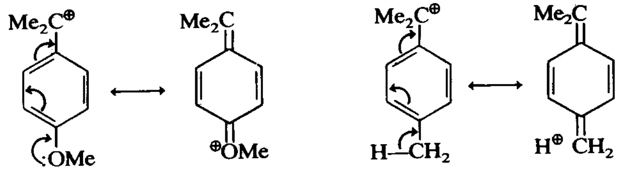


Fig. 13.5

Solvolysis of the p-MeO and p-Me chlorides is found to be faster (p-MeO ≈ 800 times) than would have been predicted from their $\sigma_{p\text{-}}$ values. This stems from the stabilisation, by through-conjugation, of the carbocationic intermediates (21*a* and 21*b*) which are developing during the slow, rate-limiting step of the overall reaction:



p-MeO (21*a*) p-Me(21*b*)

The fact that development of +ve charge, in the transition state for reaction centre and the leaving group, the magnitude of r can perhaps be construed as some indication of the extent of such bond-breaking by the time the transition state has been reached.

It is, however, important to resist the temptation to introduce new parameters into the Hammett equation merely to achieve a better 'fit' with the experimental data. This is particularly true where, as in some cases, it may be difficult to ascribe real significance, in physical terms, to the new parameter anyway. It is in fact possible, as we shall see, to obtain much highly relevant information about reaction pathways using simple Hammett plots only.

13.4 USES OF HAMMETT PLOTS

Having now given some consideration to the significance that can be attached to σ_X and ρ in more familiar physical terms, it is possible to go on and discuss the actual uses that can be made of them in providing information about reactions and the pathways by which they take place.

13.4.1 Calculation of *k* and *K* values

The simplest possible use that can be made of the Hammett equation is to calculate k or K for a specific reaction of a specific compound, where this information is not available in the literature, or indeed where the actual compound has not even been prepared yet. Thus it is known that the base-catalysed hydrolysis of ethyl *m*-nitrobenzoate is 63·5 times as fast as the hydrolysis of the corresponding unsubstituted ester under parallel conditions; what then will be the comparable rate for base-catalysed hydrolysis of ethyl *p*-methoxybenzoate under the same conditions? Looking at the table of σ_X values (p. 363), we find that $\sigma_{m\text{-NO}_2} = 0{\cdot}71$, while $\sigma_{p\text{-MeO}} = -0{\cdot}27$. Then from the Hammett equation [6] (p. 363):

① $$\log\frac{k_{m\text{-NO}_2}}{k_\text{H}} = \rho\sigma_{m\text{-NO}_2} \qquad [6a]$$

i.e. $$\log\frac{63{\cdot}5}{1} = \rho\times 0{\cdot}71 \qquad \therefore\ \rho = 2{\cdot}54$$

② $$\log\frac{k_{p\text{-MeO}}}{k_\text{H}} = \rho\sigma_{p\text{-MeO}} \qquad [6b]$$

i.e. $$\log\frac{k_{p\text{-MeO}}}{k_\text{H}} = 2{\cdot}54\times -0{\cdot}27 \quad \therefore\ \frac{k_{p\text{-MeO}}}{k_\text{H}} = 0{\cdot}21$$

When $k_{p\text{-MeO}}$ subsequently came to be determined experimentally, $k_{p\text{-MeO}}/k_\text{H}$ was indeed found to be 0·21, so the calculated value was pretty satisfactory! In fact, σ_X and ρ values are rarely used for such a purpose, they are employed much more often in providing salient data about reaction pathways.

13.4.2 Deviations from straight line plots

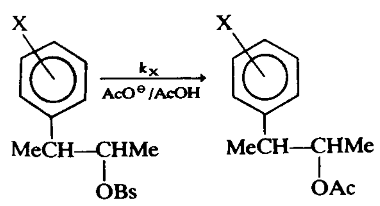
We have already seen (p. 368) how the sign and magnitude of ρ, the reaction constant, can provide useful information about the development (or dissipation) of charge (+ve or −ve) on going from starting materials to the transition state for the rate-limiting step of a reaction. We have also seen (p. 369) how deviations from straight line plots using normal σ_X, substituent constant, values led to the definition of σ_X^+ or σ_X^- values to take into account through-conjugation between certain p-substituents and the reaction centre. The need to use other than the normal σ_X values indicates the occurrence of such through-conjugation in a particular reaction, and the Yukawa–Tsuno parameter, r, then provides a measure of its extent.

Paradoxically, Hammett plots are usually most informative at the very point at which they depart from linearity, but the major inference that can be drawn from this departure is found to differ depending on whether the deviation is concave 'upwards' or concave 'downwards'.

13.4.3 Concave upwards deviations

13.4.3.1 Acetolysis of 3-aryl-2-butyl brosylates

An interesting case in point is the acetolysis of 3-aryl-2-butyl *p*-bromobenzenesulphonates or brosylates (25), for which the Hammett plot is shown in Fig. 13.6. The lower right-hand side of the



(25) (26)

[Bs = p-BrC$_6$H$_4$SO$_2$]
brosylate

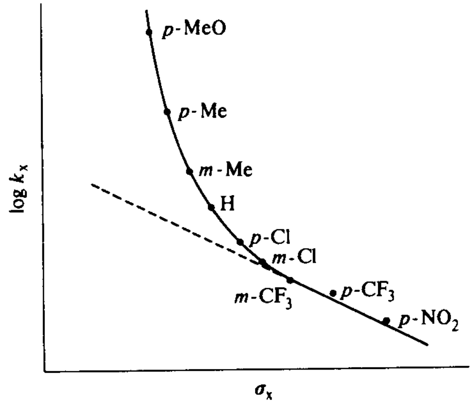
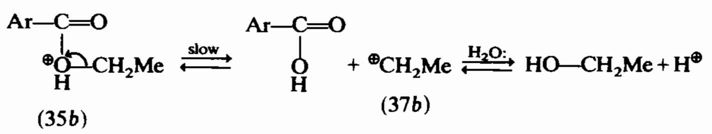


Fig. 13.6

hydrolysis ($A_{AL}1$, p. 241) that would fulfil this requirement:



(35*b*) (37*b*)

Loss of $MeCH_2^{\oplus}$ the ethyl cation (37*b*), leads to a marked decrease in +ve charge adjacent to the reaction centre (had it actually been from the reaction centre itself the +ve value of ρ would have been much larger); this carbocationic intermediate (37*b*) will then react rapidly with any available water to yield ethanol.

The question does then arise, given the observed shift in reaction pathway for the ethyl esters (34*b*), why does a similar shift not occur with the corresponding methyl esters (34*a*)? Such a shift would, of course, necessitate the formation of a methyl, $CH_3^{\oplus}$, rather than an ethyl, $MeCH_2^{\oplus}$ (37*b*), cation in the slow, rate-limiting step. $CH_3^{\oplus}$ is known to be considerably more difficult to form than is $MeCH_2^{\oplus}$ and this difference is apparently great enough to rule out, on energetic grounds, such an $A_{AC}1 \rightarrow A_{AL}1$ shift with the methyl esters, despite potential assistance (to $A_{AL}1$) from increasingly electron-withdrawing substituents.

13.4.4 Concave downwards deviations

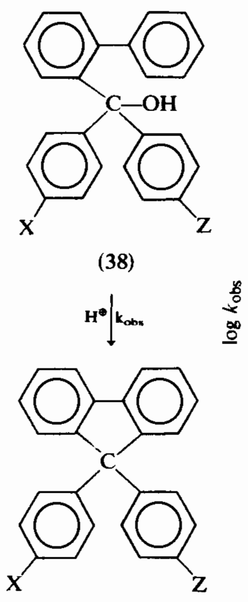
There are, however, also examples of deviations from simple Hammett plots in which the curvature is in the opposite direction, concave downwards, and these deviations have a rather different significance.

13.4.4.1 Cyclodehydration of 2-phenyltriarylmethanols

A good example is the cyclodehydration of some substituted 2-phenyltriarylmethanols (38), in 80% aqueous ethanoic acid containing 4% H_2SO_4 at 25°, to yield the corresponding tetraarylmethanes (39), as shown in Fig. 13.8 (p. 381).

Two of the benzene rings in (38) each carry a *p*-substituent (X and Z, respectively), and the value of σ actually plotted is $\Sigma\sigma$: the *sum* of the σ values for X and Z. The plot in Fig. 13.8—of log k_{obs} for the reaction against $\Sigma\sigma$—is clearly a composite of two straight lines, one on the left with $\rho = +2{\cdot}67$, and one on the right with $\rho = -2{\cdot}51$.

There seems little doubt that the overall reaction follows a four-step pathway, the first two steps constituting an E1 (p. 247) elimination of water to yield a carbocationic intermediate (40), which then, in the last two steps, effects internal electrophilic



(38)

(39)

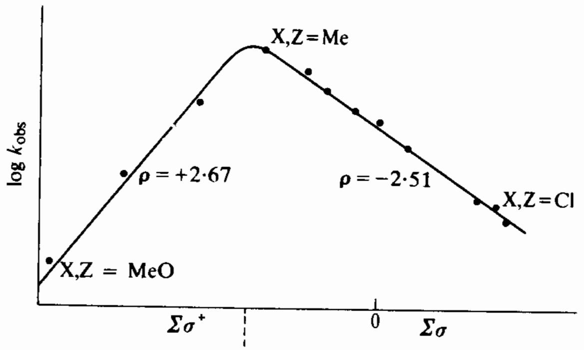
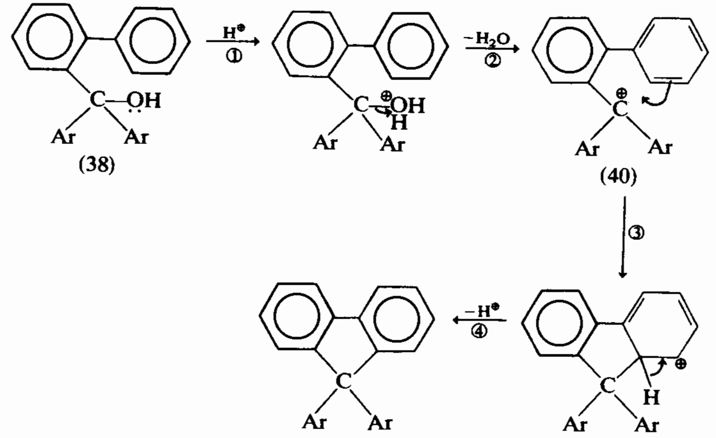


Fig. 13.8

substitution on the 2-phenyl nucleus to yield the product tetraarylmethane (39):

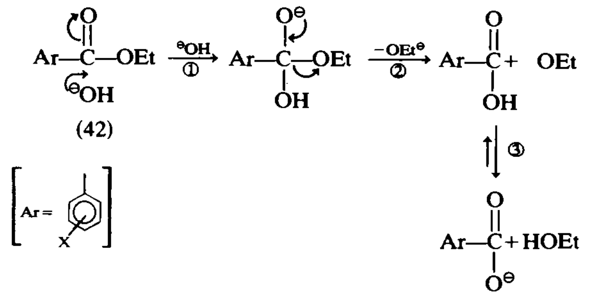


The question then arises—which step in the overall reaction is likely to be the slow, and hence rate-limiting, one? It's unlikely to be

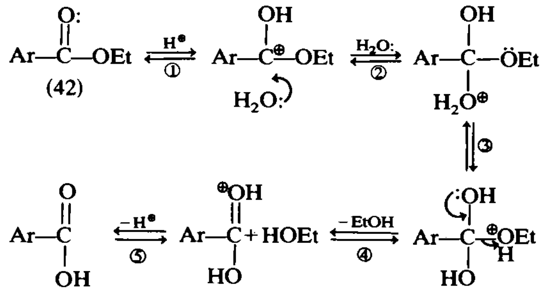
13.5.1 Taft equation

Acting on a suggestion originally made by Ingold, Taft began by comparing the relative susceptibility to polar substituent effects (the ρ value) of the hydrolysis—under acid-catalysed ($A_{AC}2$, p. 241) and under base-catalysed ($B_{AC}2$, p. 239) conditions—of *m*- and *p*-substituted benzoate esters (42).

The ρ value for base-catalysed hydrolysis (+2·51) is +ve and quite large, reflecting the development of not inconsiderable −ve charge at the reaction centre in the rate-limiting step—attack on this centre by $^{\ominus}OH$ (step ① in the $B_{AC}2$ pathway). By contrast, the ρ value for acid-catalysed hydrolysis (+0·03) is very nearly zero; which means, of course, that the rate of this hydrolysis does not vary significantly from one ester to another, no matter what the *m*- or *p*-substituent present. The ρ value for this hydrolysis is so small, despite their being considerable redistribution of +ve charge in the slow step (step ②), because the overall rate of reaction, i.e. k_{obs} (which is plotted to evaluate ρ), is determined not solely by k_2 for this slow step, but involves also K_1 for the preceding, reversible, step ①. These two terms all but cancel each other out, in so far as susceptibility of the two steps to electron-donation/-withdrawal by polar substituents is concerned, and the overall ρ value for the reaction is thus virtually zero.

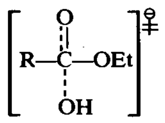


Base-catalysed hydrolysis($B_{AC}2$): $\rho = 2{\cdot}51$



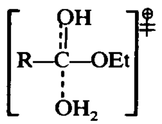
Acid-catalysed hydrolysis($A_{AC}2$): $\rho = 0{\cdot}03$

If we now extend our consideration of base-catalysed ($B_{AC}2$), and acid-catalysed ($A_{AC}2$), hydrolysis to esters in general, including aliphatic ones (RCO_2Et), we see that there is a close similarity between the transition states (42*b* or 42*a*) for the rate-limiting step in each of the two pathways: they are both tetrahedral; and differ only in the second of them having two protons more than the first. Protons, being very small, exert comparatively little steric influence; it is therefore a not unreasonable assumption that any steric effect stemming from the group R is, because of the close spatial similarity of the two transition states, substantially the same in both acid- and base-catalysed hydrolysis.† It then becomes possible to write a Hammett type equation, [9], to represent the operation of the *polar* effect only of substituent R in ester hydrolysis:



(42*b*)

T.S. for base-catalysed
hydrolysis ($B_{AC}2$)



(42*a*)

T.S. for acid-catalysed
hydrolysis ($A_{AC}2$)

$$\log\left[\frac{k_R}{k_0}\right]_{base} - \log\left[\frac{k_R}{k_0}\right]_{acid} = \rho^*\sigma_R^* \qquad [9]$$

As the steric effect exerted by R is essentially the same in both modes of hydrolysis, the two steric terms will cancel each other out, and will thus not appear in equation [9].

Taft then gave ρ^* in [9], the value 2·48, derived by subtracting the ρ value for acid-catalysed hydrolysis of benzoate esters (0·03) from the ρ value for base-catalysed hydrolysis of the same esters (2·51). He took as his reference substituent R = Me, rather than R = H, so that k_0 in [9] refers to $\underline{Me}CO_2Et$ rather than $\underline{H}CO_2Et$. Then by kinetic measurements on the acid- and base-catalysed hydrolysis of a series of esters containing R groups other than Me, it is possible—using [9]—to evaluate σ_R^* for each of these different R groups with respect to Me, for which by definition $\sigma_{Me}^* = 0$ (*cf.* $\underline{H}$ with $\sigma_H = 0$ for benzoic acid ionisation, p. 363). By giving ρ^* here the value 2·48, the resulting σ_R^* values—which are a measure of the polar effect only exerted by R—do not differ too greatly in mag-

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† Such an assumption does, however, neglect the possibility that the degree of solvation of +vely and −vely charged T.S.s could be markedly different, thereby greatly influencing the relative rates of the two hydrolyses.