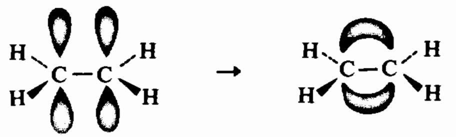
minimum; whereas in the eclipsed conformation they are suffering the maximum of crowding [0·230 nm (2·3 Å), slightly less than the sum of their van der Waals radii]. The long cherished principle of free rotation about a carbon–carbon single bond is not contravened, however, as it has been shown that the eclipsed and staggered conformations differ by only ≈12 kJ (3 kcal) mol^{-1} in energy content at 25°, and this is small enough to allow their ready interconversion through the agency of ordinary thermal motions at room temperature—the rotation frequency at 25° being $\approx 10^{12}\,\text{sec}^{-1}$. That such crowding *can* lead to a real restriction of rotation about a carbon–carbon single bond has been confirmed by the isolation of two forms of $CHBr_2CHBr_2$, though admittedly only at low temperatures where collisions between molecules do not provide enough energy to effect the interconversion.

1.3.2 Carbon–carbon double bonds

In ethene each carbon atom is bonded to only *three* other atoms, two hydrogens and one carbon. Strong σ bonds are formed with these three atoms by the use of *three* orbitals derived by hybridising the 2*s* and, this time, *two* only of the carbon atom's 2*p* atomic orbitals—an atom will normally only mobilise as many hybrid orbitals as it has atoms or groups to form strong σ bonds with. The resultant sp^2 hybrid orbitals all lie in the same plane, and are inclined at 120° to each other (*plane trigonal orbitals*). In forming the molecule of ethene, two of the sp^2 orbitals of each carbon atom are seen as overlapping with the 1*s* orbitals of two hydrogen atoms to form two strong σ C—H bonds, while the third sp^2 orbital of each carbon atom overlap axially to form a strong σ C—C bond between them. It is found experimentally that the H—C—H and H—C—C bond angles are in fact 116·7° and 121·6°, respectively. The departure from 120° is hardly surprising seeing that different trios of atoms are involved.

This then leaves, on each carbon atom, *one unhybridised* 2*p* atomic orbital at right angles to the plane containing the carbon and hydrogen atoms. When these two 2*p* orbitals become parallel to each other they can themselves overlap, resulting in the formation of a bonding molecular orbital spreading over both carbon atoms and situated above and below the plane (i.e. it has a node in the plane of the molecule) containing the two carbon and four hydrogen atoms (⋱ indicates bonds to atoms lying *behind* the plane of the paper, and ◣ bonds to those lying in *front* of it):



This new bonding molecular orbital is known as a π orbital,* and the electrons that occupy it as π electrons. The new π bond that is thus formed has the effect of drawing the carbon atoms closer together, and the C═C distance in ethene is found to be 0·133 nm (1·33 Å), compared with a C—C distance of 0·154 nm (1·54 Å) in ethane. The *lateral* overlap of the *p* atomic orbitals that occurs in forming a π bond is less effective than the axial overlap that occurs in forming a σ bond, and the former is thus weaker than the latter. This is reflected in the fact that the energy of a carbon–carbon double bond, though more than that of a single bond is, indeed, less than twice as much. Thus the C—C bond energy in ethane is 347 kJ (83 kcal) mol^{-1}, while that of C═C in ethene is only 598 kJ (143 kcal) mol^{-1}.

The lateral overlap of the two 2*p* atomic orbitals, and hence the strength of the π bond, will clearly be at a maximum when the two carbon and four hydrogen atoms are exactly coplanar, for it is only in this position that the *p* atomic orbitals are exactly parallel to each other, and will thus be capable of maximum overlap. Any disturbance of this coplanar state, by twisting about the σ bond joining the two carbon atoms, would lead to reduction in π overlapping, and hence a decrease in the strength of the π bond: it will thus be resisted. A theoretical justification is thus provided for the long observed resistance to rotation about a carbon–carbon double bond. The distribution of the π electrons in two lobes, above and below the plane of the molecule, and extending beyond the carbon–carbon bond axis, means that a region of negative charge is effectively waiting there to welcome any electron-seeking reagents (e.g. oxidising agents); so that it comes as no surprise to realise that the characteristic reactions of a carbon–carbon double bond are predominantly with such reagents (*cf.* p. 178). Here the classical picture of a double bond has been replaced by an alternative, in which the two bonds joining the carbon atoms, far from being identical, are considered to be different in nature, strength and position.

1.3.3 Carbon–carbon triple bonds

In ethyne each carbon atom is bonded to only *two* other atoms, one hydrogen and one carbon. Strong σ bonds are formed with these two atoms by the use of *two* hybrid orbitals derived by hybridising the 2*s* and, this time, *one* only of the carbon atom's 2*p* atomic orbitals. The resultant *digonal* sp^1 hybrid orbitals are co-linear. Thus, in forming the molecule of ethyne, these hybrid orbitals are used to form strong σ bonds between each carbon atom and one hydrogen atom, and between the two carbon atoms themselves, resulting in a linear molecule

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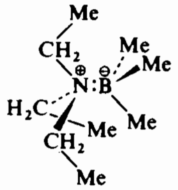
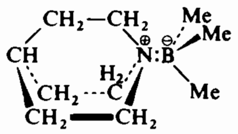
* An anti-bonding, π^*, molecular orbital is also formed (*cf.* p. 12).

atom, is very stable:


(34)

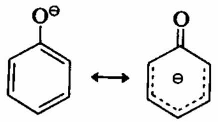

(35)

That this difference is not due to differing electron availability at the nitrogen atom in the two cases is confirmed by the fact that the two amines differ very little in their strengths as bases (*cf.* p. 72): the uptake of a proton constituting very much less of a steric obstacle than the uptake of the relatively bulky BMe_3. Esterification and ester hydrolysis are other reactions particularly susceptible to steric inhibition (*cf.* p. 241).

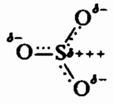
It should be emphasised that such steric inhibition is only an extreme case, and any factors which disturb or inhibit a particular orientation of the reactants with respect to each other, short of preventing their close approach, can also profoundly affect the rate of reactions: a state of affairs that is often encountered in reactions in biological systems.

1.7 REAGENT TYPES

Reference has already been made to electron-donating and electron-withdrawing groups, their effect being to render a site in a molecule electron-rich or electron-deficient, respectively. This will clearly influence the type of reagent with which the compound will most readily react. An electron-rich species such as phenoxide anion (36)

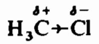

(36*a*) (36*b*)

will tend to be most readily attacked by positively charged cations such as $C_6H_5N_2^{\oplus}$, a diazonium cation (p. 146), or by other species which, though not actually cations, possess an atom or centre that is electron-deficient; for example, the sulphur atom of sulphur trioxide (37) in sulphonation (p. 140):


(37)

Such reagents, because they tend to attack the substrate at a position (or positions) of high electron density, are referred to as *electrophilic* reagents or *electrophiles*.

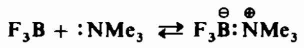
Conversely, an electron-deficient centre, such as the carbon atom in chloromethane (38)


$$H_3\overset{\delta+}{C}\text{+}\!\!-\overset{\delta-}{Cl}$$
(38)

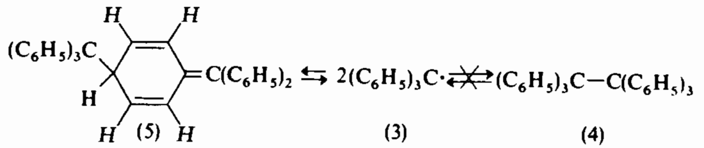
will tend to be attacked most readily by (negatively charged) anions such as $^{\ominus}OH$, $^{\ominus}CN$, etc., or by other species which, though not actually anions, possess an atom or centre which is electron-rich; for example, the nitrogen atom in ammonia or amines, $H_3N\!:$ or $R_3N\!:$. Such reagents, because they tend to attack the substrate at a position (or positions) of low electron density, i.e. where the atomic nucleus is short of its normal complement of orbital electrons, are referred to as *nucleophilic* reagents or *nucleophiles*.

It must be emphasised that only a *slightly* unsymmetrical distribution of electrons is required for a reaction's course to be dominated: the presence of a full-blown charge on a reactant certainly helps, but is far from being essential. Indeed the requisite unsymmetrical charge distribution may be induced by the mutual polarisation of reagent and substrate on their close approach, as when bromine adds to ethene (p. 180).

This electrophile/nucleophile dichotomy can be looked upon as a special case of the acid/base idea. The classical definition of acids and bases is that the former are proton donors, and the latter proton acceptors. This was made more general by Lewis, who defined acids as compounds prepared to accept electron pairs, and bases as substances that could provide such pairs. This would include a number of compounds not previously thought of as acids and bases, e.g. boron trifluoride (39),


$$F_3B + :NMe_3 \rightleftarrows F_3\overset{\ominus}{B}:\overset{\oplus}{N}Me_3$$
(39) (40)

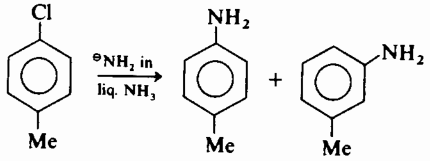
which acts as an acid by accepting the electron pair on nitrogen in trimethylamine to form the complex (40), and is therefore referred hydrogen atoms. Only after nearly seventy years (in 1968) did the n.m.r. spectrum (*cf.* p. 18) of the dimer (with only *twenty-five* 'aromatic' (H), *four* 'dienic' (*H*), and *one* 'saturated' (**H**), hydrogen atoms) demonstrate that it could not have the hexaphenylethane structure (4) and was, in fact (5):



(5) (3) (4)

At which point numerous small details of the behaviour of (3) and of its dimer, that had previously appeared anomalous, promptly became understandable.

Information about the products of a reaction can be particularly informative when one of them is quite unexpected. Thus the reaction of chloro-4-methylbenzene (*p*-chlorotoluene, 6) with amide ion, $^{\ominus}NH_2$, in liquid ammonia (p. 173) is found to lead not only to the expected 4-methylphenylamine (*p*-toluidine, 7), but also to the quite unexpected 3-methylphenylamine (*m*-toluidine, 8), which is in fact the major product:



(6) (7) (8)

Expected Unexpected

The latter clearly cannot be obtained from (6) by a simple substitution process, and either must be formed from (6) *via* a different pathway than (7), or if the two products are formed through some common intermediate then clearly (7) cannot be formed by a direct substitution either.

2.3.2 Kinetic data

The largest body of information about reaction pathways has come—and still does come— from kinetic studies as we shall see, but the interpretation of kinetic data in mechanistic terms (*cf.* p. 39) is not always quite as simple as might at first sight be supposed. Thus the effective reacting species, whose concentration really determines the reaction rate, may differ from the species that was put into the reaction mixture to start with, and whose changing concentration we are actually seeking to measure. Thus in aromatic nitration the effective attacking species is usually $^{\oplus}NO_2$ (p. 134), but it is HNO_3 that we put into the reaction mixture, and whose changing concentration we are measuring; the relationship between the two may well be complex and so, therefore, may be the relation between the rate of reaction and $[HNO_3]$. Despite the fact that the essential reaction is a simple one, it may not be easy to deduce this from the quantities that we can readily measure.

Then again, if the hydrolysis in aqueous solution of the alkyl halide, RHal, is found to follow the rate equation,

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

it is not necessarily safe to conclude that the rate-determining step does <u>not</u> involve the participation of water, simply on the grounds that $\overline{[H_2O]}$ does not appear in the rate equation; for if water is being used as the solvent it will be present in very large excess, and its concentration would remain virtually unchanged whether or not it actually participated in the rate-limiting stage. The point could perhaps be settled by carrying out the hydrolysis in another solvent, e.g. HCO_2H, and by using a much smaller concentration of water as a potential nucleophile. The hydrolysis may then be found to follow the rate equation,

$$\text{Rate} = k_2[\text{RHal}][H_2O]$$

but the actual mechanism of hydrolysis could well have changed on altering the solvent, so that we are not, of necessity, any the wiser about what actually went on in the original aqueous solution.

The vast majority of organic reactions are carried out in solution, and quite small changes in the solvent used can have the profoundest effects on reaction rates and mechanisms. Particularly is this so when polar intermediates, for example carbocations or carbanions as constituents of ion pairs, are involved, for such species normally carry an envelope of solvent molecules about with them. This greatly affects their stability (and their ease of formation), and is strongly influenced by the composition and nature of the solvent employed, particularly its polarity and ion-solvating capabilities. By contrast, reactions that involve radicals (p. 299) are much less influenced by the nature of the solvent (unless this is itself capable of reacting with radicals), but are greatly influenced by the addition of radical sources (e.g. peroxides) or radical absorbers (e.g. quinones), or by light which may initiate reaction through the production of radicals by photochemical activation, e.g. $Br_2 \xrightarrow{h\nu} Br\cdot\ \cdot Br$.

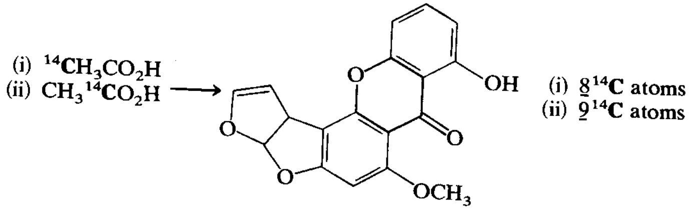
A reaction that is found, on kinetic investigation, to proceed unexpectedly faster or slower than the apparently similar reactions, under comparable conditions, of compounds of related structure suggests the operation of a different, or modified, pathway from the

9) that is formed, comes from the solvent (H_2O) or from a second molecule of benzaldehyde. Carrying out the reaction in D_2O is found to lead to the formation of no PhCHDOH, thus demonstrating that the second hydrogen atom could not have come from water, and must therefore have been provided by direct transfer from a second molecule of benzaldehyde.

A wide range of other isotopic labels, e.g. ^3H (or T), ^{13}C, ^{14}C, ^{15}N, ^{32}P, ^{35}S, ^{37}Cl, ^{131}I, etc., have also been used to provide important mechanistic information. The major difficulties encountered in such labelling studies have always been: (*a*) ensuring that the label is incorporated *only* into the desired position(s) in the test compound; and (*b*) finding exactly where the label has gone to in the product(s) after the reaction being studied has taken place.

The enormous increase in selectivity of modern synthetic methods has all but eliminated (*a*), but (*b*) long remained a major problem; particularly when isotopes of carbon were being used: these being especially valuable because carbon atoms are present in all organic compounds. The ^{14}C isotope has been much used in investigating biosynthetic pathways: the routes by which living organisms build up the highly elaborate molecules that may be obtained from them.

Thus there was reason to believe that the pentacyclic compound *sterigmatocystin*,

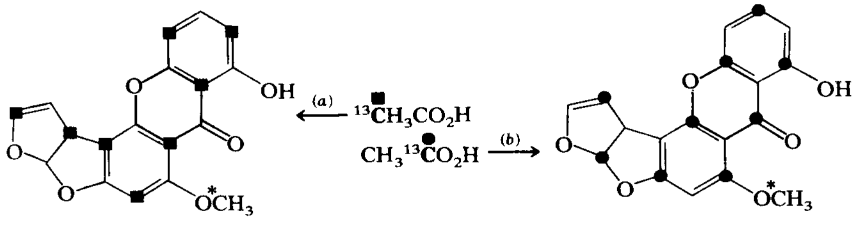


sterigmatocystin

found in cultures of several fungi, was built up stepwise from molecules of ethanoic acid. General confirmation of this hypothesis was obtained through feeding suitable fungal cultures, in separate experiments, with $^{14}CH_3CO_2H$ and $CH_3{}^{14}CO_2H$, respectively. It was then found from radioactive counting measurements (^{14}C is a β emitter), on the two extracted samples of sterigmatocystin ($C_{18}H_{12}O_6$) that: (i) $^{14}CH_3CO_2H$ led to the introduction of $\underline{8}\,^{14}C$ atoms, and $CH_3{}^{14}CO_2H$ to the introduction of $\underline{9}\,^{14}C$ atoms. But that still leaves open the question of exactly where in the sterigmatocystin molecule these two sets of labelled carbon atoms are located.

Not long ago this could have been determined only by extremely laborious, and often equivocal, selective degradation experiments; but the coming of carbon n.m.r. spectroscopy has now made all the difference. Neither the ^{12}C nor the ^{14}C carbon isotopes produce an n.m.r. signal but the ^{13}C isotope, which occurs in ordinary carbon to the extent of 1·11%, does. It is thus possible, with suitable instrumentation, to record ^{13}C n.m.r. spectra of all carbon-containing compounds (because of their 1·11% ^{13}C content): each carbon atom, or group of identically situated carbon atoms, in a molecule producing a distinguishably different signal.

The ^{13}C spectrum of normal sterigmatocystin can thus be compared with the spectra of the molecules resulting from separate feeding experiments with ^{13}C enriched (*a*) $^{13}CH_3CO_2H$ and (*b*) $CH_3{}^{13}CO_2H$, respectively. Those carbon atoms, in each case, which now show enhanced ^{13}C signals can thereby be identified:

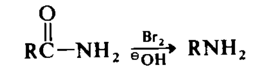


(*a*) $\underline{8}\,^{13}C$■ atoms (*b*) $\underline{9}\,^{13}C$● atoms

Knowing which of the two carbon atoms in CH_3CO_2H molecules are incorporated into which positions in sterigmatocystin, it becomes possible to make pertinent suggestions about the synthetic pathway employed by the fungal cultures. Incidentally, it also shows that the methyl carbon of the $*CH_3O$ group does *not* come from CH_3CO_2H.

2.3.4 The study of intermediates

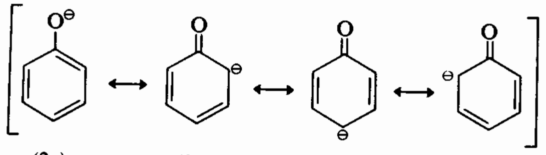
Among the most concrete evidence obtainable about the mechanism of a reaction is that provided by the actual isolation of one or more intermediates from the reaction mixture. Thus in the Hofmann reaction (p. 122), by which amides are converted into amines,



$$R\overset{\overset{\displaystyle O}{\|}}{C}{-}NH_2 \xrightarrow[\ominus OH]{Br_2} RNH_2$$

it is, with care, possible to isolate the N-bromoamide, RCONHBr, its anion, $RCONBr^{\ominus}$, and an isocyanate, RNCO; thus going some considerable way to elucidate the overall mechanism of the reaction. It is of course necessary to establish beyond all doubt that any species isolated really is an intermediate—and not merely an alternative product—by showing that it may be converted, under the normal reaction conditions, into the usual reaction products at a rate at least as fast as the overall reaction under the same conditions. It is also important to establish that the species isolated really is on the direct place in the methanoic acid molecule also, this involves separation of charge and will consequently be much less effective as a stabilising influence (*cf.* p. 20). The effect of this differential stabilisation is somewhat to discourage the recombination of proton with the methanoate anion, the equilibrium is to this extent displaced to the right, and methanoic acid is, by organic standards, a moderately strong acid.

With alcohols there is no such factor stabilising the alkoxide anion $RO^{\ominus}$, relative to the alcohol itself, and alcohols are thus very much less acidic than carboxylic acids. With phenols, however, there is again the possibility of relative stabilisation of the anion (2), by delocalisation of its negative charge through interaction with the π orbitals of the aromatic nucleus:



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

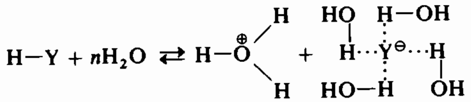
Delocalisation also occurs in the undissociated phenol molecule (*cf.* p. 23) but, involving charge separation, this is less effective than in the anion (2), thus leading to some reluctance on the part of the latter to recombine with a proton. Phenols are indeed found to be stronger acids than alcohols (the pK_a of phenol itself is 9·95) but considerably weaker than carboxylic acids. This is due to the fact that delocalisation of the negative charge in the carboxylate anion involves structures of identical energy content (see above), and of the centres involved two are highly electronegative oxygen atoms; whereas in the phenoxide anion (2) the structures involving negative charge on the nuclear carbon atoms are likely to be of higher energy content than the one in which it is on oxygen and, in addition, of the centres involved here only one is a highly electronegative oxygen atom. The relative stabilisation of the anion, with respect to the undissociated molecule, is thus likely to be less effective with a phenol than with a carboxylic acid, leading to the lower relative acidity of the former.

3.1.3 The influence of the solvent

Despite the above discussion on the influence of internal structural features on a compound's acidity, the real determining role is often exerted by the solvent, and this is particularly the case when, as commonly, the solvent is water.

Water has the initial disadvantage as an ionising solvent for organic compounds that some of them are insufficiently soluble in their unionised form to dissolve in it in the first place. That limitation apart, water is a singularly effective ionising solvent on account (*a*) of its high dielectric constant ($\epsilon = 80$), and (*b*) of its ion-solvating ability. The first property exerts its effect because the higher the dielectric constant (polarity) of a solvent the lower the electrostatic energy of any pairs of ions present in it will be: the more readily will such ion pairs thus be formed, the more stable will they be in solution, and the less ready will they be, therefore, to recombine with each other.

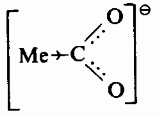
Ions in solution strongly polarise nearby solvent molecules, thereby collecting a solvation envelope of solvent molecules around them: the greater the extent to which this can take place, the greater the stabilisation of the ion, which is in effect stabilising itself by spreading or delocalising its charge. The peculiar effectiveness of water, as an ion-solvating medium, arises from the fact that H_2O is extremely readily polarised, and also relatively small in size; because of this it can solvate, and thereby stabilise, both cations and anions. The effect is particularly marked with anions for powerful 'hydrogen-bonded' type solvation can occur (see below). Similar H-bonded type solvation cannot in general occur with cations, but in the particular case of acids, the initial cation, $H^{\oplus}$, can also solvate through hydrogen bonding with the solvent water molecules:

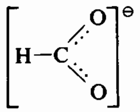


Alcohols, just so long as they are not too bulky, e.g. MeOH, share something of water's abilities and, for example, HCl is found to be a strong acid in methanol also. It should not, however, be forgotten that the prime requirement of the solvent is that it should be capable of functioning as a base: the weaker the base, the smaller the dissociation of the acid. Thus we find that in, for example, methylbenzene (toluene) HCl occurs as such, i.e. it is almost wholly undissociated.

3.1.4 Simple aliphatic acids

The replacement of the non-hydroxylic hydrogen atom of methanoic acid by an alkyl group might be expected to produce a weaker acid, as the electron-donating inductive effect of the alkyl group would reduce the residual electron affinity of the oxygen atom carrying the incipient proton, and so reduce the strength of the acid. In the alkyl-substituted anion the increased electron availability on oxygen would serve to promote its recombination with proton, as compared with the methanoate anion/methanoic acid system:





We should thus expect the equilibrium to be shifted to the left compared with that for methanoic acid/methanoate anion, and it is in fact found that the pK_a of ethanoic acid is 4·76, compared with 3·77 for methanoic acid. However, the degree of structural change effected in so small a molecule as methanoic acid by replacement of H by CH_3 makes it doubtful whether so simple an argument is really valid; it could well be that the relative solvation possibilities in the two cases are markedly affected by the considerably different shapes of, as well as by the relative charge distribution in, the two small molecules.

It is important to remember that the value of the acidity constant, K_a, of an acid is related to the standard free energy change for the ionisation, $\Delta G^{\ominus}$, by the relation

$$-\Delta G^{\ominus} = 2{\cdot}303RT \log K_a$$

and that $\Delta G^{\ominus}$ includes both enthalpy and entropy terms:

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

Thus it is found for the ionisation of ethanoic acid in water at 25° ($K_a = 1{\cdot}79 \times 10^{-5}$) that $\Delta G^{\ominus} = 27{\cdot}2$ kJ (6·5 kcal), $\Delta H^{\ominus} = -0{\cdot}5$ kJ ($-0{\cdot}13$ kcal), and $\Delta S^{\ominus} = -92$ J (-22 cal) deg^{-1} [i.e. $T\Delta S^{\ominus} = -27{\cdot}6$ kJ ($-6{\cdot}6$ kcal)]; while for methanoic acid ($K_a = 17{\cdot}6 \times 10^{-5}$) the corresponding figures are: $\Delta G^{\ominus} = 21$ kJ (5·1 kcal), $\Delta H^{\ominus} = -0{\cdot}3$ kJ ($-0{\cdot}07$ kcal), and $\Delta S^{\ominus} = -74$ J (-18 cal) deg^{-1} [i.e. $T\Delta S^{\ominus} = -21{\cdot}3$ kJ ($-5{\cdot}17$ kcal)]. The surprisingly small $\Delta H^{\ominus}$ values almost certainly arise from the fact that the energy required for dissociation of the O—H bond in the undissociated carboxylic acids is cancelled out by that evolved in solvating the resultant ions.

The differing $\Delta G^{\ominus}$s, and hence the differing K_as, for the two acids thus result from the different values of the two entropy ($\Delta S^{\ominus}$) terms. There are two species on each side of the equilibrium and differences in translational entropy on dissociation will thus be small. However, the two species are neutral molecules on one side of the equilibrium and ions on the other. The main feature that contributes to $\Delta S^{\ominus}$ is thus the solvation sheaths of water molecules that surround $RCO_2^{\ominus}$ and $H_3O^{\oplus}$, and the consequent restriction, in terms of increased orderliness, that is thereby imposed on the solvent water molecules; the increase in orderliness not being quite so great as might have been expected as there is already a good deal of orderliness in liquid water itself. The difference in strength between methanoic and ethanoic acids thus does indeed relate to the differential solvation of their anions, as was suggested above.

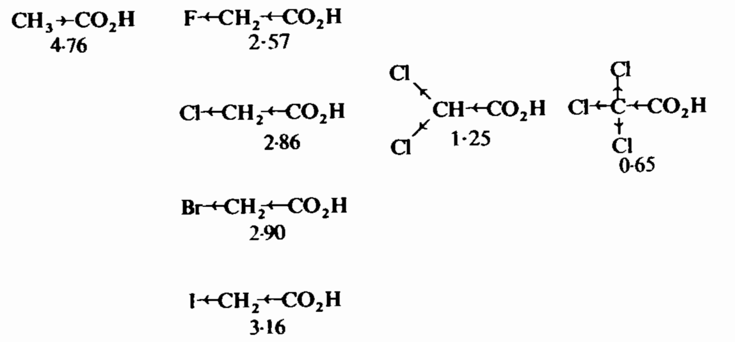
Further substitution of alkyl groups in ethanoic acid has much less effect than this first introduction and, being now essentially a second-order effect, the influence on acid strength is not always regular, steric and other influences playing a part; pK_a values are observed as follows:

Me_2CHCO_2H	4·86
Me_3CCO_2H	5·05
CH_3CO_2H	4·76
$MeCH_2CO_2H$	4·88
$Me(CH_2)_2CO_2H$	4·82
$Me(CH_2)_3CO_2H$	4·86

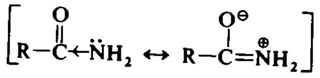
If there is a doubly bonded carbon atom adjacent to the carboxyl group the acid strength is increased. Thus propenoic (acrylic) acid, $CH_2{=}CHCO_2H$, has a pK_a of 4·25 compared with 4·88 for the saturated analogue, propanoic acid. This is due to the fact that the unsaturated α-carbon atom is sp^2 hybridised, which means that electrons are drawn closer to the carbon nucleus than in a saturated, sp^3 hybridised atom due to the rather larger *s* contribution in the sp^2 hybrid. The result is that sp^2 hybridised carbon atoms are less electron-donating that saturated sp^3 hybridised ones, and so propenoic acid though still weaker than methanoic acid is stronger than propanoic. The effect is much more marked with the sp^1 hybridised carbon atom of a triple bond, thus the pK_a of propynoic (propiolic) acid, $HC{\equiv}CCO_2H$, is 1·84. An analogous situation occurs with the hydrogen atoms of ethene and ethyne; those of the former are little more acidic than the hydrogens in ethane, whereas those of ethyne are sufficiently acidic to be readily replaceable by a number of metals (*cf.* p. 272).

3.1.5 Substituted aliphatic acids

The effect of introducing electron-withdrawing substituents into simple aliphatic acids is more marked. Thus halogen, with an inductive effect acting in the opposite direction to alkyl, might be expected to increase the strength of an acid so substituted, and this is indeed observed as pK_a values show:

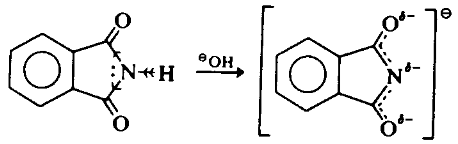


The change is also pronounced with C=O, for not only is the nitrogen atom, with its electron pair, bonded to an electron-withdrawing group through an sp^2 hybridised carbon atom (*cf.* p. 59), but an electron-withdrawing mesomeric effect can also operate:



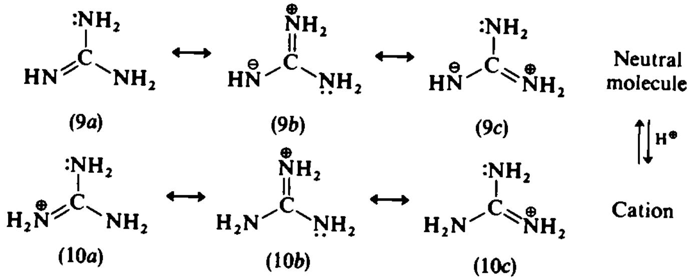
$$\left[R-\overset{O}{\overset{\|}{C}}\leftarrow\ddot{N}H_2 \leftrightarrow R-\overset{O^{\ominus}}{\overset{|}{C}}=\overset{\oplus}{N}H_2\right]$$

Thus amides are found to be only very weakly basic in water [pK_a for ethanamide(acetamide) is ≈0·5], and if two C=O groups are present the resultant imides, far from being basic, are often sufficiently acidic to form alkali metal salts, e.g. benzene-1,2-dicarboximide (phthalimide, 8):



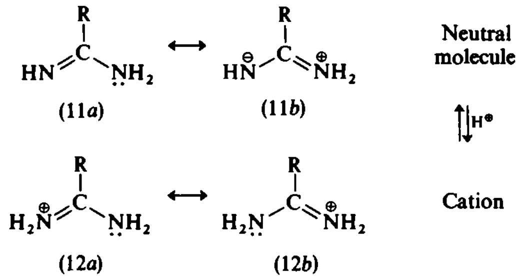
(8)

The effect of delocalisation in *increasing* the basic strength of an amine is seen in guanidine, $HN=C(NH_2)_2$ (9), which, with the exception of the tetraalkylammonium hydroxides above, is among the strongest organic nitrogenous bases known, with a related pK_a of ≈13·6. Both the neutral molecule, and the cation, $H_2\overset{\oplus}{N}=C(NH_2)_2$ (10), resulting from its protonation, are stabilised by delocalisation;



but in the cation the positive charge is spread symmetrically by contribution to the hybrid of three exactly equivalent structures of equal energy. No comparably effective delocalisation occurs in the neutral molecule (in which two of the contributing structures involve separation of charge), with the result that the cation is greatly stabilised with respect to it, thus making protonation 'energetically profitable' and guanidine an extremely strong base.

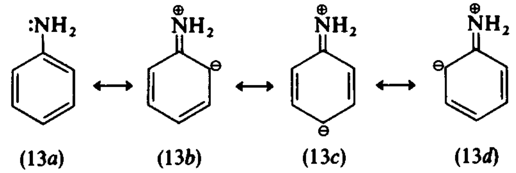
A somewhat analogous situation occurs with the amidines, $RC(=NH)NH_2$ (11):



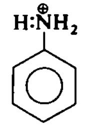
While stabilisation by delocalisation in the cation (12) would not be expected to be as effective as that in the guanidine cation (10) above, ethanamidine, $CH_3C(=NH)NH_2$ (pK_a = 12·4), is found to be a much stronger base than ethylamine, $MeCH_2NH_2$ (pK_a = 10·67).

3.2.3 Aromatic bases

The exact reverse of the above is seen with aniline (13), which is a very weak base (pK_a = 4·62) compared with ammonia (pK_a = 9·25) or cyclohexylamine (pK_a = 10·68). In aniline the nitrogen atom is again bonded to an sp^2 hybridised carbon atom but, more significantly, the unshared electron pair on nitrogen can interact with the delocalised π orbitals of the nucleus:



If aniline is protonated, any such interaction, with resultant stabilisation, in the anilinium cation (14) is prohibited, as the electron pair on N is no longer available:

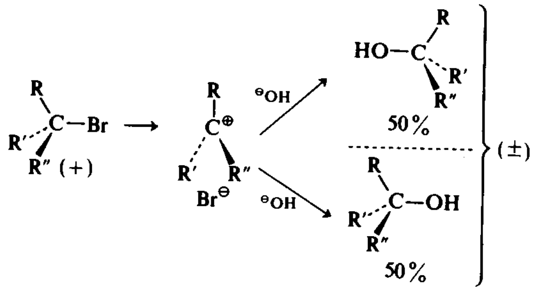


(14)

(25*a*), which 'pairs off' with a second molecule of (+) (25) to form a (±) racemate: the observed rate of *racemisation* will thus be twice the rate of inversion. The reaction was monitored polarimetrically, the rate of racemisation measured thereby, and the rate of inversion calculated from it: it was found to have $k = 2{\cdot}88 \pm 0{\cdot}03 \times 10^{-5}$ (at 30°).

The rate of displacement and of inversion are thus identical within the limits of experimental error, and it thus follows that each act of bimolecular displacement must thus proceed with inversion of configuration. Having shown that S_N2 reactions are attended by inversion of configuration, independent demonstration that a particular reaction occurs *via* the S_N2 mode is often used to correlate the configuration of product and starting material in the reaction.

4.4.3 S_N1 mechanism: racemisation?



As the carbocation formed in the slow, rate-limiting step of the reaction is planar, it might be expected that subsequent attack by a nucleophile such as ⊖OH, or the solvent (H_2O:), would take place with equal readiness from either side of this planar carbocation; leading to a 50/50 mixture of species having the same, and the opposite, configuration as the starting material, i.e. that *racemisation* would take place yielding an optically inactive (±) product.

In practice, however, the expected racemisation—and nothing but racemisation—is rarely observed, it is almost always accompanied by some degree of inversion. The relative proportions of the two are found to depend on: (*a*) the structure of the halide, in particular the relative stability of the carbocation to which it can give rise; and (*b*) the solvent, in particular on its ability as a nucleophile. The more stable the carbocation, the greater is the proportion of racemisation; the more nucleophilic the solvent, the greater is the proportion of inversion. These observations become understandable if the rate-limiting S_N1 ionisation follows the sequence:

$$\overset{\delta+}{R}—\overset{\delta-}{Br} \rightleftarrows \underset{(26)}{\boxed{R^{\oplus}Br^{\ominus}}} \rightleftarrows \underset{(27)}{\boxed{R^{\oplus}}\boxed{Br^{\ominus}}} \rightleftarrows \underset{(28)}{\boxed{R^{\oplus}}} + \boxed{Br^{\ominus}}$$

Here (26) is an *intimate* ion pair in which the jointly solvated gegen-ions are in very close association with no solvent molecules between them, (27) is a *solvent-separated* ion pair, and (28) represents the now dissociated, and separately solvated, pair of ions.

In a solvolysis reaction, attack on $R^{\oplus}$ by a solvent molecule, e.g. H_2O:, in (26) is likely to lead to inversion, as attack can take place (by the solvent envelope) on the 'back' side of $R^{\oplus}$, but not on the 'front' side where there are no solvent molecules, and which is shielded by the $Br^{\ominus}$ gegen ion. Attack in (27) is more likely to lead to attack from either side, leading to racemisation, while attack on (28) can clearly happen with equal facility from either side. Thus the longer the life of $R^{\oplus}$, i.e. the longer it escapes nucleophilic attack, the greater the proportion of racemisation that we should expect to occur. The life of $R^{\oplus}$ is likely to be longer the more stable it is—(*a*) above—but the shorter the more powerfully nucleophilic the solvent—(*b*) above.

Thus solvolysis of $(+)C_6H_5CHMeCl$, which can form a stabilised benzyl type carbocation (*cf.* p. 84), leads to 98% racemisation while $(+)C_6H_{13}CHMeCl$, where no comparable stabilisation can occur, leads to only 34% racemisation. Solvolysis of $(+)C_6H_5CHMeCl$ in 80% acetone/20% water leads to 98% racemisation (above), but in the more nucleophilic water alone to only 80% racemisation. The same general considerations apply to nucleophilic displacement reactions by Nu: as to solvolysis, except that $R^{\oplus}$ may persist a little further along the sequence because part at least of the solvent envelope has to be stripped away before Nu: can get at $R^{\oplus}$. It is important to notice that racemisation is clearly very much less of a stereochemical requirement for S_N1 reactions than inversion was for S_N2.

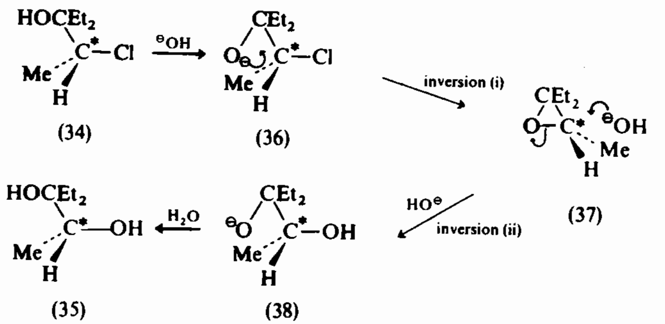
4.4.4 The mechanistic borderline

Reference has already been made (p. 82) to the fact that the reactions of some substrates, e.g. secondary halides, may follow a mixed first/second order rate equation. The question then arises whether such a reaction is proceeding *via* both S_N2 and S_N1 pathways simultaneously (their relative proportions depending on the solvent, etc.) or whether it is proceeding *via* some specific, 'in between' mechanistic pathway.

In solvolytic reactions like those we have just been considering, where the solvent itself is the nucleophile, such mixed kinetics may not be detectable, irrespective of what is actually happening, as both S_N1 and S_N2 pathways are likely to follow a rate equation of the form:

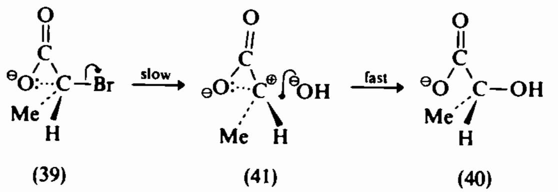
$$\text{Rate} = k[\text{R—X}]$$

This is so because in the S_N2 pathway the concentration of nucleophile will remain essentially constant throughout the reaction as—being also the solvent—it is present in very large, unchanging pair available. This *neighbouring group* can use its electron pair to interact with the 'backside' of the carbon atom undergoing substitution, thus preventing attack by the nucleophilic reagent; attack can thus take place only 'from the frontside', leading to retention of configuration. Thus base hydrolysis of the 1,2-chlorohydrin (34) is found to yield the 1,2-diol (35) with the same configuration (retention):



Initial attack by base on (34) yields the alkoxide anion (36), *internal* attack by this $RO^{\ominus}$ then yields the epoxide (37) with inversion of configuration at C* (these cyclic intermediates can actually be isolated in many cases); this carbon atom†, in turn, undergoes ordinary S_N2 attack by $^{\ominus}OH$, with a second inversion of configuration at C*. Finally, this second alkoxide anion (38) abstracts a proton from the solvent to yield the product 1,2-diol (35) with the same configuration as the starting material (34). This *apparent* retention of configuration has, however, been brought about by two successive inversions.

Another example of oxygen as a neighbouring group occurs in the hydrolysis of the 2-bromopropanoate anion (39) at low $[^{\ominus}OH]$, which is also found to proceed with retention of configuration (40). The rate is found to be independent of $[^{\ominus}OH]$, and the reaction is believed to proceed:

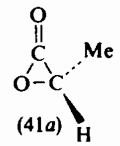


Whether the intermediate (41) is a zwitterion as shown or a highly

---

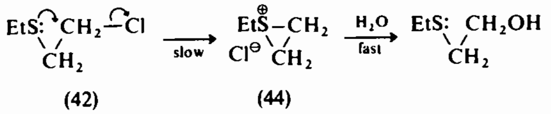
† Preferential attack takes place on this, rather than the other, carbon of the three-membered ring as it will be the more positive of the two, carrying as it does only one electron-donating alkyl group.

labile α-lactone (41*a*)

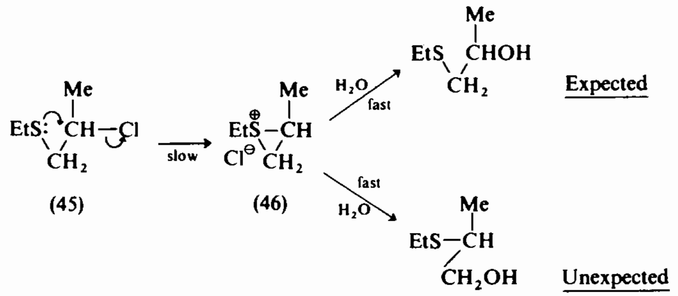


has not been clearly established. As the concentration of nucleophile, $[^{\ominus}OH]$, is increased an increasing proportion of normal S_N2 'attack from the back', with inversion of configuration, is observed.

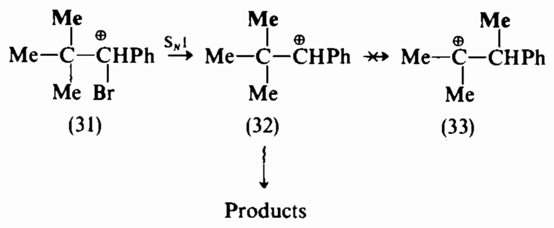
Neighbouring group effects have also been observed with atoms other than oxygen, e.g. sulphur and nitrogen, and in situations where, though no stereochemical point is at issue, unexpectedly rapid rates suggest a change in reaction pathway. Thus $EtSCH_2CH_2Cl$ (42) is found to undergo hydrolysis 10^4 times faster than $EtOCH_2CH_2Cl$ (43) under comparable conditions, and this has been interpreted as involving S: acting as a neighbouring group:



By contrast, O: in (43) is sufficiently electronegative not to donate an electron pair (unlike $O^{\ominus}$ in $RO^{\ominus}$ and $RCO_2^{\ominus}$ above), and hydrolysis of $EtOCH_2CH_2Cl$ thus proceeds *via* ordinary S_N2 attack by an external nucleophile—which is likely to be very much slower than the *internal* nucleophilic attack in (42) ⟶ (44). That a cyclic sulphonium salt such as (44) is involved is demonstrated by the hydrolysis of the analogue (45), which yields two alcohols (the unexpected one in greater yield) indicating the participation of the unsymmetrical intermediate (46):



N: can act as a neighbouring group in similar circumstances, e.g. the hydrolysis of $Me_2NCH_2CH_2Cl$, but the rate is markedly slower,

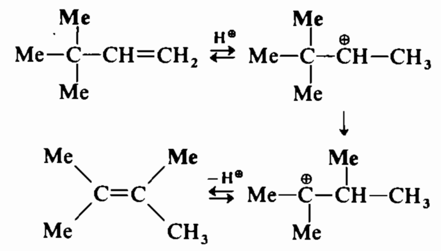


This reflects the greater stability of the benzylic cation (32), though only secondary, compared with the tertiary cation (33) that would be—but in fact is not—obtained by its rearrangement (*cf.* p. 105).

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:

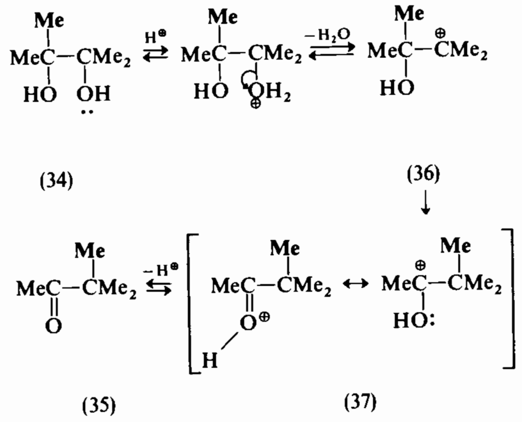


This relatively ready rearrangement can be a nuisance in the preparative addition of acids, e.g. hydrogen halides (p. 184) to alkenes, or in their acid-catalysed hydration (p. 187): mixed products that are difficult to separate may result or, in unfavourable cases, practically none of the desired product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

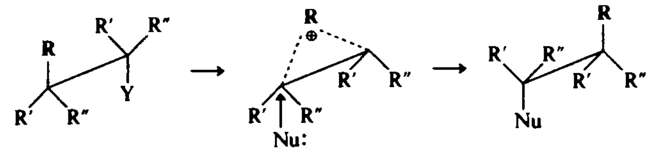
Rearrangement of di- and poly-alkylbenzenes also takes place readily in the presence of Lewis acid catalysts (p. 163), and in the dienone/phenol rearrangement (p. 115).

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):

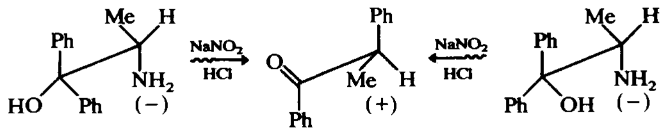


The fact that a 1,2-shift of Me takes place in (36), which is already a tertiary carbocation, results from the extra stabilisation conferred on the rearranged carbocation (37) by delocalisation of charge through an electron pair on the oxygen atom; (37) can also readily lose a proton to yield a stable 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 bromium ion, p. 180) or transition state:



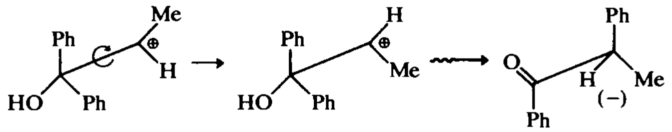
Actual bridging during rearrangement is not, however, by any means universal even when the migrating group is C_6H_5, whose π orbital system might well be expected to assist in the stabilisation of a bridged carbocation through delocalisation (*cf.* p. 105).

This is clearly demonstrated in the pinacolinic deamination (*cf.* p. 114) of an optically active form of the amino-alcohol (50). Such reactions proceed from a conformation (***antiperiplanar***; 50*a* or 50*b*) in which the migrating (Ph) and leaving (NH_2: as N_2; *cf.* p. 114) groups are TRANS to each other. Rearrangement *via* a bridged carbocation would necessarily lead to 100% ***inversion*** at the migration terminus in the product ketone (51*ab*), whichever initial conformation, (50*a*) or (50*b*), was involved:



(50*a*) (51*ab*) (50*b*)

It was actually found, however, that though inversion was predominant (51*ab*: 88%), the product ketone contained a significant amount of the mirror image (51*d*: 12%): thus 12% of the total reaction can not have proceeded *via* a bridged carbocation. The simplest explanation is that part at least of the total rearrangement is proceeding *via* a *non*-bridged carbocation (52c), in which some rotation about the C_1—C_2 bond can take place (52*c* → 52*d*), thereby yielding ketone (51*d*) in which the original configuration has been retained [*cf.* (50*a*) or (50*b*) with (51*d*)]:

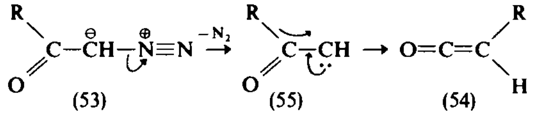


(52*c*) (52*d*) (51*d*)

The ratio of inversion (51*ab*) to retention (51*d*) in the product ketone would then be determined by the relative rate of rotation about C_1—C_2 in (52*c*) compared with the rate of migration of Ph.

5.4.2.5 Wolff rearrangements

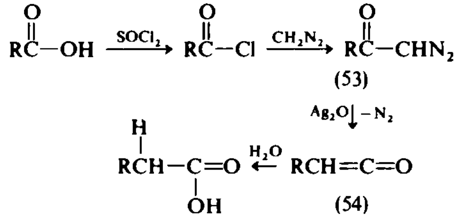
This rearrangement has been separated from carbocationic rearrangements proper as it involves migration to an uncharged, albeit electron-deficient, carbene-like carbon (*cf.* p. 266) atom rather than to a positively charged one. The reaction involves the loss of nitrogen from α-diazoketones (53), and rearrangement to highly reactive *ketenes* (54):



(53) (55) (54)

The ketenes will then react readily with any nucleophiles present in the system, e.g. H_2O below. The reaction can be brought about by photolysis, thermolysis, or by treatment with silver oxide. In the first two cases an actual carbene intermediate (55) is probably formed as shown above, in the silver catalysed reaction loss of nitrogen and migration of R may be more or less simultaneous. In the case where R is chiral, e.g. $C_4H_9C^*MePh$, it has been shown to migrate with retention of its configuration (*cf.* p. 117).

Diazoketones (53) may be obtained by the reaction of diazomethane, CH_2N_2, on acid chlorides, and a subsequent Wolff rearrangement in the presence of water is of importance because it constitutes part of the Arndt–Eistert procedure, by which an acid may be converted into its homologue:



$$\mathrm{R\overset{\overset{O}{\|}}{C}{-}OH \xrightarrow{SOCl_2} R\overset{\overset{O}{\|}}{C}{-}Cl \xrightarrow{CH_2N_2} R\overset{\overset{O}{\|}}{C}{-}CHN_2}\ (53)$$

$$\downarrow \mathrm{Ag_2O}, -\mathrm{N_2}$$

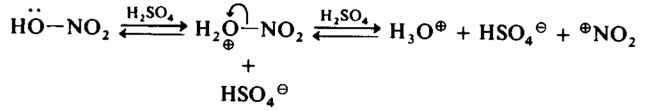
$$\mathrm{R\overset{\overset{H}{|}}{C}H{-}\underset{\underset{OH}{|}}{C}{=}O \xleftarrow{H_2O} RCH{=}C{=}O}\ (54)$$

As well as in water, the reaction can be carried out in ammonia or in an alcohol when addition again takes place across the C=C bond of the ketene to yield an amide or an ester, respectively, of the homologous acid.

The Wolff rearrangement has a close formal resemblance to the Hofmann and related reactions (p. 122), in which migration takes place to an electron-deficient nitrogen atom to form an isocyanate, RN=C=O, intermediate.

5.5 DIAZONIUM CATIONS

The nitrosation of primary amines, RNH_2, with, for example, sodium nitrite and dilute acid (*cf.* p. 107) leads to the formation of diazonium and so prevents the reverse reaction from proceeding. This explanation is unsatisfactory in a number of respects, not least in that nitrobenzene, once formed, appears not to be attacked by water under the conditions of the reaction! What is certain is that nitration is slow in the absence of sulphuric acid, yet sulphuric acid by itself has virtually no effect on benzene under the conditions normally employed. It would thus appear that the sulphuric acid is acting on the nitric acid rather than the benzene in the system. This is borne out by the fact that solutions of nitric acid in pure sulphuric acid show an almost four-fold molecular freezing-point depression (actually $i \approx 3{\cdot}82$), which has been interpreted as being due to formation of the four ions:

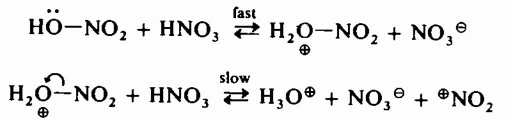


$$\mathrm{H\ddot{O}{-}NO_2} \underset{}{\overset{\mathrm{H_2SO_4}}{\rightleftarrows}} \underset{\underset{\mathrm{HSO_4}^{\ominus}}{+}}{\mathrm{H_2\underset{\oplus}{O}{-}NO_2}} \overset{\mathrm{H_2SO_4}}{\rightleftarrows} \mathrm{H_3O^{\oplus} + HSO_4{}^{\ominus} + {}^{\oplus}NO_2}$$

$$i.e.\ \mathrm{HNO_3 + 2H_2SO_4} \rightleftarrows \underbrace{\mathrm{{}^{\oplus}NO_2 + H_3O^{\oplus} + 2HSO_4{}^{\ominus}}}$$

The slight shortfall of i below 4 is probably due to incomplete protonation of H_2O under these conditions.

The presence of $^{\oplus}NO_2$, the *nitronium ion*, both in this solution and in a number of salts (some of which, e.g. $^{\oplus}NO_2\ ClO_4{}^{\ominus}$, have actually been isolated) has been confirmed spectroscopically: there is a line in the Raman spectrum of each of them at 1400 cm^{-1} which can only originate from a species that is both linear and triatomic. Nitric acid itself is converted in concentrated sulphuric acid virtually entirely into $^{\oplus}NO_2$, and there can be little doubt left that this is the effective electrophile in nitration under these conditions. If the purpose of the sulphuric acid is merely to function as a highly acid medium in which $^{\oplus}NO_2$ can be released from $HO{-}NO_2$, it would be expected that other strong acids, e.g. $HClO_4$, would also promote nitration. This is indeed found to be the case, and HF plus BF_3 are also effective. The poor performance of nitric acid by itself in the nitration of benzene is thus explained for it contains but little $^{\oplus}NO_2$; the small amount that is present is obtained by the two-stage process



$$\mathrm{H\ddot{O}{-}NO_2 + HNO_3} \overset{\text{fast}}{\rightleftarrows} \mathrm{H_2\underset{\oplus}{O}{-}NO_2 + NO_3{}^{\ominus}}$$

$$\mathrm{H_2\underset{\oplus}{O}{-}NO_2 + HNO_3} \overset{\text{slow}}{\rightleftarrows} \mathrm{H_3O^{\oplus} + NO_3{}^{\ominus} + {}^{\oplus}NO_2}$$

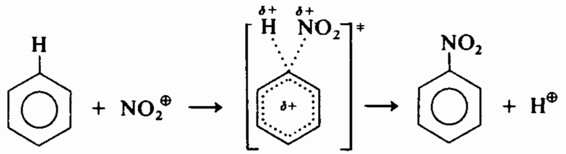
in which nitric acid is first converted rapidly into its conjugate acid, and that then more slowly into $^{\oplus}NO_2$. The rate of nitration of aromatic species more reactive than benzene itself is often found to be independent of [Ar—H], indicating that here it is the actual formation of $^{\oplus}NO_2$ that is the slow, and hence rate-limiting, step in the overall nitration reaction. That $^{\oplus}NO_2$, once formed, is a highly effective nitrating agent is borne out by the rapid nitration that may be effected, of even relatively unreactive aromatic species, by the salt $^{\oplus}NO_2BF_4{}^{\ominus}$ at room temperature or below.

Many nitration reactions with nitrating mixture are, however, found to follow an 'idealised' rate equation of the form,

$$\text{Rate} = k[\mathrm{Ar{-}H}][{}^{\oplus}\mathrm{NO_2}]$$

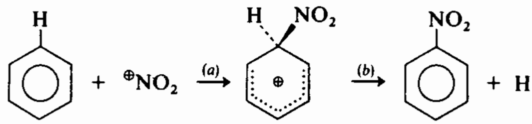
but, in practice, the actual kinetics are not always easy to follow or to interpret for a variety of reasons. Thus the solubility of, for example, benzene itself in nitrating mixture is sufficiently low for the rate of nitration to be governed by the rate at which the immiscible hydrocarbon dissolves in the acid layer. With nitrating mixture, $[^{\oplus}NO_2]$ is related directly to $[HNO_3]$ added, as HNO_3 is converted rapidly and completely into $^{\oplus}NO_2$, but with nitrations in other solvents complex equilibria may be set up. The relation of the concentration of the effective electrophile (nearly always $NO_2{}^{\oplus}$) to the concentration of HNO_3, or other potential nitrating agent, actually added may then be far from simple.

The above general, idealised rate law is compatible with at least three different potential pathways for nitration: one-step, concerted pathway [1] that involves a single transition state (5),



(5) .....[1]

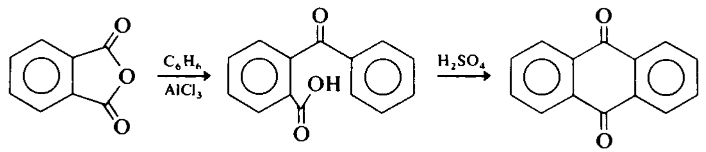
in which $C{-}NO_2$ bond-formation and C—H bond-breaking are occurring simultaneously; or two-step pathways [2] involving a Wheland intermediate or σ complex (6),



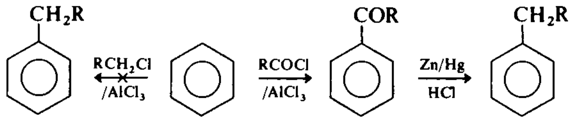
(6) .....[2]

in which *either* step (*a*)— $C{-}NO_2$ bond-formation—*or* step (*b*)— C—H bond-breaking—could be slow and rate-limiting. The C—H bond must, of course, be broken at some stage in all three of the above pathways, but a partial distinction between them is that it must be broken in the slow, rate-limiting step in [1] (only one step, anyway) and in [2*b*], but *not* in [2*a*]. If the C—H bond is, in fact, broken in a rate-limiting step, then the reaction will exhibit a primary kinetic

This latter acylation is used particularly in ring-closures:



Because polyacylation does not occur (*cf.* p.145), it is often preferable to prepare alkyl-benzenes by acylation, followed by Clemmensen or other reduction, rather than by direct alkylation:



6.6 DIAZO COUPLING

Another classical electrophilic aromatic substitution reaction is diazo coupling, in which the effective electrophile has been shown to be the diazonium cation (*cf.* p. 120):

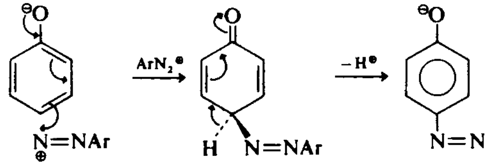
$$Ph\overset{\oplus}{N}{\equiv}N \leftrightarrow PhN{=}\overset{\oplus}{N}$$

This is, however, a weak electrophile compared with species such as $^{\oplus}NO_2$ and will normally only attack highly reactive aromatic compounds such as phenols and amines; it is thus without effect on the otherwise highly reactive PhOMe. Introduction of electron-withdrawing groups into the *o*- or *p*-positions of the diazonium cation enhances its electrophilic character, however, by increasing the positive charge on the diazo group:

Thus the 2,4-dinitrophenyldiazonium cation will couple with PhOMe and the 2,4,6-compound with even the hydrocarbon 2,4,6-trimethylbenzene (mesitylene). Diazonium cations exist in acid and slightly alkaline solution (in more strongly alkaline solution they are converted first into diazotic acids, PhN=N—OH, and then into diazotate anions, $PhN{=}N{-}O^{\ominus}$) and coupling reactions are therefore carried out under these conditions, the optimum pH depending on the species being attacked. With phenols this is at a slightly alkaline pH as it is $PhO^{\ominus}$, and not PhOH, that undergoes attack by $ArN_2^{\oplus}$:

$$\text{Rate} = k[ArN_2^{\oplus}][PhO^{\ominus}]$$

Coupling with phenoxide ion could take place either on oxygen or on carbon, and though relative electron-density might be expected to favour the former, the strength of the bond that is formed is also of significance. Thus here, as with other electrophilic attacks on phenols, it is found to be the C-substituted product (31) that is formed:

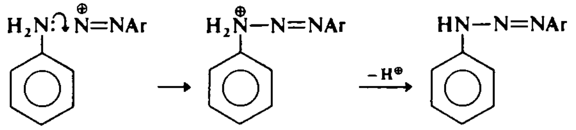


(32) (31)

Removal of the proton (usually non rate-limiting) from (32) is assisted by one or other of the basic species present in solution. Coupling normally takes place largely in the *p*-, rather than the *o*-, position (*cf.* p. 154)—provided this is available—because of the considerable bulk of the attacking electrophile, $ArN_2^{\oplus}$ (*cf.* p. 159).

Aromatic amines are in general somewhat less readily attacked than phenols and coupling is often carried out in slightly acid solution, thus ensuring a high $[PhN_2^{\oplus}]$ without markedly converting the amine, $Ar\ddot{N}H_2$, into the unreactive, protonated cation, $Ar\overset{\oplus}{N}H_3$—such aromatic amines are very weak bases (*cf.* p. 69). The initial diazotisation of aromatic primary amines is carried out in strongly acid media to ensure that as yet unreacted amine *is* converted to the cation and so prevented from coupling with the diazonium salt as it is formed.

With aromatic amines there is the possibility of attack on either nitrogen or carbon, and, by contrast with phenols, attack is found to take place largely on nitrogen, with primary and secondary (i.e. N-alkylanilines) amines, to yield *diazo-amino* compounds (33):



(33)

With most primary amines this is virtually the sole product, but with secondary amines (i.e. N-alkylanilines) some coupling may also take place on a carbon atom of the nucleus, while with tertiary amines (i.e. N,N-dialkylanilines) only the product coupled on carbon (34) is and for attack on chlorobenzene by several different electrophiles:

Increase in size of $E^{\oplus}$ ↓

Reaction	% *o*-	% *p*-	$f_{o\text{-}}/f_{p\text{-}}$
Chlorination	39	55	0·35
Nitration	30	70	0·21
Bromination	11	87	0·06
Sulphonation	1	99	0·005

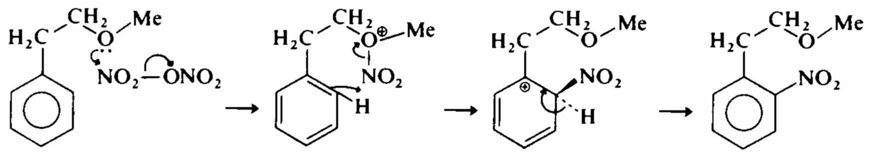
That the steric factor is not the sole determinant is, however, seen in the figures for the nitration of the halobenzenes, which are *o*-/*p*-directing but on which overall attack is slightly slower than on benzene (p. 155):

Increase in size of Y ↓

Y	% *o*-	% *p*-	$f_{o\text{-}}/f_{p\text{-}}$
F	12	88	0·07
Cl	30	69	0·22
Br	37	62	0·30
I	38	60	0·32

Despite the increase in size of the substituent Y from F → I, the proportion of *o*-isomer, and thus the $f_{o\text{-}}/f_{p\text{-}}$ ratio, is actually found to *increase*. An increasing steric effect will, as with the alkyl benzenes, be operating to inhibit *o*-attack, but this must here be outweighed by the electron-withdrawing inductive/field effect exerted by the halogen atom (Y). This effect will tend to decrease with distance from Y, being exerted somewhat less strongly on the distant *p*-position compared with the adjacent *o*-position. Electron-withdrawal will be particularly marked *o*- to the highly electronegative F, and relatively little *o*-attack thus takes place on C_6H_5F, despite the small size of F. The electron-withdrawing effect of the halogen (Y) decreases considerably from F to I (the biggest change being between F and Cl), resulting in increasing attack at the *o*-position *despite* the increasing bulk of Y.

There are some cases where *o*-substitution occurs to the almost total exclusion of any *p*-attack. These commonly arise from complexing of the substituent already present with the attacking electrophile so that the latter is 'steered' into the adjacent *o*-position. Thus when the ether 1-methoxy-2-phenylethane (58) is nitrated with nitrating mixture, 32% *o*- and 59% *p*-isomers are obtained (quite a normal distribution); but nitration with N_2O_5 in MeCN results in the formation of 69% *o*- and 28% *p*-isomers. This preferential *o*-attack in the second case is believed to proceed:

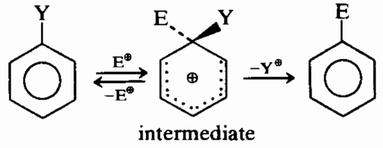


(58)

Finally it should be said that *o*-/*p*-ratios can be considerably influenced by the solvent in which the reaction is carried out. This can arise from changes in the relative stabilisation by solvent molecules of the transition states for *o*- and *p*-attack, but it may also involve the actual attacking electrophile being different in two different solvents: the species actually added complexing with solvent molecules to form the electrophile proper—a different one in each case. This almost certainly occurs in halogenation without Lewis acid catalysts, e.g. in the chlorination of toluene at 25°, where $f_{o\text{-}}/f_{p\text{-}}$ ratios between 0·75 and 0·34 have been observed depending on the solvent.

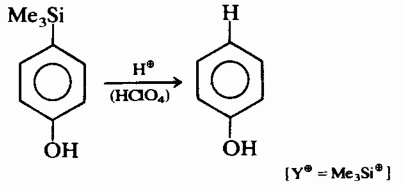
6.7.4 *Ipso* substitution

In addition to *o*-, *m*- and *p*-attack on C_6H_5Y there is, in theory at least, the possibility of attack by an electrophile occurring on the ring carbon atom to which the substituent Y is already attached:

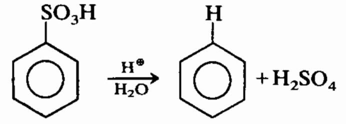


The net result, if the reaction is to involve more than merely reversible formation of an intermediate, would thus be displacement of $Y^{\oplus}$ (by $E^{\oplus}$). Such an overall reaction is referred to as *ipso* substitution.

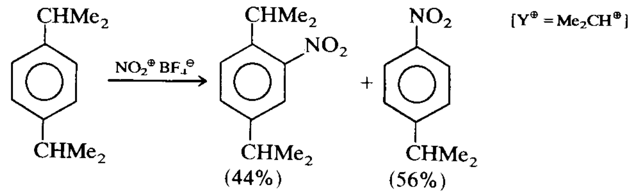
A number of such reactions are known in which the attacking electrophile is $H^{\oplus}$:

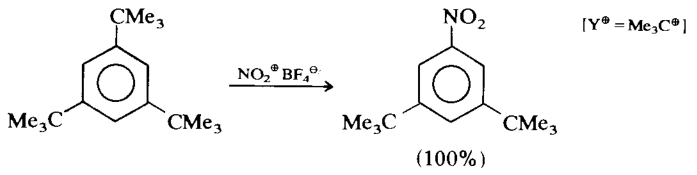


An Me_3Si substituent may be displaced particularly readily in this way (*protodesilylation*), but we have already seen similar displacement of a more familiar substituent (*protodesulphonylation*), in the reversal of sulphonation (p. 140):

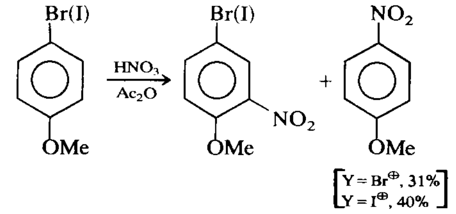


A major feature promoting overall *ipso* substitution will be ease of formation of $Y^{\oplus}$, and we might thus expect to see some such displacement of secondary and tertiary alkyl substituents, because of the relative stability of the resultant carbocations, $R^{\oplus}$. This is found to happen in the nitration (*nitrodealkylation*) reactions below:

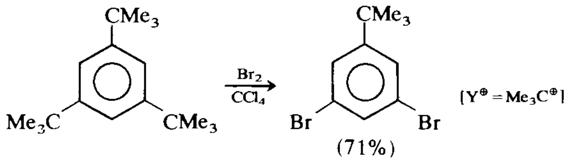




Groups other than alkyl may also be displaced, however (e.g. *nitrodehalogenation*):



Analogous *nitrodechlorination* is not observed, however, owing to the greater resistance to the formation of $Cl^{\oplus}$, compared with $Br^{\oplus}$ and $I^{\oplus}$. Though many of the *ipso* substitutions that have been observed are nitrations, it does also occur during attack by other electrophiles (e.g. *bromodealkylation*):



No doubt *ipso* attack is also promoted here, and in some other of the dealkylations above, through the inhibition of normal electrophilic attack at positions in the ring which are flanked by massive alkyl groups. Perhaps the most important point to note about *ipso* substitution, however, is not to overlook its possible occurrence when contemplating preparative electrophilic substitution of more heavily substituted benzene derivatives.

6.8 KINETIC versus THERMODYNAMIC CONTROL

In all that has gone before a tacit assumption has been made: that the proportions of alternative products formed in a reaction, e.g. *o*-, *m*- and *p*-isomers, are determined by their relative rates of formation, i.e. that the control is kinetic (p. 42). This is not, however, always what is observed in practice; thus in the Friedel–Crafts alkylation of methylbenzene (Me: *o*-/*p*-directing) with benzyl bromide and $GaBr_3$ (as Lewis acid catalyst) at 25°, the isomer distribution is found to be:

Time (sec)	%*o*-	%*m*-	%*p*-
0·01	40	21	39
10	23	46	31

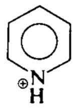
Even after a very short reaction time (0·01 sec) it is doubtful whether the isomer distribution (in the small amount of product that has as yet been formed) is *purely* kinetically controlled—the proportion of *m*-isomer is already relatively large—and after 10 sec it clearly is not: *m*-benzyltoluene, the thermodynamically most stable isomer, predominating and the control now clearly being equilibrium or thermodynamic (p. 43).

This is a situation that must rise where the alternative products are mutually interconvertible under the conditions of the reaction, either by direct isomerisation or by reversal of the reaction to form the starting material which then undergoes new attack to yield a more thermodynamically stable isomer. It is important to emphasise that the relative proportions of alternative products formed will be defined by their relative thermodynamic stabilities *under the conditions of the reaction*, which may possibly differ from those of the isolated molecules. Thus if *m*-dimethylbenzene is heated at 82° with HF and a catalytic amount of BF_3 the proportions of the three isomeric dimethylbenzenes in the product resemble very closely those calculated thermodynamically:

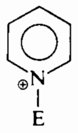
	Experimental	Calculated
%*o*-	19	18
%*m*-	60	58
%*p*-	21	24

If, however, an excess of BF_3 is used the reaction product is found to contain >97% of *m*-dimethylbenzene; this is because the dimethyl-

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):



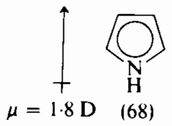
(66)



(67)

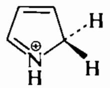
The positive charge will clearly further destabilise any of the σ complexes for electrophilic substitution, as did a substituent such as $^{\oplus}NR_3$ on the benzene nucleus (p. 152), but the destabilisation will be much more marked than with $^{\oplus}NR_3$ as the ⊕ charge is now on an atom of the 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:



(68)

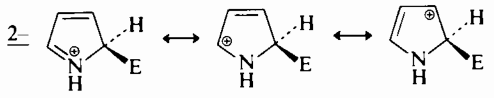
Pyrrole is thus referred to as a *π-excessive* heterocycle and behaves rather like a reactive benzene derivative, e.g. aniline (p. 153), undergoing very ready electrophilic attack. This may be complicated by the fact that in strongly acid solution protonation (69) is forced even on the weakly basic pyrrole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



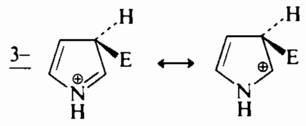
(69)

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*)



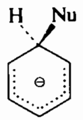
(71*a*) (71*b*)

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.

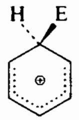
6.10 NUCLEOPHILIC ATTACK ON AROMATIC SPECIES

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):



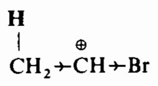
(72)



(73)

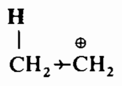
Both (*a*) and (*b*) would be overcome to some extent if a sufficiently powerful electron-withdrawing substituent was present, and nucleophilic attack might then become possible (*cf.* the *addition* of nucleophiles to alkenes carrying electron-withdrawing substituents, p. 198).

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):



$$\overset{\displaystyle H}{\overset{|}{CH_2}} \rightarrow \overset{\oplus}{CH} \rightarrow Br$$

(29)



$$\overset{\displaystyle H}{\overset{|}{CH_2}} \rightarrow \overset{\oplus}{CH_2}$$

(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.

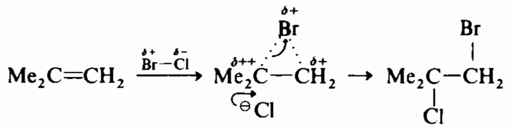
7.4 OTHER ADDITION REACTIONS

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:

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

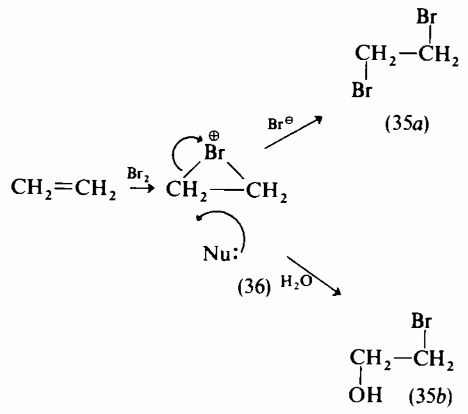
Addition is initiated by the positively polarised end (the less electronegative halogen atom) of the unsymmetrical molecule, and a cyclic halonium ion intermediate probably results. Addition of I—Cl is particularly stereoselective (ANTI) because of the ease of formation (and relative stability compared 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):



$$Me_2C{=}CH_2 \xrightarrow{\overset{\delta+}{Br}-\overset{\delta-}{Cl}} \overset{\delta++}{Me_2C}\!-\!\overset{\delta+}{CH_2}\ (\text{bridged by } \overset{\delta+}{Br};\ {}^{\ominus}Cl) \rightarrow Me_2\underset{\displaystyle Cl}{\underset{|}{C}}-\overset{\displaystyle Br}{\overset{|}{CH_2}}$$

(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):

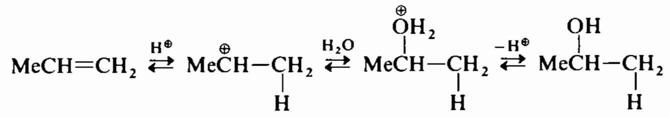


$$CH_2{=}CH_2 \xrightarrow{Br_2} \overset{\overset{\oplus}{Br}}{CH_2\!-\!CH_2} \xrightarrow{Br^{\ominus}} \underset{\displaystyle Br}{\underset{|}{CH_2}}-\overset{\displaystyle Br}{\overset{|}{CH_2}}\ (35a)$$

$$\overset{\overset{\oplus}{Br}}{CH_2\!-\!CH_2}\ (36) \xrightarrow{H_2O} \underset{\displaystyle OH}{\underset{|}{CH_2}}-\overset{\displaystyle Br}{\overset{|}{CH_2}}\ (35b)$$

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:



$$MeCH{=}CH_2 \overset{H^{\oplus}}{\rightleftarrows} Me\overset{\oplus}{C}H-\underset{\displaystyle H}{\underset{|}{CH_2}} \overset{H_2O}{\rightleftarrows} Me\overset{\overset{\oplus}{O}H_2}{\overset{|}{C}}H-\underset{\displaystyle H}{\underset{|}{CH_2}} \overset{-H^{\oplus}}{\rightleftarrows} Me\overset{OH}{\overset{|}{C}}H-\underset{\displaystyle H}{\underset{|}{CH_2}}$$

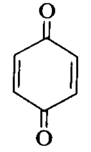
(37)

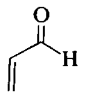
The formation of the carbocationic intermediate (37), either directly or *via* an initial π complex, appears to be rate-limiting, and the overall orientation of addition is Markownikov. There is evidence of some ANTI stereoselectivity, but this is not very marked and is dependent on the alkene and on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

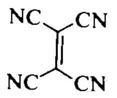
Anti-Markownikov hydration of alkenes may be effected indirectly by addition of B_2H_6 (*hydroboration*), followed by oxidation of the

These reactions are found to be promoted by electron-donating substituents in the diene, and by electron-withdrawing substituents in the alkene, the *dienophile*. Reactions are normally poor with simple, unsubstituted alkenes; thus butadiene (63) reacts with ethene only at 200° under pressure, and even then to the extent of but 18%, compared with ≈100% yield with maleic anhydride (79) in benzene at 15°. Other common dienophiles include cyclohexadiene-1,4-dione (*p*-benzoquinone, 83), propenal (acrolein, 84), tetracyanoethene (85), benzyne (86, *cf.* p. 175), and also suitably substituted alkynes, e.g. diethyl butyne-1,4-dioate ('acetylenedicarboxylic ester', 87):


(83)



(84)



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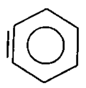
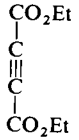
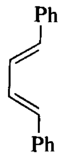

(86)

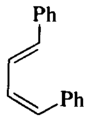


(87)

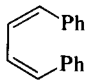
The reaction is also sensitive to steric effects; thus of the three isomerides of 1,4-diphenylbutadiene (88*a* → 88*c*), only the *trans–trans* form (88*a*) will undergo a Diels–Alder reaction:



(88*a*)
trans–trans



(88*b*)
trans–cis



(88*c*)
cis–cis

Diels–Alder reactions are found to be little influenced by the introduction of radicals (*cf.* p. 300), or by changes in the polarity of the solvent: they are thus unlikely to involve either radical or ion pair intermediates. They are found to proceed stereoselectively SYN with respect both to the diene and to the dienophile, and are believed to take place *via* a concerted pathway in which bond-formation and bond-breaking occur more or less simultaneously, though not necessarily to the same extent, in the transition state. This cyclic transition state is a planar, aromatic type, with consequent stabilisation because of the cyclic overlap that can occur between the six *p* orbitals of the constituent diene and dienophile. Such *pericyclic* reactions are considered further below (p. 341).

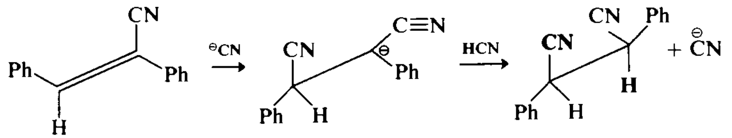
7.6 NUCLEOPHILIC ADDITION

As we saw above, the introduction of electron-withdrawing groups into an aromatic nucleus tended to inhibit electrophilic substitution

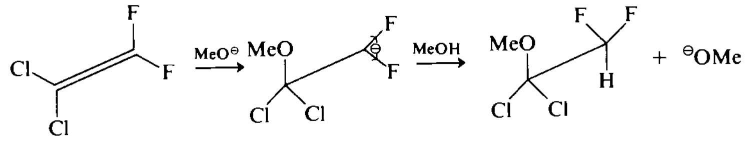
(p. 151), and to make nucleophilic substitution possible (p. 167): exactly the same is true of addition to alkenes. Thus we have already seen that the introduction of electron-withdrawing groups tends to inhibit addition initiated by electrophiles (p. 183); the same groups are also found to promote addition initiated by nucleophiles. A partial order of effectiveness is found to be,

$$\mathrm{CHO > COR > CO_2R > CN > NO_2}$$

but SOR, SO_2R and F also act in the same way. Such substituents operate by reducing π electron density at the alkene carbon atoms, thereby facilitating the approach of a nucleophile, $Y^{\ominus}$, but more particularly by delocalising the -ve charge in the resultant carbanion intermediate, e.g. (89) and (90). This delocalisation is generally more effective when it involves mesomeric delocalisation (89), rather than only inductive electron-withdrawal (90):



(89)



(90)

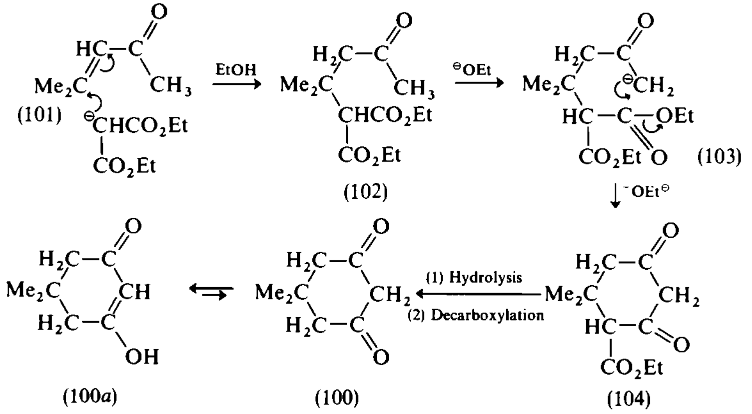
The orientation of addition of an unsymmetrical adduct, HY or XY, to an unsymmetrically substituted alkene will be defined by the preferential formation of the more stabilised carbanion, as seen above (*cf.* preferential formation of the more stabilised carbocation in electrophilic addition, p. 184). There is little evidence available about stereoselectivity in such nucleophilic additions to acyclic alkenes. Nucleophilic addition also occurs with suitable alkynes, generally more readily than with the corresponding alkenes.

A number of these nucleophilic addition reactions are of considerable synthetic importance:

7.6.1 Cyanoethylation

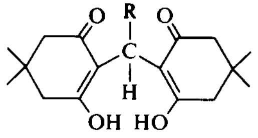
Among the more important of these reactions of general synthetic significance is one in which ethene carries a cyano-substituent (acrylonitrile, 91). Attack of $Y^{\ominus}$ or Y: on the unsubstituted carbon, followed addition at the other; thus PhCH=CHCHO was found to undergo ≈100% C=O addition with PhMgBr, whereas PhCH=CHCOCMe$_3$ underwent ≈100% C=C addition with the same reagent. This also reflects decreasing 'carbonyl' reactivity of the C=O group in the sequence aldehyde > ketone > ester (*cf.* p. 205), with consequent increase in the proportion of C=C addition.

Amines, thiols, $^{\ominus}$OH (p. 226), etc., will also add to the β-carbon atom of $\alpha\beta$-unsaturated carbonyl compounds and esters, but the most important reactions of C=C—C=O systems are in Michael reactions with carbanions: reactions in which carbon–carbon bonds are formed. A good example is the synthesis of 1,1-dimethylcyclohexan-3,5-dione (dimedone, 100) starting from 2-methylpent-2-ene-4-one (mesityl oxide, 101) and the carbanion $^{\ominus}$CH(CO$_2$Et)$_2$:



The Michael reaction as such is complete on formation of the adduct (102), but treatment of this with base ($^{\ominus}$OEt) yields the carbanion (103), which can, in turn, attack the carbonyl carbon atom of one of the CO$_2$Et groups; $^{\ominus}$OEt, a good leaving group, is expelled resulting in cyclisation to (104)—reminiscent of a *Dieckmann* reaction (*cf.* p. 230). Hydrolysis and decarboxylation of the residual CO$_2$Et group then yields the desired end-product dimedone (100), which exists to the extent of ≈100% in the enol form (100*a*).

Dimedone is of value as a reagent for the differential characterisation, and separation, of aldehydes and ketones as it readily yields derivatives (105) with the former, but not with the latter, from a mixture of the two:



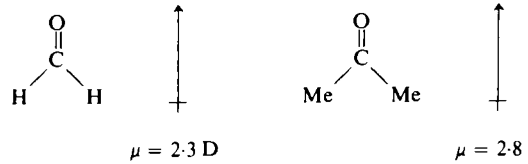
(105)

This selectivity is no doubt due largely to steric reasons.

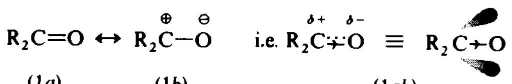
8

Nucleophilic addition to C=O

Carbonyl compounds exhibit dipole moments (μ) because the oxygen atom of the C=O group is more electronegative than the carbon:



As well as the C→O inductive effect in the σ bond joining the two atoms, the more readily polarisable π electrons are also affected (*cf.* p. 22) so that the carbonyl group is best represented by a hybrid structure (1):

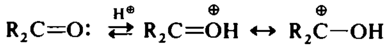


$$R_2C{=}O \leftrightarrow R_2\overset{\oplus}{C}{-}\overset{\ominus}{O} \quad \text{i.e. } R_2\overset{\delta+}{C}{\cdots}\overset{\delta-}{O} \equiv R_2C{\to}O$$

(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.

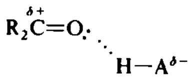
Protonation will clearly increase the positive character of the carbonyl carbon atom (2),



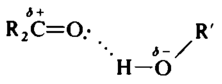
$$R_2C{=}O\colon \overset{H^{\oplus}}{\rightleftarrows} R_2C{=}\overset{\oplus}{O}H \leftrightarrow R_2\overset{\oplus}{C}{-}OH$$

(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)

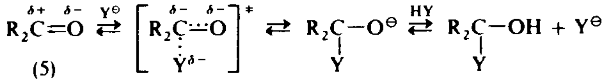


(4)

In the absence of such activation, weak nucleophiles, e.g. $H_2O\colon$, 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. $HCN + \text{base} \rightarrow {}^{\ominus}CN$. Further, while acids may activate the carbonyl carbon atom to nucleophilic attack, they may simultaneously reduce the effective concentration of the nucleophile, e.g. $^{\ominus}CN + HA \rightarrow HCN + A^{\ominus}$, $RNH_2 + HA \rightarrow RNH_3^{\oplus} + A^{\ominus}$. 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

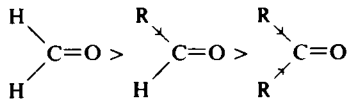
In simple nucleophilic additions where the rate-limiting step is attack by Y$^{\ominus}$, the positive character of the carbonyl carbon atom is reduced on going from the starting material (5) to the transition state (6):



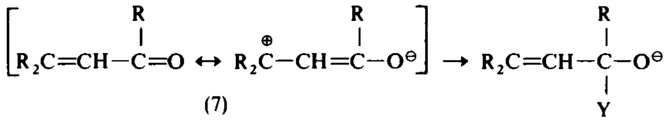
$$R_2\overset{\delta+}{C}{=}\overset{\delta-}{O} \overset{Y^{\ominus}}{\rightleftarrows} \left[R_2\overset{\delta-}{C}{\cdots}\overset{\delta-}{O}\right]^{\ddagger} \rightleftarrows R_2C(Y){-}O^{\ominus} \overset{HY}{\rightleftarrows} R_2C(Y){-}OH + Y^{\ominus}$$

(5) (6)

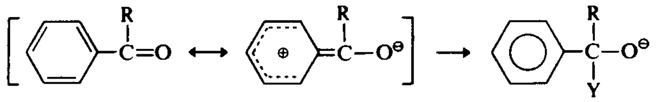
We should thus expect the rate of addition to be reduced by electron-donating R groups and enhanced by electron-withdrawing ones; this is borne out by the observed sequence:



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:

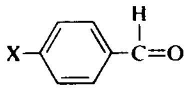


(7) (9)



(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):



(11)

Relative rates: X=NO_2 > H > OMe

(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 $C{=}O \rightsquigarrow CH_2$:

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

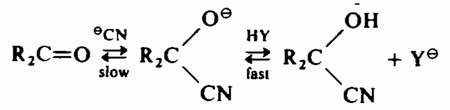
This is a conversion that is usually difficult to effect directly for preparative purposes.

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:

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

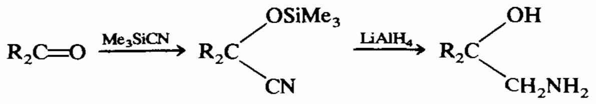
The addition of $^{\ominus}CN$ is reversible, and tends to lie over in favour of starting materials unless a proton donor is present; this pulls the reaction over to the right, as the equilibrium involving the cyanohydrin is more favourable than that involving the intermediate anion (32):



(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).

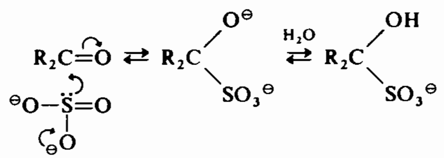
Those carbonyl compounds for which the equilibrium with HCN does not lie over in favour of cyanohydrin formation may often be converted satisfactorily into a derivative of the cyanohydrin through reaction with Me_3SiCN;



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 $HSO_3^{\ominus}$ ($HO^{\ominus} + HSO_3^{\ominus} \rightleftarrows H_2O + SO_3^{2\ominus}$), as though the latter will be present in higher relative concentration the former is a much more effective nucleophile:

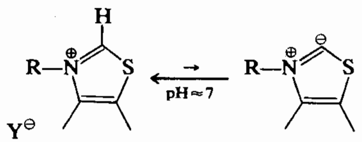


(34) (33)

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

2-hydroxyketone (131). Where Ar = Ph, the product is called benzoin. The reaction is completely reversible.

$^{\ominus}$CN was for long the only species known to catalyse this reaction. It was thought to owe this capacity to: (*a*) its ability as a nucleophile; (*b*) its ability as a leaving group; but, most particularly, (*c*) its ability, through electron-withdrawal, to increase the acidity of the C—H bond in (126) and to stabilise the carbanion (127*a* ↔ 127*b*) that results from loss of this proton. More recently it has been found that the *ylids* (132), formed in low concentration at pH ≈ 7 in solutions of N-alkylthiazolium salts (lacking a 2-substituent),



(132)

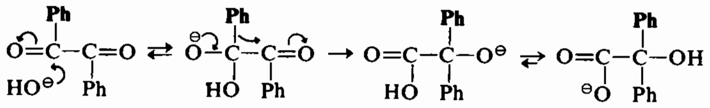
are excellent catalysts for the benzoin condensation. Ylids, which are species which have charges of opposite sign on adjacent atoms, seem a far cry from $^{\ominus}$CN, but it is significant that they would indeed be expected to fulfil roles (*a*), (*b*) and, most notably, (*c*) particularly well.

8.4.10 Benzilic acid rearrangement

Oxidation of benzoin, PhCH(OH)COPh (above) yields benzil, PhCOCOPh (133), and this, in common with non-enolisable 1,2-diketones in general, undergoes base-catalysed rearrangement to yield the anion of an α-hydroxy acid, benzilate anion, $Ph_2C(OH)CO_2^{\ominus}$ (134). This is, almost certainly, the first molecular rearrangement to be recognised as such. The rate equation is found to be,

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

and the reaction is believed to follow the general pathway:



(133) (135) (134)

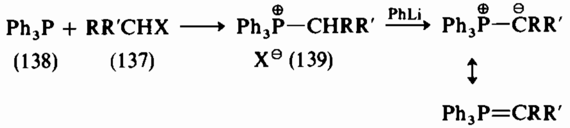
The slow, rate-limiting step is almost certainly the migration of phenyl that occurs in the initial $^{\ominus}$OH adduct (135). This is essentially the analogue for 1,2-diketones of the intramolecular Cannizzaro reaction on the 1,2-dialdehyde glyoxal, OHCCHO (p. 217). In the latter

it was an H atom that migrated with its electron pair, i.e. as hydride ion, to the adjacent C═O group, whereas in benzil (133) it is Ph that migrates with its electron pair, i.e. as a carbanion; hence the reason for considering this reaction as an (intramolecular) carbanion addition to C═O.

The 1,2-ketoaldehyde, PhCOCHO, also reacts with $^{\ominus}$OH, thereby being converted into $PhCH(OH)CO_2^{\ominus}$. This same product could, however, be formed by migration of either H or Ph; experiments with suitably D, and ^{14}C, labelled PhCOCHO show that, in fact, it is only H that migrates. There seem to be no examples of the equivalent of intermolecular Cannizzaro reactions on ketones, involving, as they necessarily must, migration of R with its electron pair from one molecule to another, i.e. $2R_2CO \rightsquigarrow RCO_2^{\ominus} + R_3COH$.

8.4.11 Wittig reaction

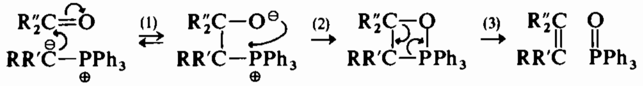
This is an extremely useful reaction for the synthesis of alkenes. It involves the addition of a phosphonium ylid, e.g. (136), also known as a *phosphorane*, to the carbonyl group of an aldehyde or ketone; the ylid is indeed a carbanion having an adjacent hetero atom. Such species are generated by the reaction of an alkyl halide, RR′CHX (137), on a trialkyl- or triaryl-phosphine (138)—very often Ph_3P—to yield a phosphonium salt (139), followed by abstraction of a proton from it by a very strong base, e.g. PhLi:



$$\underset{(138)}{Ph_3P} + \underset{(137)}{RR'CHX} \longrightarrow \underset{X^{\ominus}\,(139)}{Ph_3\overset{\oplus}{P}\text{—}CHRR'} \xrightarrow{PhLi} Ph_3\overset{\oplus}{P}\text{—}\overset{\ominus}{C}RR' \updownarrow \underset{(136)}{Ph_3P{=}CRR'}$$

Addition of the Wittig reagent (136) to C═O, e.g. (140), is believed to follow the pathway:

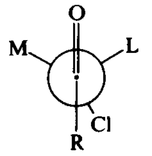
(140)



(136) (141) (142)

All Wittig reactions do not, however, follow the same detailed pathway: step (1) may, or may not, be an equilibrium, and the rate-limiting step may also differ. It is, in some cases, possible to detect (at −80°) the *oxaphosphetane* intermediate (141), which then decomposes to products on raising the temperature (→0°). The driving force underlying this rather unusual reaction is the large amount of energy that is evolved through forming the very strong P═O bond (535 kJ mol^{-1}). If the original phosphonium salt (139) is 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,

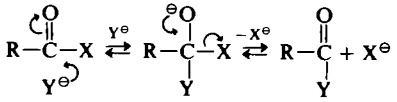


(155)

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.

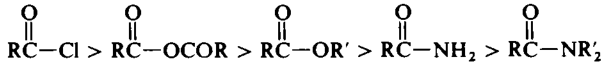
8.6 ADDITION/ELIMINATION REACTIONS OF CARBOXYLIC DERIVATIVES

The general reactions of this series are of the form:



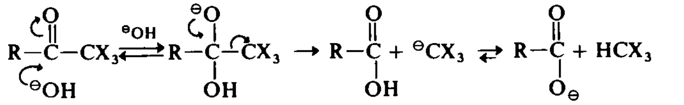
(156) (157)

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:



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

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):

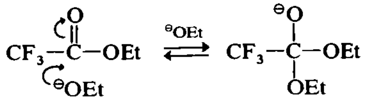


(158)

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

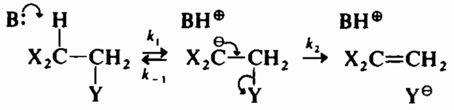
$$\text{Rate} = k[\text{RCOX}][\text{Y}^{\ominus}]$$

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 this is referred to as the E1 mechanism (*Elimination, unimolecular*). It is reminiscent of S_N1 (*cf.* p. 79), and the carbocationic intermediates for S_N1 and E1 are, of course, identical. Finally, the H—C bond could be broken first, (*c*), involving a carbanion intermediate (6);



(6)

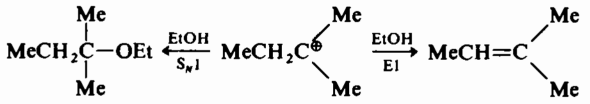
this is referred to as the E1cB mechanism [*Elimination*, from *conjugate Base*, i.e. (6)]. Examples of reactions proceeding by all three mechanisms are known: E1cB is the least, and E2 probably the most, common. The three mechanisms will now be considered in turn, but it should be realised that they are only limiting cases (*cf.* S_N1/S_N2), and that in fact a continuous mechanistic spectrum, in the relative time of breaking of the two bonds, is available and is indeed observed in practice.

9.2 E1 MECHANISM

If, as is normally the case, carbocation, e.g. (5), formation is slow and rate-limiting (i.e. $k_2 > k_{-1}$), then the rate law observed with, for example, the bromide $MeCH_2CMe_2Br$ is;

$$\text{Rate} = k[MeCH_2CMe_2Br]$$

the overall elimination is then completed (7) by rapid, non rate-limiting removal of a proton from (8) usually by a solvent molecule, in this case EtOH:



(9) (8) (7)

It could be claimed that such an E1 solvolytic elimination would be indistinguishable kinetically from a bimolecular (E2) elimination, in which EtOH was acting as base, because the [EtOH] term in the E2 rate law,

$$\text{Rate} = k[MeCH_2CMe_2Br][EtOH]$$

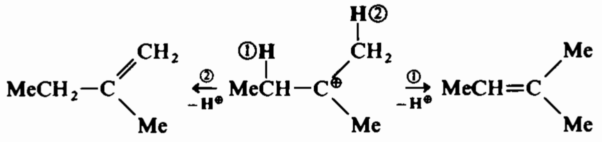
would remain constant. The two can often be distinguished, however, by adding a little of the conjugate base of the solvent, i.e. $^{\ominus}$OEt in this case. If no significant change in rate is observed, an E2 mechanism cannot be operating, for if $^{\ominus}$OEt is not participating as a base the much weaker EtOH certainly cannot be.

The carbocation (8) is identical with that from S_N1 solvolysis (p. 79), and the latter reaction to yield the substitution product (9) is commonly a competitor with E1 elimination. Some evidence that the two processes do have a common intermediate is provided by the fact that the $E1/S_N1$ ratio is reasonably constant for a given alkyl group irrespective of the leaving group, $Y^{\ominus}$. The two processes do, however, proceed from (8) to products—(7) and (9), respectively—*via* different T.S.s, and the factors that influence elimination *v.* substitution are discussed subsequently (p. 260).

The factors that promote unimolecular, as opposed to bimolecular (E2), elimination are very much the same as those that promote S_N1 with respect to S_N2, namely: (*a*) an alkyl group in the substrate that can give rise to a relatively stable carbocation, and (*b*) a good ionising, ion-solvating medium. Thus (*a*) is reflected in the fact that with halides, increasing E1 elimination occurs along the series,

primary < secondary < tertiary

reflecting the relative stability of the resultant carbocations; primary halides hardly ever undergo E1 elimination. Branching at the β-carbon atom also favours E1 elimination; thus $MeCH_2CMe_2Cl$ is found to yield only 34% of alkene, while Me_2CHCMe_2Cl yields 62%. This is probably related to the fact that Me_2CHCMe_2Cl can lead to a more heavily substituted, and hence thermodynamically more stable (*cf.* p. 26), alkene than the first. This is, with E1 reactions, also the major controlling factor (Saytzeff elimination, p. 256) in orientation of elimination, where more than one alkene can be derived by loss of different β-protons from a carbocationic intermediate (8):



(10) (8) (7)

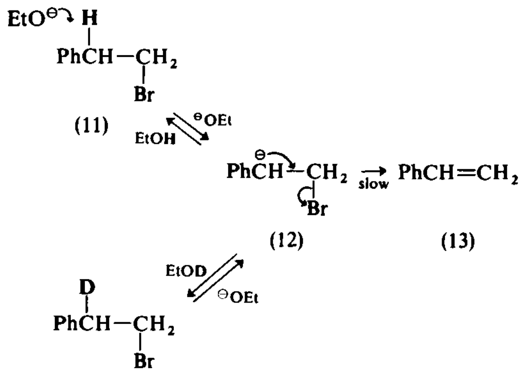
Thus in the above case the elimination product is found to contain 82% of (7). Unexpected alkenes may arise, however, from rearrangement of the initial carbocationic intermediate before loss of proton. E1 elimination reactions have been shown as involving a dissociated carbocation; they may in fact often involve ion pairs, of varying degrees of intimacy depending on the nature of the solvent (*cf.* S_N1, p. 90).

9.3 E1cB MECHANISM

If, as might be expected for this pathway, formation of the carbanion intermediate (6) is fast and reversible, while subsequent loss of the leaving group, Y$^{\ominus}$, is slow and rate-limiting, i.e. $k_{-1} > k_2$, then this reaction will follow the rate law,

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

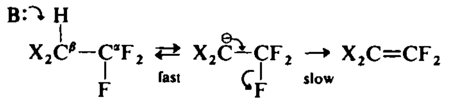
and will be kinetically indistinguishable from the concerted (E2) pathway. It should be possible to distinguish between them, however, by observing exchange of isotopic label, between as yet unchanged substrate and solvent, arising during fast, reversible carbanion (6) formation—something that clearly could not happen in the one-step, concerted (E2) pathway. A good example to test would be $PhCH_2$-CH_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)

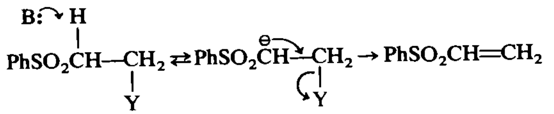
The reaction was carried out with $^{\ominus}$OEt in EtOD, and (11) re-isolated after ≈ half-conversion to (13): it was found to contain no deuterium, i.e. no (14); nor did the alkene (13) contain any deuterium, as might have been expected by elimination from any (14) formed. This potentially favourable 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 $\approx$30–60 kJ (7–14 kcal) mol^{-1} (the reverse of step 2 would require addition of Y$^{\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:

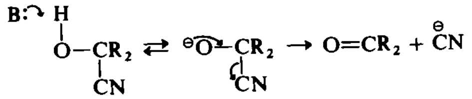


(18) (19)

Y: $PhSe > PhO > PhS \approx PhSO_2 > PhSO > MeO \gg CN$

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

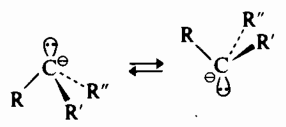
By far the commonest elimination mechanism is the one-step concerted (E2) pathway exhibiting, e.g. for the base-induced elimination of HBr from the halide RCH_2CH_2Br (21), the rate law:

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

As B is often a nucleophile as well as a base, elimination is frequently accompanied by one-step, concerted (S_N2) nucleophilic substitution

10.3 CARBANION CONFIGURATION

In theory a simple carbanion of the type $R_3C^{\ominus}$ could assume a pyramidal (sp^3) or a planar (sp^2) configuration, or possibly something in between depending on the nature of R. The pyramidal configuration would be preferred on energy grounds, as the unshared electron pair would then be accommodated in an sp^3 orbital (19) rather than in the higher energy, unhybridised p orbital of the planar configuration. The pyramidal configuration is, of course, the one adopted by tertiary amines, R_3N:, with which simple carbanions, $R_3C^{\ominus}$ are isoelectronic; no doubt ready inversion of configuration takes place with carbanions (19*a* ⇄ 19*b*) just as it does with the amines:

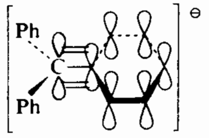


(19*a*) (19*b*)

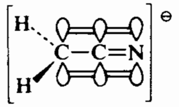
Evidence in support of a preferred sp^3 configuration is provided by the observation that reactions which involve the formation of carbanion intermediates at bridgehead positions often take place readily; while those that would have involved the corresponding carbocation (sp^2) intermediates do not (*cf.* p. 86).

In organometallic compounds of the form RR′R″C—M, pretty well the whole spectrum of bonding is known from the essentially covalent, *via* the polar-covalent, $RR'R''C^{\delta-}{-}M^{\delta+}$, to the essentially ionic, $RR'R''C^{\ominus}M^{\oplus}$. In their reactions, predominant retention, racemisation, and inversion of configuration have all been observed; the outcome in a particular case depending not only on the alkyl residue, but also on the metal, and particularly on the solvent. Even with the most ionic examples it seems unlikely that we are dealing with a simple carbanion; thus in the reaction of EtI with $[PhCOCHMe]^{\ominus}\ M^{\oplus}$, the relative rates under analogous conditions are found to differ over a range of $\approx 10^4$ for M = Li, Na and K.

Carbanions which have substituents capable of conjugative delocalisation of the electron pair will perforce be planar (sp^2), in order to allow the maximum orbital overlap of the p orbital with those of the substituent, e.g. (4) and (10):

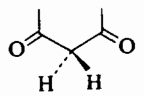


(4)

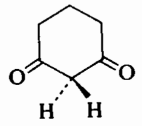


(10)

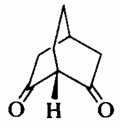
Where such alignment is prevented by structural or steric features, the expected stabilisation may not take place. Thus while pentan-2,4-dione (20), with a pK_a value of 8·8, and cyclohexan-1,3-dione (21) are both readily soluble in aqueous NaOH (though not in water), and give a red colour with $FeCl_3$ solution (*cf.* phenol), the formally similar 1,3-diketone (22) does neither:



(20)



(21)

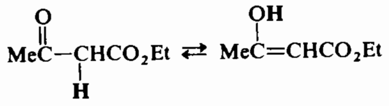


(22)

The H atom flanked by the two C=O groups in (22) exhibits hardly any more acidic character than the analogous one in the corresponding hydrocarbon. The different behaviour of (22) stems from the fact that after proton removal, the carbanion's lone pair would be in an sp^3 orbital more or less at right angles to the p orbitals on each of the adjacent carbonyl carbon atoms (*cf.* p. 259): no sp^3/p overlap could thus take place, consequently there would be no stabilisation of the −ve charge through delocalisation, and the (unstabilised) carbanion does not, therefore, form.

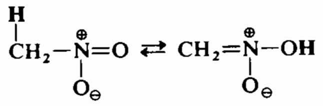
10.4 CARBANIONS AND TAUTOMERISM

Tautomerism, strictly defined, could be used to describe the reversible interconversion of isomers, in all cases and under all conditions. In practice, the term has increasingly been restricted to isomers that are fairly readily interconvertible, and that differ from each other only (*a*) in electron distribution, and (*b*) in the position of a relatively mobile atom or group. The mobile atom is, in the great majority of examples, hydrogen, and the phenomenon is then referred to as *prototropy*. Familiar examples are β-ketoesters, e.g. ethyl 2-ketobutanoate (ethyl acetoacetate, 23), and aliphatic nitro compounds, e.g. nitromethane (24):



$$\mathrm{Me}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}{-}\underset{\mathrm{H}}{\underset{|}{\mathrm{C}}}\mathrm{HCO_2Et} \rightleftarrows \mathrm{Me}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}{=}\mathrm{CHCO_2Et}$$

(23*a*) Keto (23*b*) Enol



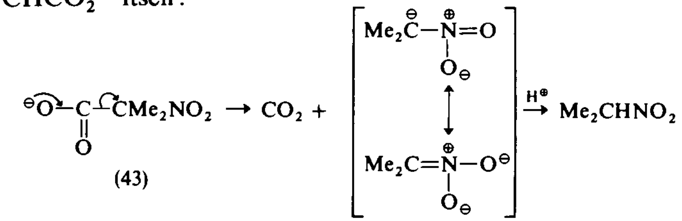
$$\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}\mathrm{H_2}{-}\underset{\mathrm{O}_{\ominus}}{\underset{|}{\overset{\oplus}{\mathrm{N}}}}{=}\mathrm{O} \rightleftarrows \mathrm{CH_2}{=}\underset{\mathrm{O}_{\ominus}}{\underset{|}{\overset{\oplus}{\mathrm{N}}}}{-}\mathrm{OH}$$

(24*a*) (24*b*)

Pseudo-acid Aci-form

Such interconversions are catalysed by both acids and bases.

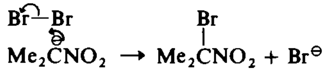
$Me_2CHCO_2{}^{\ominus}$ itself:


(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 $MeCO_2{}^{\ominus}$.

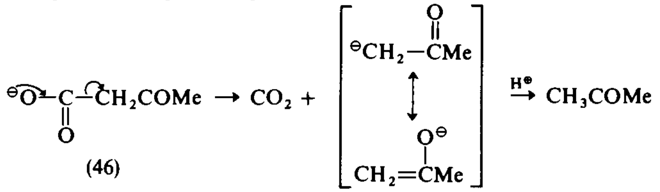
Evidence that carbanion intermediates, e.g. (44), are involved is provided by carrying out the decarboxylation in the presence of bromine. This is without effect on the overall rate of the reaction but the end-product is now Me_2CBrNO_2 rather than Me_2CHNO_2—under conditions where neither $Me_2C(NO_2)CO_2{}^{\ominus}$ 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):



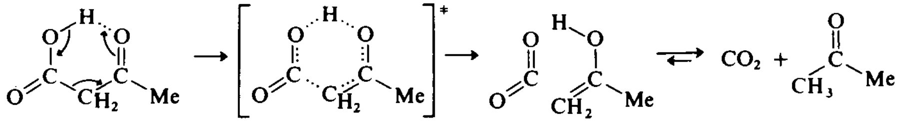
$$\overset{Br-Br}{Me_2\overset{\ominus}{C}NO_2} \rightarrow \overset{Br}{\underset{}{Me_2CNO_2}} + Br^{\ominus}$$

(44) (45)

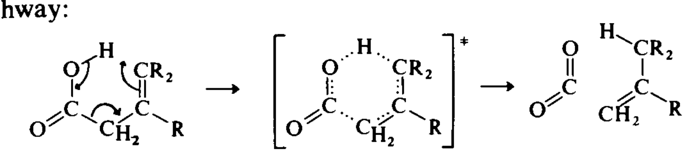
C=O can also act like NO_2, and the anions of *β*-ketoacids (46) are decarboxylated very readily:


(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):

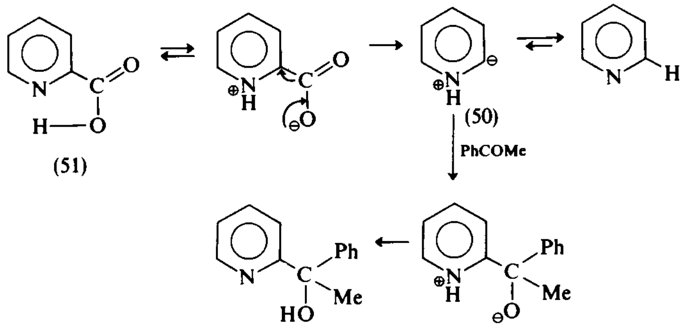

(47) (48)

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


(49)

αβ-unsaturated acids, $R_2CHCR{=}CHCO_2H$, probably decarboxylate by this pathway also, as it has been shown that they isomerise to the corresponding *βγ*-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)

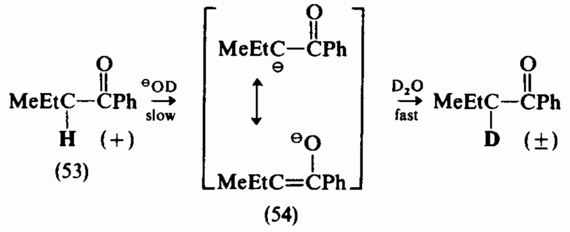
The ylid intermediate (50) can be 'trapped' by carrying out the decarboxylation in the presence of carbonyl compounds, e.g. PhCOMe, to yield the carbanion addition product, e.g. (52); this process can indeed be used preparatively. The reason for the much easier decarboxylation of (51), than of its 3-, 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.

10.5.3.1 Deuterium exchange

The ketone (53) is found to undergo exchange of its α-hydrogen atom for deuterium when treated with base ($^{\ominus}OD$) in solution in D_2O. When the reaction was carried out on an optically active form of (53), it underwent loss of optical activity (*racemisation*) at the same rate as deuterium exchange. When the analogous compound containing D in place of H underwent exchange in H_2O, there was found to be a kinetic isotope effect (k_H/k_D) on comparing the rates of exchange for the two compounds:



(53) (54)

This all suggests slow, rate-limiting breaking of the C—H bond to form the stabilised carbanion intermediate (54), followed by fast uptake of $D^{\oplus}$ from the solvent D_2O. Loss of optical activity occurs at each C—H bond breakage, as the bonds to the carbanion carbon atom will need to assume a planar configuration if stabilisation by delocalisation over the adjacent C=O is to occur. Subsequent addition of $D^{\oplus}$ is then statistically equally likely to occur from either side. This slow, rate-limiting formation of a carbanion intermediate, followed by rapid electrophilic attack to complete the overall substitution, is formally similar to rate-limiting carbocation formation in the S_N1 pathway; it is therefore referred to as the S_E1 pathway.

10.5.3.2 Carbanion nucleophiles

Both overt carbanions and organometallic compounds, such as Grignard reagents, are powerful nucleophiles as we have seen in their addition reactions with C=O (p. 221 *et seq.*); they tend therefore to promote an S_N2 pathway in their displacement reactions. Particularly useful carbanions, in preparative terms, are those derived from $CH_2(CO_2Et)_2$, β-ketoesters, 1,3-(β-)diketones, e.g. (55), α-cyanoesters, nitroalkanes, etc.—the so-called 'reactive methylenes':

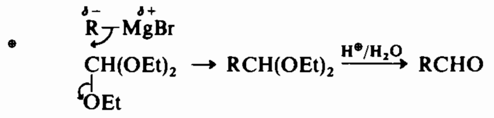
$$\underset{(55)}{(MeCO)_2CH_2} \overset{^{\ominus}OEt}{\rightleftarrows} (MeCO)_2\overset{\ominus}{C}H + R{-}Br \xrightarrow{RBr} \underset{(56)}{(MeCO)_2CH{-}R} + Br^{\ominus}$$

The S_N2 character of the process has been confirmed kinetically, and in suitable cases inversion of configuration has been demonstrated at the carbon atom attacked in RBr above. The alkylated product (56) still contains an acidic hydrogen, and the process may be repeated to yield the dialkyl product, $(MeCO)_2CRR'$. Synthetically useful alkylations can also be effected on acetylide anion (57):

$$HC{\equiv}CH \overset{^{\ominus}NH_2}{\rightleftarrows} \underset{(57)}{HC{\equiv}C^{\ominus}} + R{-}Br \xrightarrow{RBr} HC{\equiv}C{-}R + Br^{\ominus}$$

Here too, a second alkylation can be made to take place yielding RC≡CR or R′C≡CR. It should, however, be remembered that the above carbanions—particularly the acetylide anion (57)—are the anions of very weak acids, and are thus themselves strong bases, as well as powerful nucleophiles. They can thus induce elimination (p. 260) as well as displacement, and reaction with tertiary halides is often found to result in alkene formation to the exclusion of alkylation.

Grignard reagents can also act as sources of negative carbon in displacement reactions, e.g. in the synthetically useful reaction with triethoxymethane (ethyl orthoformate, 58) to yield acetals (59) and, subsequently, their parent aldehydes (60):

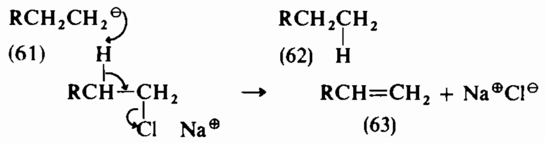


(58) (59) (60)

It is also possible, under suitable conditions, to generate the alkyls (61) of more electropositive metals, e.g. sodium, and then subsequently to react these with alkyl halides:

$$RCH_2CH_2{-}Cl \xrightarrow{2Na\cdot} \underset{(61)}{RCH_2CH_2{}^{\ominus}Na^{\oplus}} \xrightarrow{R'Br} RCH_2CH_2R'$$

This is, of course, the Wurtz reaction, and support for such a mechanism involving carbanions (radicals may be involved under some conditions, however) is provided by the observation that in some cases it is possible, with optically active halides, to demonstrate inversion of configuration at the carbon atom undergoing nucleophilic attack. The carbanion, e.g. (61), can also act as a base and promote elimination:



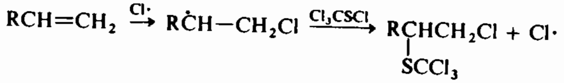
(61) (62) (63)

Thus leading to the disproportionation—alkane (62) + alkene (63)—that is often observed as a side-reaction to the normal Wurtz coupling.

to that for HBr. The addition is of preparative value for making dialkyl sulphides, but is reversible:

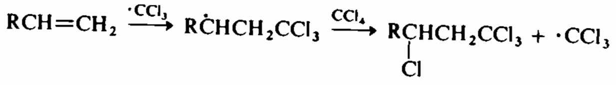
$$RCH{=}CH_2 + R'SH \overset{Ra\cdot}{\rightleftarrows} RCH_2CH_2SR'$$

Sulphenyl chlorides, e.g. Cl_3CSCl, can also be used as sources of thiyl radicals, but here the addition is initiated by Cl· and the R′S will thus become attached to the other carbon atom of the double bond:



$$RCH{=}CH_2 \xrightarrow{Cl\cdot} R\dot{C}H{-}CH_2Cl \xrightarrow{Cl_3CSCl} \underset{\displaystyle SCCl_3}{RCHCH_2Cl} + Cl\cdot$$

Carbon–carbon bonds may be formed by the addition, among other things, of halomethyl radicals to alkenes. The $\cdot CX_3$ (X = Br, Cl) may be generated by the action of peroxides on, or by photolysis of, CX_4:



$$RCH{=}CH_2 \xrightarrow{\cdot CCl_3} R\dot{C}HCH_2CCl_3 \xrightarrow{CCl_4} \underset{\displaystyle Cl}{RCHCH_2CCl_3} + \cdot CCl_3$$

(74) (75)

That the relatively inert CCl_4 adds in this way may seem a little surprising, but the ΔH values for both steps of the reaction chain are exothermic: −75(−18), and −17(−4) kJ (kcal) mol^{-1}. The first formed radical (74) may, however, compete with $\cdot CCl_3$ in adding to $RCH{=}CH_2$, so that low molecular weight polymers are formed under some conditions, as well as the normal addition product (75).

11.5.1.4 Vinyl polymerisation

This reaction has been the subject of a great deal of theoretical and mechanistic study, largely because of the commercial importance of the polymers to which it can give rise. Like the other radical reactions we have discussed, it can be said to involve three stages—(*a*) initiation, (*b*) propagation, and (*c*) termination:

(*a*) *Initiation*:
  (i) Formation of initiator, Ra·, from, e.g. peroxides or azo compounds.
  (ii) $Ra\cdot + CH_2{=}CH_2 \rightarrow RaCH_2CH_2\cdot$

(*b*) *Propagation*:

$$RaCH_2CH_2\cdot \rightsquigarrow\!\xrightarrow{(n-1)CH_2=CH_2} Ra(CH_2)_{2n}\cdot$$

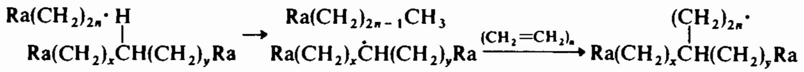
(*c*) *Termination*:
  (i) $Ra(CH_2)\cdot_{2n} + \cdot Ra \rightarrow Ra(CH_2)_{2n}Ra$
  (ii) $Ra(CH_2)\cdot_{2n} + \cdot(CH_2)_{2n}Ra \rightarrow Ra(CH_2)_{4n}Ra$
  (iii) $Ra(CH_2)_xCH_2\cdot + \cdot CH_2CH_2(CH_2)_yRa \rightarrow Ra(CH_2)_xCH_3 + CH_2{=}CH(CH_2)_yRa$

The propagation step is usually very rapid.

As the alkene monomers can absorb oxygen from the air, forming peroxides (*cf.* p. 329) whose ready decomposition can effect auto-initiation of polymerisation, it is usual to add a small quantity of inhibitor, e.g. quinone, to stabilise the monomer during storage. When subsequent polymerisation is carried out, sufficient radical initiator must therefore be added to 'saturate' the inhibitor before any polymerisation can be initiated; an induction period is thus often observed.

The radical initiators are not, strictly speaking, catalysts—though often referred to as such—for each radical that initiates a polymer chain becomes irreversibly attached to it and, if of suitable composition, may be detected in the molecules of product. The efficiency of some initiators may be so great that, after any induction period, every radical generated leads to a polymer chain.

Termination of a growing chain can result from collision with either an initiator radical (*c* i) or with another growing chain (*c* ii), but of these the latter is much the more frequent, as the initiator radicals will have been largely used up in starting the chains. Termination has been shown above as dimerisation (*c* ii), but it can also involve disproportionation (*cf.* p. 305) between growing chains (*c* iii). H-abstraction can also occur by attack of a growing chain on 'dead' (no longer growing) polymer, leading to a new growing point and, hence, to *branching* (76):



$$\begin{matrix} Ra(CH_2)_{2n}\cdot\ H \\ Ra(CH_2)_x\underset{}{C}H(CH_2)_yRa \end{matrix} \rightarrow \begin{matrix} Ra(CH_2)_{2n-1}CH_3 \\ Ra(CH_2)_x\dot{C}H(CH_2)_yRa \end{matrix} \xrightarrow{(CH_2=CH_2)_n} \begin{matrix} (CH_2)_{2n}\cdot \\ Ra(CH_2)_xCH(CH_2)_yRa \end{matrix}$$

(76)

The extent to which branching occurs can, hardly surprisingly, have a profound effect on the physical and mechanical properties of the resultant polymer.

Another major influence on the properties of the polymer is the average molecular weight, i.e. the average length of polymer molecules; this may vary from only a few monomer units to many thousand. Apart from the average length of polymer molecules, the actual spread of lengths among the polymer molecules also has a considerable influence; thus the properties of two polymers of approximately the same average m.w. will differ greatly if one is made up of molecules all of much the same length, while the other includes both very long and very short polymer molecules in its make-up. The length of molecules in a polymer may be controlled in a number of ways. Thus increase in the concentration of initiator, relative to that of alkene, will lead to shorter chain lengths: the number of growing chains is increased, and termination thus becomes more probable relative to continued propagation. Alternatively, actual terminators may be added or, more usually, *chain transfer agents*. These are compounds, usually of the form XH, that suffer H-abstraction by a growing polymer chain, 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:

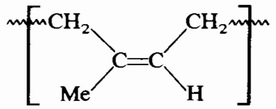
$$\text{Ra(CH}_2)_n\text{CH}_2\cdot + \text{RSH} \longrightarrow \text{Ra(CH}_2)_n\text{CH}_3 + \text{RS}\cdot \xrightarrow{n\text{CH}_2=\text{CH}_2} \underset{(77)}{\text{RS(CH}_2)_{2n}\cdot}$$

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.

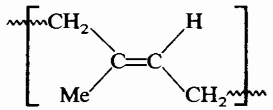
Radical-induced polymerisation of simple alkenes, e.g. ethene and propene, requires vigorous conditions including very high pressure, but many other alkene monomers carrying substituents polymerise readily. These include $CH_2{=}CHCl$ → polyvinyl chloride (p.v.c.) for making pipes, etc., $CH_2{=}CMeCO_2Me$ → 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 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 $$\log \frac{k_{m\text{-NO}_2}}{k_H} = \rho\sigma_{m\text{-NO}_2} \qquad [6a]$$

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

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

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

When $k_{p\text{-MeO}}$ subsequently came to be determined experimentally, $k_{p\text{-MeO}}/k_H$ 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

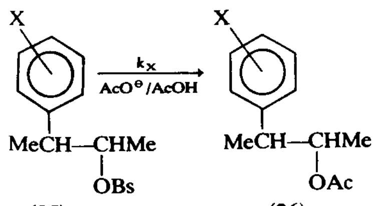
We have already seen (p. 368) how the sign and magnitude of ρ, the reaction constant, can provide useful information about the development (or dissipation) of charge (+ve or −ve) on going from starting materials to the transition state for the rate-limiting step of a reaction. We have also seen (p. 369) 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

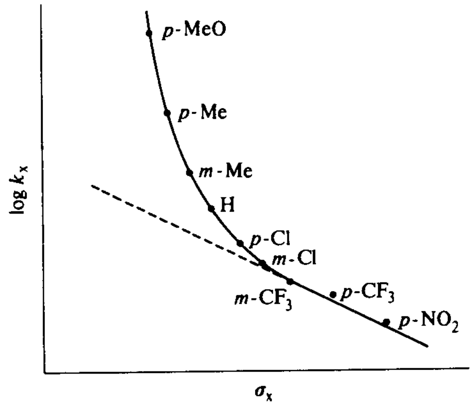


Fig. 13.6

nitude from the values of σ_X, σ_X^+ and σ_X^- with which we are already familiar (p. 363).

Then, employing the more general equation [10], it is possible to use these σ_R^* values, in conjunction with suitable kinetic measurements of k_R and k_{Me}, to evaluate ρ^* for other

$$\log \frac{k_R}{k_{Me}} = \rho^* \sigma_R^* \qquad [10]$$

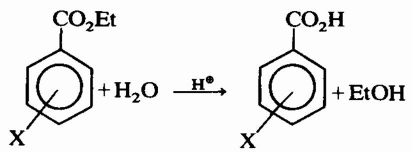
reactions of a whole range of aliphatic compounds in addition to esters. Using [10] in this way, straight line plots were obtained for a number of different reactions of aliphatic compounds.

13.5.2 Steric parameters, E_S and δ

After all the emphasis we placed earlier (p. 361) on steric effects, obtaining a straight line plot may at first sight seem a rather surprising result; especially, given that the relation [10] takes into account only the *polar* effect exerted by R. However, obtaining a straight line plot, using [10], does not necessarily mean that *no* steric effects are operating in a reaction. It means only that there is no substantial *change* in the operation of such effects on going from starting materials to the transition state for the rate-limiting step of the overall reaction (or on going from starting materials to products for an equilibrium).

It is not necessary to look very far to find aliphatic reactions that do *not* yield straight line plots with [10], however; and, as with previous deviations from linearity (p. 375), these departures are commonly much more informative about the details of reaction pathways than are neat straight lines. Where such departures from linear (polar effects only) plots are observed, suggesting the operation of significant—and changing—steric effects, it is possible to incorporate a *steric substituent parameter*, E_S, whose evaluation is based on an earlier observation.

Thus we have already seen (p. 384) that the acid-catalysed hydrolysis of *m*- and *p*-substituted benzoate esters (42) is (with a ρ value of 0·03) essentially uninfluenced by any polar effect exerted by the substituent, X; and this substituent is sufficiently far removed from the reaction centre to be clearly incapable of exerting any steric effect on it either. These esters thus all undergo acid-catalysed hydrolysis at essentially the same rate. There is no reason to believe that acid-catalysed hydrolysis of aliphatic esters, RCO_2Et, will be any more susceptible to polar effects than was the corresponding hydrolysis of benzoate esters. If then different hydrolysis rates *are* observed with aliphatic esters as R is varied, these must reflect differing steric effects exerted by the different R groups. Such aliphatic esters are indeed found to undergo hydrolysis at markedly different rates, so it is possible, taking Me as the standard substituent once again, to use equation [11]



(42)

$$\log \left[\frac{k_{RCO_2Et}}{k_{MeCO_2Et}}\right]_{acid} = E_S \qquad [11]$$

to evaluate E_S, the steric substituent parameter, for R. E_S values, obtained in this way for a number of different substituents, are listed below:

R in RCO_2Et	E_S		R in RCO_2Et	E_S
H	+1·24		$Me(CH_2)_3$	−0·39
Me	0	(by definition)	Me_2CHCH_2	−1·13
Et	−0·07		Me_3C	−1·54
$ClCH_2$	−0·24		Me_3CCH_2	−1·74
ICH_2	−0·37		Ph_2CH	−1·76
$PhCH_2$	−0·38		Et_3C	−3·81

From the form of equation [11], the E_S value for Me, the reference substituent, will of course be 0. All substituents other than H have −ve E_S values because all substituents other than H are larger than Me, and the rate of hydrolysis of any ester RCO_2Et ($R \neq H$) will thus be slower than that of $MeCO_2Et$, in a reaction whose rate is governed solely by the steric effect of R.

It is found in practice that the value of the steric parameter, E_S, for a particular group, R, differs to some extent from one reaction to another. This is not altogether surprising as both the local environment of R and the size of the attacking reagent will vary from one reaction to another. It means, however, that on incorporating E_S into the Hammett type equation, [12], it is necessary to introduce a yet further parameter, δ, as a measure of a particular reaction's

$$\log \frac{k_R}{k_{Me}} = \rho^* \sigma_R^* + \delta E_S \qquad [12]$$

susceptibility towards steric effects. In that sense δ is the steric parallel to ρ^*—which measures the reaction's susceptibility towards polar effects. The δ parameter is given the value 1·00 for acid-catalysed ester hydrolysis, as the standard reaction, and its value for other reactions can then be determined experimentally in the usual way.

WENTRUP, C. *Reactive Molecules: The Neutral Reactive Intermediate in Organic Chemistry* (Wiley, 1984).

Review series

Advances in Physical Organic Chemistry. GOLD, V. and BETHELL, D. (Eds) (Academic Press, Vol. I, 1963–).

Organic Reaction Mechanisms. KNIPE, A. C. and WATTS, W. E. (Eds) (Interscience, Vol. I, 1966–).

Progress in Physical Organic Chemistry. TAFT, R. W. (Ed.) (Interscience, Vol. I, 1963–).

Reactive Intermediates—A Serial Publication. JONES, M. and MOSS, R. A. (Eds) (Wiley-Interscience, Vol. I, 1978–).

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Index