

alternative reactions is reversible, or if the products are readily interconvertible directly under the conditions of the reaction, the composition of the final product mixture may be dictated not by the relative rates of formation of the different products, but by their relative thermodynamic stabilities in the reaction system: we are then seeing *thermodynamic* or *equilibrium control*. Thus the nitration of methylbenzene is found to be kinetically controlled, whereas the Friedel–Crafts alkylation of the same species is often thermodynamically controlled (p. 163). The form of control that operates may also be influenced by the reaction condition, thus the sulphonation of naphthalene with concentrated H_2SO_4 at 80° is essentially kinetically controlled, whereas at 160° it is thermodynamically controlled (p. 164).

2.3 INVESTIGATION OF REACTION MECHANISMS

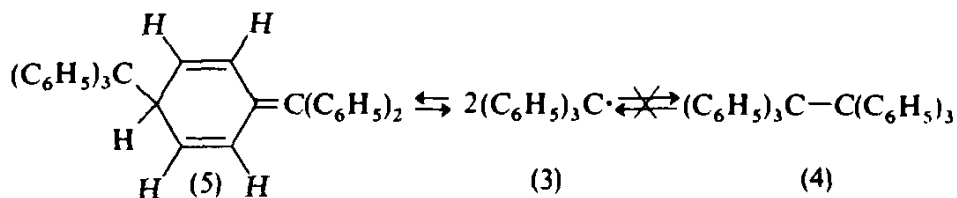
It is seldom, if ever, possible to provide complete and entire information, structural, energetic, and stereochemical, about the pathway that is traversed by any chemical reaction: no reaction mechanism can ever be proved to be correct! Sufficient data can nevertheless usually be gathered to show that one or more theoretically possible mechanisms are just not compatible with the experimental results, and/or to demonstrate that of several remaining alternatives one is a good deal more likely than the others.

2.3.1 *The nature of the products*

Perhaps the most fundamental information about a reaction is provided by establishing the structure of the products that are formed during its course, and relating this information to the structure of the starting material. Where, as is often the case with organic reactions, more than one product is obtained then it is usually an advantage to know also the relative proportions in which the products are obtained, e.g. in establishing, among other things, whether kinetic or thermodynamic control is operating (*cf.* p. 42). In the past this had to be done laboriously—and often imprecisely—by manual isolation of the products, but may now often be achieved more easily, and precisely, by sophisticated chromatographic methods or, indirectly, by suitable spectroscopic ones.

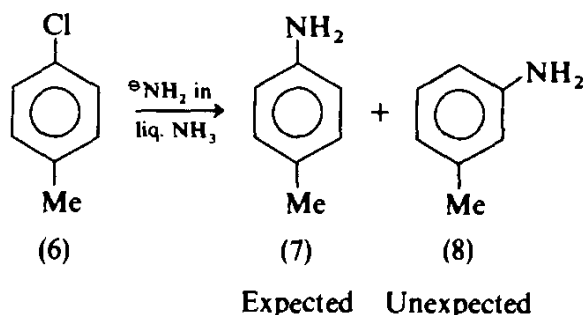
The importance of establishing the correct structure of the reaction product is best illustrated by the confusion that can result when this has been assumed, wrongly, as self-evident, or established erroneously. Thus the yellow triphenylmethyl radical (3, *cf.* p. 300), obtained from the action of silver on triphenylmethyl chloride in 1900, readily forms a colourless dimer (m.w. = 486) which was—reasonably enough—assumed to be hexaphenylethane (4) with *thirty* ‘aromatic’

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):



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, $\ominus\text{NH}_2$, 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:



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 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 $[\text{HNO}_3]$. 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 not involve the participation of water, simply on the grounds that $[\text{H}_2\text{O}]$ 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,

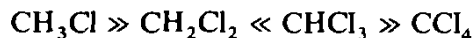
$$\text{Rate} = k_2[\text{RHal}][\text{H}_2\text{O}]$$

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. $\text{Br}_2 \xrightarrow{h\nu} \text{Br}\cdot + \text{Br}\cdot$.

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

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

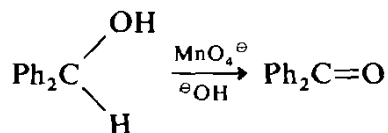


clearly suggesting that trichloromethane undergoes hydrolysis in a different manner from the other compounds (*cf.* p. 267).

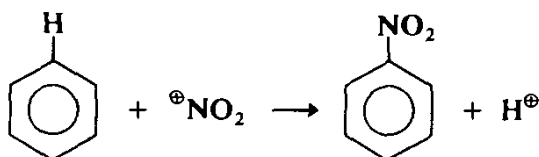
2.3.3 The use of isotopes

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

Thus in the oxidation



it is found that Ph_2CHOH is oxidised 6.7 times as rapidly as Ph_2CDOH ; the reaction is said to exhibit a *primary kinetic isotope effect*, and breaking of the C—H bond must clearly be involved in the rate-limiting step of the reaction. By contrast benzene, C_6H_6 , and hexa-deuterobenzene, C_6D_6 , are found to undergo nitration at essentially the same rate, and C—H bond-breaking, that must occur at some stage in the overall process,



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