THE USE OF ISOTOPES IN ACID AND BASIC CATALYSIS

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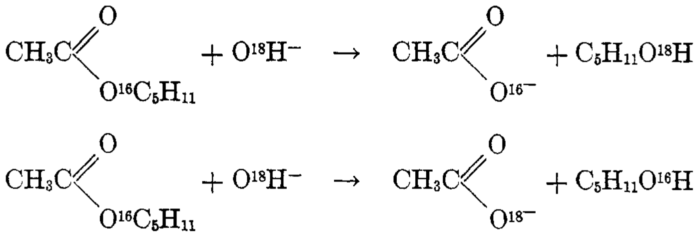
In the study of reactions catalyzed by acids and bases there are two main problems,—the mechanism of the change in the molecule, and the function of the catalyst. The theory of these reactions advanced by Brönsted (2) has been amply verified by the work of Dawson (4), Hammett (7), Pedersen (18), and others, but an examination of the various reactions studied shows that we have not yet been able to solve completely the two problems stated. Thus for many reactions we cannot state what is the change that occurs in the reactant, nor can we explain why the relation between catalytic activity and dissociation constant is different for different reactions, and why some reactions appear to be catalyzed specifically by hydrogen or hydroxide ions. Fortunately, however, the questions which face us in this field are well defined, and it seems probable that we shall be able to answer at least some of them through the use of isotopes.

A very beautiful example of the value of isotopes in deciding the mechanism of a reaction is afforded by the work of Polanyi and Szabo (19), who used the isotope of oxygen, O^{18}, to distinguish between the alternative mechanisms for saponification of esters



$$CH_3C\begin{matrix}\nearrow O\\ \searrow O^{16}C_5H_{11}\end{matrix} + O^{18}H^- \rightarrow CH_3C\begin{matrix}\nearrow O\\ \searrow O^{16-}\end{matrix} + C_5H_{11}O^{18}H$$

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They saponified amyl acetate in water containing 1 per cent of O^{18} and found that the oxygen in the alcohol produced was of normal isotopic composition. This proved that the saponification followed the second course, and also demonstrated that amyl alcohol does not ionize to $C_5H_{11}^+$ and OH^-. The weight of earlier evidence, while strongly indicating the probability of both these ideas, was inadequate to establish them definitely.

There are of course many other reactions that may be similarly investigated, but until O^{18} is available in considerably greater amounts the technique of such measurements will remain difficult.

The hydrogen isotope, deuterium, is of peculiar interest in acid and basic catalysis because it gives rise to a series of acids and bases distinct from but closely related to the ordinary protium series. Thus if we define the ordinary acids and bases by the scheme of Brönsted

$$\text{Acid} = \text{Base} + \text{Proton}$$

we can define deutero-acids and bases by the scheme

$$\text{Acid} = \text{Base} + \text{Deuton}$$

As a consequence of the different masses and zero point energies of proto- and deutero-compounds, we find that the equilibria are shifted on proceeding from ordinary to heavy water and also that the velocities of prototropic and deuterotropic changes are different. In general, we can predict that the velocity of transfer of a proton will be greater than the velocity of transfer of a deuton, and this enables us to distinguish between reactions catalyzed by acids and bases in general and reactions catalyzed specifically by hydrogen or hydroxide ions, which probably involve addition compounds.

It is also possible to investigate the statistical factor, which was introduced by Brönsted and Pedersen (3) to take account of the probability of ionization of an acid with more than one ionizable hydrogen atom.

So far six reactions have been studied in heavy water, and in spite of the preliminary nature of the work certain general features are apparent. In table 1 the data for these reactions are summarized; the first column gives the reactant, the second the catalyst, and the third the ratio of the catalytic constants in H_2O and D_2O.

The result for nitramide is for a 6 per cent solution of heavy water in which the rate was 8 per cent less than in ordinary water. The hydrolysis of palmityl chloride was studied as a surface reaction. The three reactions which proceed more slowly in heavy water have all been shown to be subject to general acid or basic catalysis, whereas for the others such general catalysis has never been definitely established. In the case of the hydrolysis of ethyl acetate, Dawson (5) has claimed to have shown general catalysis, but his results are confused by salt effect and it now seems probable that the effective catalysts for this reaction are the hydrogen and hydroxide ions and, possibly, the water molecule, which is of course always one of the reacting molecules.

Probably the simplest of these reactions is the neutralization of nitroethane, which has been shown by Pedersen (17) to involve simply the ionization of a hydrogen atom. The simplicity of the reaction makes it very suitable for the comparison of the rates of removal of protons and deutons, and the fact that there are two ionizable hydrogen atoms makes possible the study of the successive reactions

$$CH_3CH_2NO_2 + OD^- \rightarrow CH_3CHNO_2^- + HOD$$
$$CH_3CHDNO_2 + OD^- \rightarrow CH_3CDNO_2^- + HOD$$
$$CH_3CD_2NO_2 + OD^- \rightarrow CH_3CDNO_2^- + D_2O$$

The rate of this reaction in H_2O and the rates of the three stages in D_2O are given in table 2. It is apparent that the rate of removal of a proton is much greater than that of a deuton, which of course is the reason that we are able to isolate the second stage in heavy water. The increase in rate of the first stage on going to heavy water may indicate that OD^- is a stronger base than OH^-.

TABLE 1

Reactions in H_2O *and* D_2O

REACTANT	CATALYST	RATIO OF THE CATALYTIC CONSTANTS
Glucose (23)	H_2O	3.8
	H_3O^+	1.33
Nitroethane (23)	OH^-	6.0
Nitramide (10)	H_2O	>1
Sucrose (6)	H_3O^+	0.5
Ethyl acetate (20, 24)	H_3O^+	0.67
	OH^-	0.75
Palmityl chloride (9)	H_2O	1

TABLE 2

Neutralization of nitroethane (23)

REACTANTS	RATE OF THE REACTION
$CH_3CH_2NO_2 + OH^-$	39
$CH_3CH_2NO_2 + OD^-$	60
$CH_3CHDNO_2 + OD^-$	36
$CH_3CD_2NO_2 + OD^-$	6

The mutarotation of glucose has been studied by several workers. Pacsu (16) first showed that the rate in heavy water is much less than in ordinary water; later Moelwyn-Hughes, Klar, and Bonhoeffer (15) made a more detailed study, but their results are certainly in error since they failed to separate the effects of the various catalysts. The conclusions drawn by these authors as regards the activation energies and the mechanism of the reaction are therefore open to doubt. The importance of separating the different reactions can be seen from figure 1, in which values of log *k*, the reaction rate constant, have been plotted against the pH. Curve 1 represents the data for H_2O and curve 2 the data for D_2O; the left branch of curve 2 referring to high pH's is unknown, and the probable limits are indicated by the dotted lines. The true catalytic constants for D_2O and D_3O^+ are known only at 23.3°C.; these values have been employed in table 1.

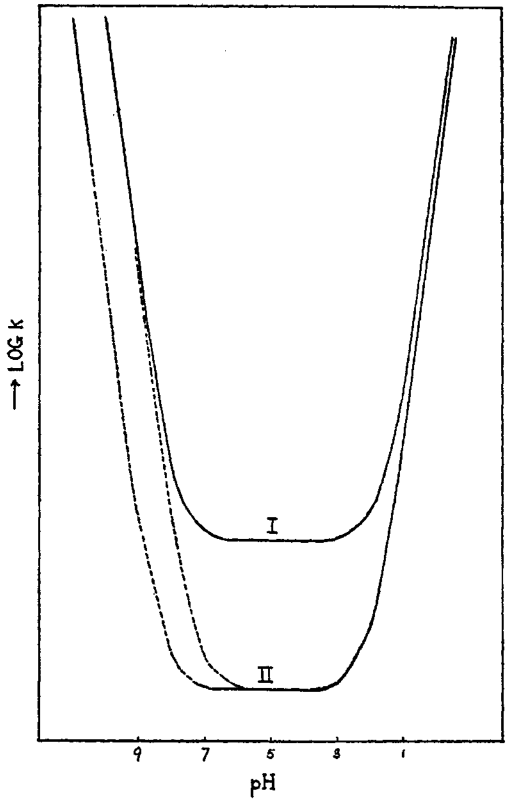

FIG. 1. Mutarotation of glucose

The rate of mutarotation in mixtures of H_2O and D_2O has been measured by Hammill and La Mer (8), and their results are shown in figure 2. By combining their results with the equilibrium constant for the reaction (21)

$$H_2O + D_2O = 2HDO$$

these authors have calculated the catalytic constant of HDO, which they find to be 0.00498 compared with 0.01037 for H_2O and 0.00273 for D_2O

at 25°C. They have also determined the catalytic constant of the hydrogen ion in H_2O–D_2O mixtures and have found that the values vary linearly with the D_2O concentration. These results are of significance in connection with the statistical factor. Brönsted and Pedersen (3) suggested that if a polybasic acid H_nA acted as a catalyst its catalytic constant would be related to the dissociation constant by the equation:

$$k = \left(\frac{p}{q} \cdot K\right)^x$$

where p is the number of protons that can dissociate, while q is the available points to which a proton can be attached. Pedersen (18) has recently suggested that, if the protons are attached to a single atom, p and q are both unity however many protons there may be. On this theory the molecule HDO should have the same activity as H_2O or D_2O, whichever is the better catalyst, and similarly the ions H_2DO^+ and HD_2O^+ should be as effective as either H_3O^+ or D_3O^+. We have seen that this is not true. Further evidence against this theory is given by the results on the neutralization of nitroethane, which showed that the rate of removal of a proton is reduced to one half when the number of protons is reduced from 2 to 1.

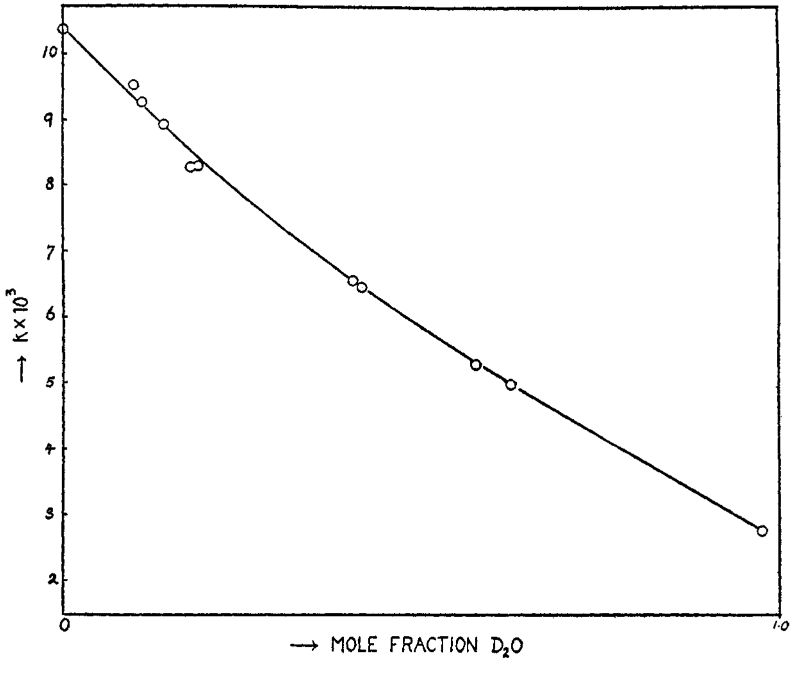

FIG. 2. Mutarotation of glucose

The measurements in heavy water showed that the mutarotation is strictly unimolecular, and hence proved that the exchange of hydrogen atoms between the sugar and water is very rapid.[1] This means that the rate-determining step is the reaction between a glucose ion and an acid or base. The change in constant between H_2O and D_2O shown in table 1 is markedly less for the hydrogen ion than for the water molecule; this may be explained on Pedersen's hypothesis that the water molecule acts as a basic catalyst. Alternatively, it may be due to changes in the acid strengths of these catalysts.

Moelwyn-Hughes and Bonhoeffer (13, 14) also investigated the inversion of cane sugar and found that in 90 per cent D_2O the catalytic effect of hydrogen ions is 60 per cent greater than in H_2O. Gross, Suess, and Steiner (6) studied this reaction in H_2O–D_2O mixtures, with the results shown in figure 3. The greater rate of reaction in D_2O suggests that there is an equilibrium of the type:

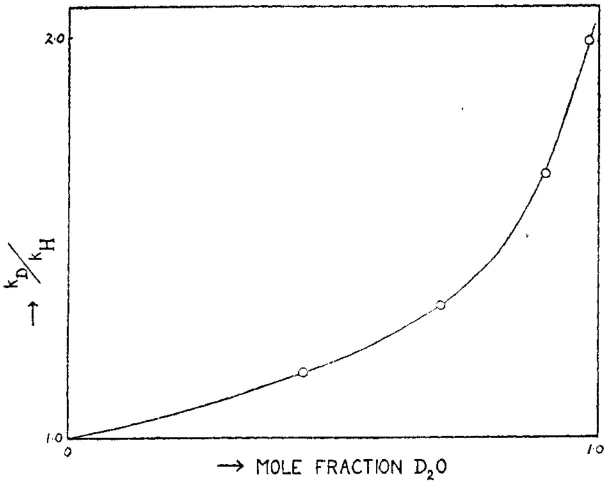

FIG. 3. Inversion of sucrose

$$\text{Sucrose} + \text{Acid} \rightleftharpoons [\text{Sucrose H}]^+ + \text{Base}$$

and the rate is determined by the decomposition of the sucrose ion. The form of the curve relating the catalytic constant of the hydrogen ion to the

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[1] This is because the mutarotation of glucose is a reaction in which equilibrium is attained between α- and β-glucose and the observed reaction constant is the sum of the constants for the forward and reverse reactions. If the exchange of deuterium for protium is not rapid, the nature of the glucose molecule will therefore be altering during the course of the reaction and the observed rate will not be unimolecular.

D_2O concentration will be explicable in terms of the effects of the ions H_2DO^+ and HD_2O^+.

The hydrolysis of esters is one of the classical reactions which have been extensively studied. Schwarz (20) examined the hydrolysis in heavy water in presence of hydrogen ions and found an increase of 50 per cent over the rate in ordinary water; this indicates that the reaction probably does not involve a keto-enol change. The hydrolysis by alkali studied by the change in the electrical conductivity also shows an increase, in this case of 33 per cent (24). From this increase we conclude that, if the reaction involves a prototropic change, this change must constitute the rate-determining step as in the neutralization of nitroethane. If, as for glucose, the exchange were instantaneous, there should be a decrease in rate. Actually it has been found that no exchange of hydrogen atoms occurs during the hydrolysis and consequently the reaction is not catalyzed by acids and bases in general.

The decomposition of nitramide is of special interest, as this was the first reaction for which general basic catalysis was established. Recently Pedersen (18) has suggested the following mechanism for the reaction:

$$H_2NNO_2 \rightleftharpoons HN{:}NO_2^- + H^+ \rightarrow N_2O + H_2O$$

Since this involves a dissociation followed by a basic catalysis, it is evident that the rate in heavy water may be considerably lower than in ordinary water; in fact, if the decrease in the dissociation is as great as for the acid examined by Lewis and Schutz (12), and, if the rate of deuton removal is less than the rate of removal of protons by the same factor as for nitroethane, the decomposition of nitramide should proceed in D_2O at about one-twentieth of the rate in H_2O.

Apart from the direct study of reaction rates, deuterium may be employed to investigate mechanisms by means of exchange of hydrogen atoms between the reactant and the catalyst. In general we may expect exchange to occur in solution and at room temperature whenever hydrogen atoms can be ionized; the conditions for exchange will therefore be similar to those for general acid and basic catalysis. The exchange of hydrogen atoms between water and acids and bases is of course inevitable and reveals nothing new, but the exchange between water and substances such as acetone, which exist in keto and enol forms, is significant. This exchange was first demonstrated by Bonhoeffer and Klar (1), who showed that, whereas the exchange proceeds slowly in neutral water, the rate is greater in acid and very rapid in alkali; these results precisely parallel the conditions for the iodination of acetone and confirm the suggestion of Lapworth (11) that the rate of iodination is simply that of the keto-enol change.

Some recent measurements show that exchange occurs with compounds not usually suspected of having keto and enol forms; thus the anions of some carboxylic acids exchange their hydrogen atoms at a slow rate with water. The results of a few exchange reactions are given in table 3. These results do not necessarily represent equilibrium values, and consequently no conclusion can be drawn from them as to the distribution of deuterium atoms between the organic molecule and water. The exchange between the anions and water is of interest because of the marked differences in the rates; the malonate ion exchanges with great rapidity, while exchange with the formate ion is very slow. These differences are explicable partly on the basis of electrical effects, as in the Bjerrum theory of the dissociation constants of dibasic acids, and partly by the enhanced effect of two carboxylic groups. The exchange between the acetate ion and water shows that it is possible that the bromination of acetic acid proceeds through the enol form as for acetone.

TABLE 3

Protium-deuterium exchange (22)

SUBSTANCE	CONDITIONS	AMOUNT OF EXCHANGE
Formate	100 hrs. at 80°C.	8.3
Acetate	200 hrs. at 80°C.	85.0
Malonate	5 hrs. at 100°C.	100.0
Succinate	100 hrs. at 80°C.	69.0
Isatin	12 hrs. at 100°C.	0.5 atom
Acetamide	1 hr. at 30°C.	2 atoms
Benzamide	10 mins. at 80°C.	1.26 atoms

TABLE 4

Dissociation constants in H_2O *and* D_2O

ACID	BASE	DISSOCIATION CONSTANT IN H_2O	DISSOCIATION CONSTANT IN D_2O
H_3O	H_2O	55.5	55.4
H_2O	OH^-	1.9×10^{-16}	3.8×10^{-17}
CH_3COOH	CH_3COO^-	1.8×10^{-5}	5×10^{-6}
$CH_2ClCOOH$	CH_2ClCOO^-	1.7×10^{-3}	6×10^{-4}
NH_4^+	NH_3	5.5×10^{-10}	2×10^{-10}

The dissociation constants of acids in heavy water are of obvious importance, and the available values are given in table 4. The values for acetic and chloroacetic acids and ammonia are those given by Lewis and Schutz (12), while the values for the water system are based on an electromotive force determination of K_W for D_2O (25). An interesting deduction is that the acid strength of the water molecule compared with the hydrogen ion is five times smaller in D_2O than in H_2O. In the further analysis of reaction rate studies in heavy water it will be essential to have the acid strengths of all the catalysts, since some of the change in catalytic activity between ordinary and heavy water may be directly related to the change in acid strength.

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