

AcidBase Reactions Involving Deuterium

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Acid-Base Reactions Involving Deuterium

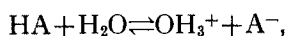
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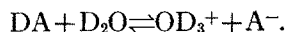
From measurements of the rate of neutralisation of a pseudo-acid, nitroethane, in heavy water, a comparison is made of the relative rates of ionisation of protium and deuterium atoms, the ratio being approximately 10 : 1. It is shown that these relative rates are of great importance in the study of catalysis by acids and bases in heavy water and some conclusions may be drawn with regard to the mechanism of the inversion of sucrose and of the mutarotation of glucose. These results also have a bearing on the question of deuterium-protium exchange in compounds when dissolved in water.

THE work of Brönsted¹ and others has established the general nature of acid-base equilibria and the application of these ideas to catalytic reactions has effectively settled the main problems of acid and basic catalysis. The discovery of deuterium, the hydrogen isotope of mass 2, however, has made it necessary to examine how far the previous ideas may be applicable to compounds containing this isotope and at the same time has provided a valuable tool for probing further into the nature of various reactions.

From the standpoint of acids and bases it is interesting to compare the strength of proto- and deuto-compounds but for such a comparison a mere determination of dissociation constants will not suffice, since the equilibria involved are different in the two cases; thus an acid HA ionises in ordinary water according to the scheme



whereas the corresponding deuto-acid will ionise in heavy water according to the scheme



These two equilibria are affected by the dielectric constants of the solvents, the degree of hydration of the ions and neutral molecules as well as by the relative affinities of the anions and water molecules for protons and deutons. It is, therefore, evident that no simple conclusion with regard to the strength of any particular bond between atoms can be drawn from the data.*

¹ Brönsted, see *Chem. Rev.* **5**, 231 (1928).

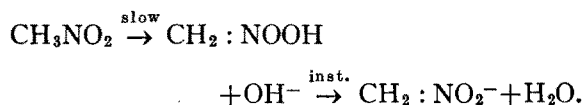
* The contrary conclusion of Lewis and Schutz (*J. Am. Chem. Soc.* **56**, 1002 (1934)) is based on a misunderstanding of the nature of acid dissociation.

Although equilibrium data will fail to give direct information of the relative strengths of proto- and deuto-acids, it should be possible to make such a comparison from the rates at which the compounds lose protons and deutons, respectively. For many chemical reactions as well as biological processes these relative rates will be of much greater significance than the dissociation constants, which in themselves can only be applicable to other equilibria such as are involved in studies of partition between phases, solubility and indicator reactions. The correspondence between acid strength and catalytic activity which is expressed in the generalised theory of acid and basic catalysis is a consequence of the relation between acid strength and the rate of proton transfer. If a deuto-acid is compared with a proto-acid this relation will almost certainly break down and, consequently, in this most characteristic property of acids—their ability to facilitate prototropic reactions—there can be no comparison of the two types of compound through their dissociation constants. It also follows that any attempt to formulate a “pD” scale for heavy water on the same basis as the pH scale for ordinary water will be quite misleading, except for equilibria, unless the different velocities of ionisation of deuterium and protium are taken into account.

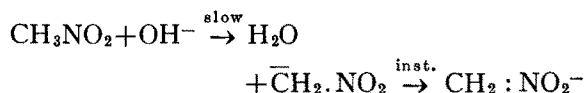
In order to compare the rates at which protons and deutons are transferred between molecules, it was decided to study the neutralisation of a pseudo-acid in heavy water. The phenomenon of the slow neutralisation of pseudo-acids was interpreted by Hantzsch² as a slow rearrange-

² Hantzsch, *Berichte* **32**, 575 (1899).

ment of the pseudo-acid into a genuine acid which is instantaneously neutralised. Thus for nitromethane Hantzsch would write

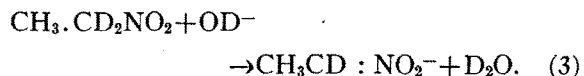
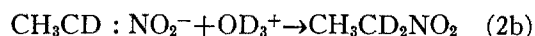
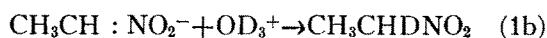


Recently Pedersen³ has shown that the isomerisation of nitromethane is a base catalysed reaction and that the rate of neutralisation by hydroxyl ion leads to a catalytic constant for this ion in good agreement with the relationship between catalytic activity and basic strength that is found for other bases. Pedersen argues convincingly from this that the neutralisation of nitromethane actually proceeds as follows



and that the slow process is the transfer of a proton from the nitromethane to the hydroxyl ion.

Assuming this mechanism, the reaction affords an excellent method of studying the problem that we have outlined. Thus if nitroethane (which has been shown by bromination experiments to contain two exchangeable hydrogen atoms) be neutralised in heavy water the following reactions will occur:



In stage (1a) the deuterioxy ion will remove a proton from the pseudo-acid while in stage (1b) a deuteron will be transferred back: in stage (2a)

the deuterioxy ion will remove either a proton or a deuteron, depending upon the relative rates of the two reactions. If the rate of proton transfer is much greater than that of deuteron transfer then the former will occur quantitatively and since the number of removable protons is one-half that in the original compound the rate of neutralisation in stage (2a) will be one-half the rate in stage (1a). In the third stage, if the separation of protons has been virtually complete, there will be left only deuterium atoms that can ionise and the measured rate will be that of deuteron transfer.

EXPERIMENTAL

In ordinary water the reaction can be followed by measurement of the electrical conductivity of the solution since the mobility of the hydroxyl ion is much greater than that of any other anion and consequently the conductivity falls off as the reaction proceeds. By analogy with the mobility of the deuterioxonium ion⁴ it was expected that a similar condition of affairs would obtain in heavy water and this was found to be true.

The general method was to add to a solution of nitroethane in a conductivity cell a measured amount of baryta solution and to measure the electrical resistance at intervals of a minute or so. When the reaction was complete just sufficient sulphuric acid was added to precipitate all the barium and the reaction could then be followed again after addition of more baryta solution.

The experimental difficulties were mainly associated with the problem of working with small quantities of solution. The cell employed had a total capacity of about 5 cc but less than 0.5 cc completely covered the electrodes and further additions only slightly affected the cell constant which was found to be 2.085 in terms of Kohlrausch's data for KCl. Solutions of nitroethane were made up directly in the cell by weighing about 2-4 milligrams of nitroethane and adding water. Solutions of baryta were prepared by weighing barium oxide and water in a stoppered tube: analysis by titration with acid showed the barium oxide to be 78 percent BaO. Sulphuric acid solutions were prepared by

³ Pedersen, Det Kgl. Danske Vid. Selskab. Math.-fys. Medd. 12, 1 (1932).

⁴ Lewis and Doody, J. Am. Chem. Soc. 55, 3504 (1933).

weight from concentrated H_2SO_4 which by analysis was found to be 95.8 percent pure. Additions of baryta solution to the cell were made by means of a 1 cc syringe pipette which could be read to 0.002 cc and which was found to be accurate to the same limit. This was found to be a very convenient instrument, as from it the solution could be delivered practically instantaneously.* Additions of sulphuric acid were made by means of a microburette which held about 0.1 cc and could be read to 0.0003 cc. With this burette it was possible to carry out a conductivity titration of 0.5 cc of baryta solution (approx. $\text{N}/10$) with sulphuric acid (1 N) with an accuracy of about 1 percent. Several such titrations were made to check the experimental method.

Since the reaction is rather rapid the measurements were made at 0°C and it is interesting that although the freezing point of heavy water is 3.8°C the solutions never froze. Dr. Selwood informs me that this is in agreement with his experience that heavy water shows considerable supercooling.

In all the runs nearly equivalent amounts of nitroethane and alkali were employed but it was found that in most runs the values of k calculated from the expression

$$k = (1/at) \cdot (r_\infty/r_0) \cdot [(r-r_0)/(r_\infty-r)]$$

showed a marked increase with time. This was due to the reactants not being present in exactly equivalent amounts and as half of the reaction was usually over before the first reading was made the effect of slightly different concentrations was rather pronounced. Fortunately it was found that a linear relation obtained between the time and the apparent constant and that extrapolated values for zero time were in good agreement: this was specifically tested by varying the relative amounts of nitroethane and alkali.

Several runs were made in ordinary water in order to test the experimental procedure. One run in which a standard solution of NaOH was used gave a constant of 37.5 moles minutes^{-1} : the other runs with baryta gave values of which the mean was 39.0 ± 5 percent. It was found

that successive neutralisations of the same sample of nitroethane, as carried out in the heavy water experiments, gave values of k which were identical within the experimental error.

The conductivity of $\text{Ba}(\text{OH})_2$ at 0°C was incidentally determined and found to vary from $\Lambda = 95$ at $c = 0.185$ N to $\Lambda = 123$ at 0.031 N; the specific conductivity of the water was 1×10^{-6} ohm $^{-1}$.

The heavy water employed was distilled from alkaline permanganate and twice from BaO : its density was 1.1059 at 20° and its specific conductivity 3×10^{-6} ohm $^{-1}$. With this water 3 cc of 0.054 N $\text{Ba}(\text{OD})_2$ solution (the strength was calculated by using the previous analysis of BaO) and 0.3 cc of 1.120 N D_2SO_4 were prepared. 0.42 cc of the $\text{Ba}(\text{OD})_2$ solution was then placed in the conductivity cell and the conductivity determined at two concentrations, 0.0267 and 0.0201 N; the mean value of Λ was found to be 71.5 . The solution in the cell was then titrated with the sulphuric acid solution by using the conductivities as the indicator of the end point: 0.0200 cc of acid was added leading to a value of 0.0534 N for the strength of the original $\text{Ba}(\text{OD})_2$ solution.

One series of runs was made with nitroethane in heavy water and the results are summarised in Table I.

TABLE I.

Weight of nitroethane	0.00167 g
Weight of added D_2O	0.505 g
1. 0.42 cc $\text{Ba}(\text{OD})_2$ added Added 0.0200 cc of D_2SO_4 to precipitate Ba .	$k = 60$
2. 0.42 cc $\text{Ba}(\text{OD})_2$ added Added 0.0200 cc of D_2SO_4	$k = 36$
3. 0.42 cc $\text{Ba}(\text{OD})_2$ added Added 0.0200 cc of D_2SO_4	$k = 15.3 \rightarrow 9.2$
4. 0.42 cc $\text{Ba}(\text{OD})_2$ added	$k = 9.5 \rightarrow 6.0$

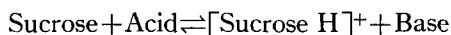
In stages 3 and 4 there are marked decreases in the values of k as the reaction proceeds. This can be explained if we suppose that the replacement of protons by deuterons is not quite complete and that in consequence there are two types of molecule reacting at different rates and making the observed velocity constant greater at the beginning of the reaction than at the end. This also explains why the rate in stage 4 is less than in stage 3.

* For the loan of this pipette I am indebted to Professor W. W. Swingle of the Biology Department, Princeton.

From the results we can draw the following conclusions: (a) the reaction proceeds in separate stages as anticipated; (b) the rate of proton transfer is at least 10 times as great as that of deuteron transfer when both are determined under the same conditions; (c) the rate of proton transfer to a deuterioyl ion in heavy water is about 50 percent greater than the rate of transfer to a hydroxyl ion in ordinary water.

Although the results were obtained at 0°C it is probable that these conclusions will be equally applicable at room temperature and other temperatures not far remote and it is of interest to consider them in relation to certain other results recently recorded.

Moelwyn-Hughes and Bonhoeffer⁵ have found that the catalytic effect of hydrogen ions on the inversion of sucrose in 90 percent D₂O is about 60 percent greater than in ordinary water. This increase in rate is analogous to conclusion (c) given above and in conjunction with conclusion (b) enables us to exclude definitely as the rate determining process the transfer of hydrogen ion (proton or deuteron) from the catalyst to the sucrose molecule. The simplest explanation is that there is an equilibrium of the type



and that the rate of inversion is determined by the rate of decomposition of the complex [Sucrose H]⁺: the velocity constant would then be given by $k = (C_{\text{H}^+}/K) \cdot k'$ where C_{H^+} is the hydrogen ion concentration, K is the dissociation constant of the sucrose ion, k' is the velocity constant for the decomposition of the sucrose ion. The relative catalytic constants for the hydrogen ion in heavy water and ordinary water will then be given by

$$\frac{k_{\text{D}_2\text{O}^+}}{k_{\text{H}_2\text{O}^+}} = \frac{K_{(\text{H}_2\text{O})}}{K_{(\text{D}_2\text{O})}} \cdot \frac{k'_{(\text{D}_2\text{O})}}{k'_{(\text{H}_2\text{O})}}.$$

The fact that $k_{\text{D}_2\text{O}^+}$ is greater than $k_{\text{H}_2\text{O}^+}$ may then be accounted for if $K_{(\text{D}_2\text{O})}$ is less than $K_{(\text{H}_2\text{O})}$.

If, however, the increase observed by Moelwyn-Hughes and Bonhoeffer and that recorded here have a common explanation, this must be sought in the variation of one or more of the

terms in the equation

$$v = Ze^{-A/RT} c_A \cdot c_B \cdot f_A f_B / f_{(AB)},$$

where Z is the collision number, A the activation energy, c_A , c_B the concentrations of the reactants, and f_A , f_B , $f_{(AB)}$ the activity coefficients of the reactants and the critical complex.

If the increased rate is due to a change in the activity factor we should expect this to be not greater than the change in the solubility of a uni-univalent salt but actually the change is about four times as great⁶ so it is probable that a change in the activation energy is the important factor. As pointed out by Topley and Eyring⁷ it is possible for the difference in zero point energies between a proto- and deuto-compound to be greater in the activated than in the normal state and this may occur in solution due to differing degrees of hydration.

Whatever may be the explanation of the increased velocity observed in heavy water the fact that there is no decrease in the catalytic constant for the inversion of sucrose is in agreement with previous observations that there is no generalised acid catalysis but only a specific effect of the hydrogen ion on the inversion process. It is evident that a mechanism such as that suggested above makes the effect of any acid indistinguishable from that of a hydrogen ion.⁸

The other important result is that of Pacsu⁹ who has shown that in 60 percent D₂O the rate of mutarotation of α -glucose is reduced to 0.53 of its value of H₂O while in pure D₂O the value is about one-third. Since the mutarotation is catalysed by acids and bases¹⁰ and, as shown by Pedersen¹¹ the "spontaneous" reaction is really a basic catalysis by water molecules, it was of

⁶ Cf. Taylor, Caley and Eyring, J. Am. Chem. Soc. **55**, 4334 (1933).

⁷ Topley and Eyring, J. Chem. Phys. to appear shortly.

⁸ Hammett and Paul (J. Am. Chem. Soc. **56**, 830 (1934)) have tentatively suggested that at very high concentrations the molecule of trichloroacetic acid has a catalytic effect but this is very doubtful.

⁹ Pacsu, J. Am. Chem. Soc. **55**, 5056 (1933); **56**, 745 (1934).

¹⁰ Cf. Brönsted and Guggenheim, J. Am. Chem. Soc. **49**, 2554 (1927); Lowry and Smith, J. Chem. Soc. **48**, 2539 (1927).

¹¹ Pedersen, Den almindelige Syre og Base-Katalyse, Copenhagen, 1932.

⁵ Moelwyn-Hughes and Bonhoeffer, Naturwiss. **22**, 174 (1934).

interest to determine the effect of D₂O on the acid catalysis. This was done under the direction of Professor Pacsu and the following results were obtained. (Table II.)

TABLE II. *Mutarotation of glucose.*

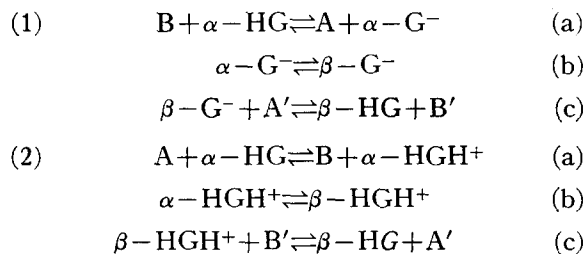
Temperature 23.3°C	Concentration of α-glucose 5%
Solution	<i>k</i> (log ₁₀ mins. ⁻¹)
H ₂ O	0.0089
+0.102 N HCl	0.0328
D ₂ O (+10 ⁻⁴ N HCl)	0.00232
+0.0051 N HCl	0.00320
+0.0095 N HCl	0.00410

The HCl solutions were prepared by adding constant boiling acid.

The values derived for the catalytic constants of H₂O and OH₃⁺ are 0.0089 and 0.24 in close agreement with the values interpolated from the data of Hudson and Dale.¹²

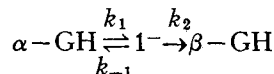
The results for heavy water lead to values of 0.0023 and 0.18, respectively, for the catalytic coefficients of D₂O and OD₃⁺, and hence the catalytic activity of the H₂O molecule is 3.8 times as great as that of the D₂O molecule whereas the activity of OH₃⁺ is only 1.33 times that of OD₃⁺. This is explicable in terms of Pedersen's hypothesis that the effect of the H₂O molecule is that of a basic catalyst.

We are now in a position to discuss the mechanism of the mutarotation of glucose and we take as the starting point the experimentally established fact that the unimolecular constant for the mutarotation of α-glucose is identical with that for β-glucose and that the observed constant is therefore $k = k_{\alpha} + k_{\beta}$. Further Lowry has shown that mutarotation requires both an acid and a basic catalyst and Pedersen¹¹ has set up on this basis the following schemes for the basic and acid catalysis, respectively.



¹² Hudson and Dale, J. Am. Chem. Soc. 39, 320 (1917).

Equilibrium (b) in each case is supposed to be set up very rapidly and the unimolecular changes that occur can therefore be written



and k_{α} (or k_{β}) the overall constant for one form going over into the other is then given by

$$k_{\alpha} = k_1 k_2 / (k_{-1} + k_2)$$

and we may distinguish three possibilities: (1) $k_{-1} \ll k_2$ and $k_{\alpha} = k_1$. In this case the measured rate is simply that of proton (or deuteron) transfer and should therefore be reduced in D₂O according to our results, to about one-sixth of the value in H₂O. However, at the beginning of the reaction this would not apply for the conversion of the α-glucose which could lose only protons, and consequently, as the reaction proceeds, the velocity constant should fall off. Such an effect is not observed nor is the reduction in rate as great as one-sixth and hence this possibility is excluded. (2) $k_{-1} \sim k_2$ and $k_{\alpha} = k_1 / (1 + k_{-1} / k_2)$. This condition would also involve a change in the constant during the progress of the reaction and so must be excluded. (3) $k_{-1} \gg k_2$ and $k_{\alpha} = (k_1 / k_{-1}) \cdot k_2$. Since k_1 / k_{-1} involves the dissociation constant of either the glucose cation or of glucose itself while k_2 is the rate at which a proton (or deuteron) is added to or removed from the intermediate complex this mechanism can be made to fit the facts.

It may also be suggested on the basis of this work that the exchange of deuterium and protium atoms in a homogeneous phase at ordinary temperatures is essentially an acid-base catalyzed reaction and probably the most expeditious method of promoting such an exchange is to add alternately acid and alkali.

I wish to express my gratitude to Professor Hugh S. Taylor, for the facilities offered me in this laboratory and to him as well as other members of the laboratory for helpful discussions.

I am also indebted to the Leverhulme Trustees for a fellowship and to the University of Reading, England, for leave of absence.