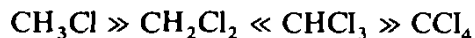


general one that might otherwise have been assumed for the series. Thus the observed rates of hydrolysis of the chloromethanes with strong bases are found, under comparable conditions, to vary as follows,

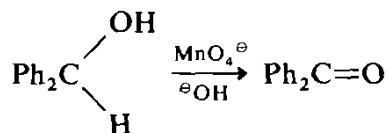


clearly suggesting that trichloromethane undergoes hydrolysis in a different manner from the other compounds (*cf.* p. 267).

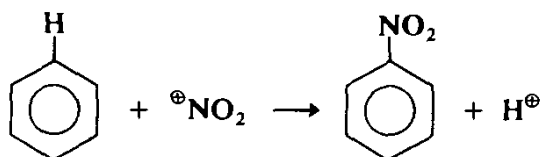
### 2.3.3 The use of isotopes

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under the same conditions, of the compound in which we are interested, and its exact analogue in which this bond has been replaced by a C—D linkage.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  $\approx 7$  at  $25^\circ$ .

Thus in the oxidation

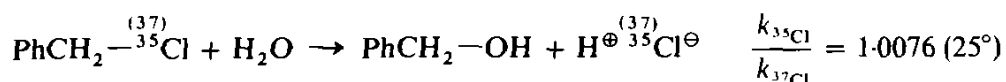
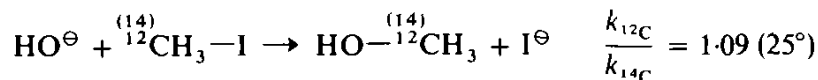


it is found that  $\text{Ph}_2\text{CHOH}$  is oxidised 6.7 times as rapidly as  $\text{Ph}_2\text{CDOH}$ ; the reaction is said to exhibit a *primary kinetic isotope effect*, and breaking of the C—H bond must clearly be involved in the rate-limiting step of the reaction. By contrast benzene,  $\text{C}_6\text{H}_6$ , and hexa-deuterobenzene,  $\text{C}_6\text{D}_6$ , are found to undergo nitration at essentially the same rate, and C—H bond-breaking, that must occur at some stage in the overall process,



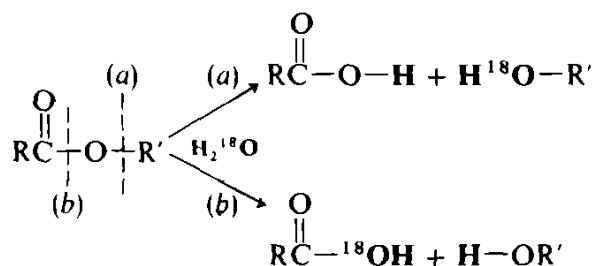
thus cannot be involved in the rate-limiting step (*cf.* p. 136).

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



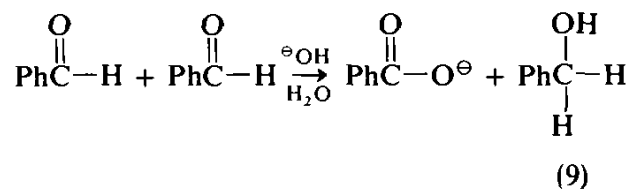
It should be emphasised that primary kinetic isotope effects are observed experimentally with values intermediate between the maximum calculated value and unity (i.e. *no isotope effect*): these too can be useful, as they may supply important information about the breaking of particular bonds in the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

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



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

Heavy water,  $\text{D}_2\text{O}$ , has often been used in a rather similar way. Thus in the Cannizzaro reaction of benzaldehyde (p. 216),



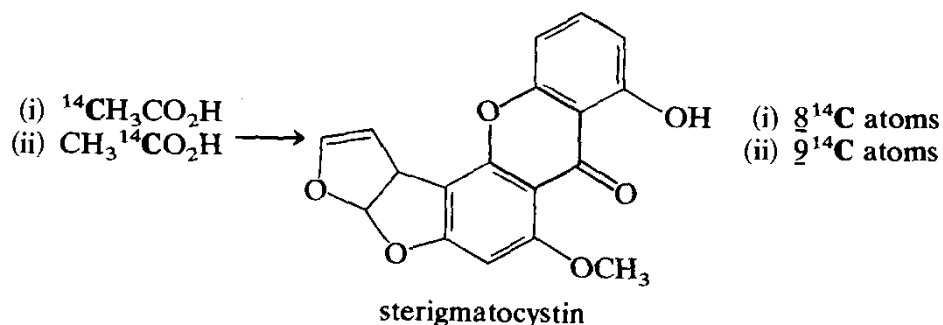
the question arises of whether the second hydrogen atom that becomes attached to carbon, in the molecule of phenylmethanol (benzyl alcohol,

9) that is formed, comes from the solvent ( $\text{H}_2\text{O}$ ) or from a second molecule of benzaldehyde. Carrying out the reaction in  $\text{D}_2\text{O}$  is found to lead to the formation of no  $\text{PhCHDOH}$ , 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.  $^3\text{H}$  (or T),  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{37}\text{Cl}$ ,  $^{131}\text{I}$ , 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  $^{14}\text{C}$  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*,



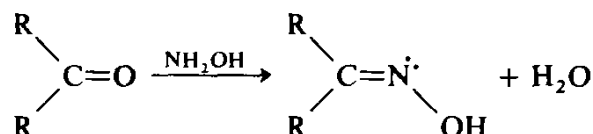
found in cultures of several fungi, was built up stepwise from molecules of ethanoic acid. General confirmation of this hypothesis was obtained through feeding suitable fungal cultures, in separate experiments, with  $^{14}\text{CH}_3\text{CO}_2\text{H}$  and  $\text{CH}_3^{14}\text{CO}_2\text{H}$ , respectively. It was then found from radioactive counting measurements ( $^{14}\text{C}$  is a  $\beta$  emitter), on the two extracted samples of sterigmatocystin ( $\text{C}_{18}\text{H}_{12}\text{O}_6$ ) that: (i)  $^{14}\text{CH}_3\text{CO}_2\text{H}$  led to the introduction of  $8^{14}\text{C}$  atoms, and  $\text{CH}_3^{14}\text{CO}_2\text{H}$  to the introduction of  $9^{14}\text{C}$  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  $^{12}\text{C}$  nor the  $^{14}\text{C}$  carbon isotopes produce an n.m.r. signal but the  $^{13}\text{C}$  isotope, which occurs in ordinary carbon to

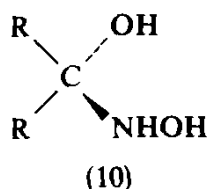


reaction pathway, and not merely in equilibrium with the true intermediate.

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

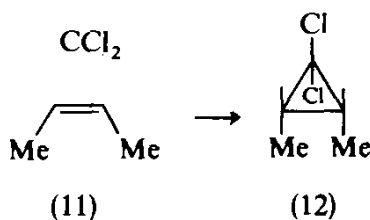


the infra-red absorption band characteristic of C=O in the starting material disappears rapidly, and may have gone completely before the band characteristic of C=N in the product even begins to appear. Clearly an intermediate must be formed, and further evidence suggests that it is the *carbinolamine*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



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

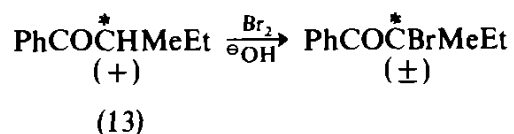
Where we have reason to suspect the involvement of a particular species as a labile intermediate in the course of a reaction, it may be possible to confirm our suspicions by introducing into the reaction mixture, with malice aforethought, a reactive species which we should expect our postulated intermediate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



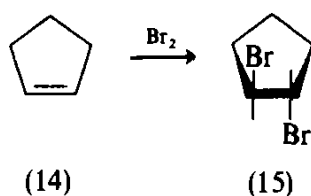
The successful study of intermediates not only provides one or more signposts which help define the detailed pathway traversed by a reaction, the intermediates themselves may also provide inferential evidence about the transition states for which they are often taken as models (*cf.* p. 41).

### 2.3.5 Stereochemical criteria

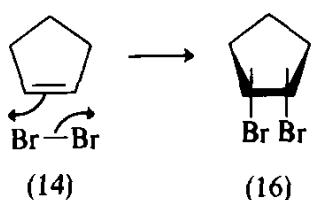
Information about the stereochemical course followed by a particular reaction can also provide useful insight into its mechanism, and may well introduce stringent criteria that any suggested mechanistic scheme will have to meet. Thus the fact that the base-catalysed bromination of an optically active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



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



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



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