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Isotope Effects in Deuterium Oxide Solution. Part II. Reaction Rates in Acid, Alkaline and Neutral Solution, Involving only Secondary Solvent Effects

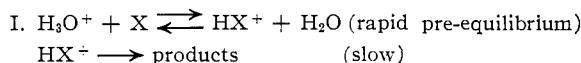
BY C. A. BUNTON AND V. J. SHINER, JR.¹

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The treatment previously used for estimating solvent deuterium oxide effects on acid-base equilibria is applied to kinetic secondary isotope effects² on reactions which do not involve a primary deuterium isotope effect. Explanations are provided for the differing solvent isotope effects upon A-1 and A-2 reactions, for the greater nucleophilic power of OD⁻ over OH⁻ and for solvent-isotope effects in solvolyses. The calculated isotope effects, necessarily based upon approximate models for reasonable transition state structures, generally bracket the observed isotope effects. However, when the mechanistic situation is complicated, unambiguous distinction of mechanism based upon isotope effects is not possible.

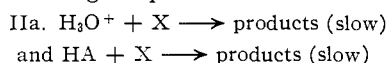
Solvent deuterium isotope effects have become an important tool in the study of acid and base catalyzed reactions. In a previous paper³ we attempted to lay a theoretical foundation for the general analysis of these phenomena, by showing that the deuterium solvent isotope effect upon acid-base equilibria, of oxygen compounds, can be understood in terms of hydrogen bonding interactions between the solvent and the acids and bases concerned. In this paper we extend our treatment to solvent deuterium isotope rate effects upon some reactions of oxygen compounds.

In acid-catalyzed reactions a major problem is the determination of the timing of the proton transfer, relative to the other electronic redistributions; proton transfer may be rapid and reversible, and precede the bond-making and breaking steps; this is the reaction sequence I.

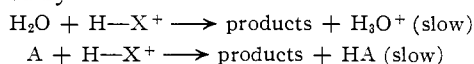
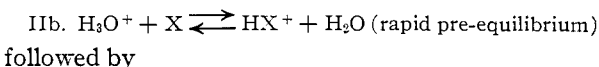


The slow stage may be a nucleophilic attack of water upon HX⁺, or this conjugate acid may decompose unimolecularly. These mechanisms have been designated A-2 and A-1, respectively, by Long and co-workers⁴ and must show specific hydrogen ion catalysis. General (undissociated) acids will be effective catalysts only to the extent of their ionization to solvated protons.

In a second reaction sequence, IIa, the proton may be transferred directly from the acid in the rate-determining step. Mechanisms IIa will be



general acid catalyzed, as will the kinetically equivalent formulations IIb



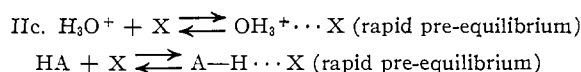
(1) National Science Foundation Senior Postdoctoral Fellow and Alfred P. Sloan Research Fellow.

(2) By secondary isotope effects we mean those effects on reaction rate due to substitution of deuterium for a hydrogen that is not being transferred in the rate-controlling step. Primary isotope rate effects are those in a hydrogen transfer reaction which are caused by replacement of the hydrogen by deuterium; solvent isotope effects are the experimentally observed effects caused by a change of solvent from water to deuterium oxide.

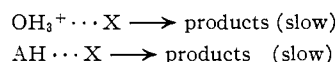
(3) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 42 (1961).

(4) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

An alternative formulation of general acid catalysis involves the rapid formation of hydrogen bonded intermediates



followed by



The catalytic power of any acid in reactions with mechanisms IIa, b or c will be related to the dissociation constant of that acid by the Brønsted catalysis law.⁵

Thus observation of general acid catalysis, following the Brønsted catalysis law, is evidence for either a slow proton transfer from the acid to the reacting molecule or for a rapid and reversible proton transfer followed by a slow removal of a proton by the conjugate base of the general acid. However, this test will fail to detect general acid catalysis if the solvated proton is a much more effective acid than the general acid, HA, *i.e.*, if the exponent α of the Brønsted catalysis law is nearly unity.^{5a,c}

Because of this limitation it is often difficult to differentiate between pre-equilibrium and rate-determining proton transfers. Therefore other criteria have been developed. Chief among these are the use of Hammett's acidity function h_0^+ and the kinetic isotope effect brought about by a change of solvent from water to deuterium oxide.⁶ The h_0^+ acidity function is useful in solutions of sufficiently high acidity for this function to differ appreciably from the hydrogen ion concentration. A generalization, the Zucker-Hammett hypothesis, states that specific acid-catalyzed reactions (class I) will show rate correlation with h_0^+ for A-1 reactions and with $[\text{H}_3\text{O}^+]$ for A-2 reactions. Some general acid-catalyzed reactions of type II(b) show rate correlation with $[\text{H}_3\text{O}^+]$. It has been suggested that a correlation between rate and Hammett acidity is proof of a rapid and reversible formation of the conjugate acid of the substrate followed by a slow step of the reaction. In a recent paper Melander and Myhre⁷ argue cogently (as

(5) For discussion of general acid-base catalysis see: (a) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, and (b) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1956, ch. 8 and (c) V. Gold, *Trans. Faraday Soc.*, **56**, 255 (1960).

(6) K. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(7) L. Melander and P. C. Myhre, *Arkiv. Kemi.*, **13**, 507 (1959).

Long and Paul⁴ had suggested earlier) that the Zucker-Hammett hypothesis does not exclude the possibility of a slow proton transfer from H_3O^+ (mechanism IIa), showing a rate correlation with k_0 . They also cast doubt upon the usefulness of the kinetic effect of a change of solvent from water to deuterium oxide as a mechanistic test.

Acid-catalyzed reactions have been placed into two general classes with regard to the kinetic effect of a change of solvent from water to deuterium oxide. Many reactions which were thought to involve prior equilibrium formation of the conjugate acid of the substrate were known to be faster in deuterium oxide than in water. This was readily understandable in terms of the known greater dissociation constants of weak acids in water than in deuterium oxide, because the conjugate acid of the substrate should be present in a greater equilibrium concentration in deuterium oxide.^{6,8} A second class of reactions were observed to be slower in deuterium oxide than in water. These reactions were considered to involve a proton or deuteron transfer in the rate-determining stage. Thus the deuterium isotope effect was thought to provide a distinction between a specific hydrogen ion and general acid catalysis. This was particularly useful for reactions in which general acid catalysis, or its absence, could not be proved directly.⁹

However the theoretical basis of this mechanistic criterion is not firmly established. It has been pointed out that the difference between the dissociation constants of weak acids in water and deuterium oxide must be due to the relative differences in zero point energy between a solvated proton and one covalently bound in an undissociated acid molecule,^{8,12} but it was also known that the ratio of the dissociation constants in water and deuterium oxide, $K_{\text{H}_2\text{O}}/K_{\text{D}_2\text{O}}$, became smaller as the acid became stronger. Therefore it is not obvious why the strong conjugate acids of very weak bases (e.g., such oxygen bases as carboxylic esters), formed by rapid proton transfer (reaction sequence I) should be present in greater concentration in deuterium oxide than in water of the same acidity. This is particularly so when the conjugate acid is stronger than H_3O^+ and structurally related to it.

The problems which have to be faced in interpreting the nature of base catalysis are analogous to those discussed for acid catalysis and the experimental approaches are similar,^{5a,b} although as yet the correlation of kinetic data with indicator measurements has not been used widely.¹³ In general it has been accepted that proton transfers to a base are slower for deuterium than for hydrogen but that the nucleophilic power of OD^- is greater

(8) G. N. Lewis and P. W. Schutz, *J. Am. Chem. Soc.*, **56**, 1913 (1934).

(9) A further extension was the Gross-Butler equation,¹⁰ which predicted the kinetic effects of a gradual change of solvent from water to deuterium oxide. Halevi, Long and Paul¹¹ have argued convincingly that this extension does not give additional mechanistically significant information.

(10) (a) P. Gross, H. Steiner and F. Krauss, *Trans. Faraday Soc.*, **32**, 877 (1936); (b) W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 957 (1938); (c) E. L. Purlee, *J. Am. Chem. Soc.*, **81**, 263 (1959).

(11) E. A. Halevi, F. A. Long and M. A. Paul, *ibid.*, **83**, 305 (1961).

(12) O. Halpern, *J. Chem. Phys.*, **3**, 456 (1935).

(13) See, however, J. H. Ridd, *Chemistry and Industry*, 1268 (1957).

than that of OH^- .⁶ There is the further point that solvolyses in initially neutral solution sometimes show an appreciable solvent isotope effect, which has not been explained satisfactorily to date.¹⁴

Long and Bigeleisen¹⁵ have applied the earlier equations of Bigeleisen to acid-catalyzed reactions and show that they provide the essential framework for consideration of isotope effects on acid and base catalysis. We found it possible to apply a simple form of the Bigeleisen equation to isotope effects on acid-base equilibria, Part I,³ and were therefore encouraged to apply a similar simple treatment to the kinetic isotope effects in acid-base catalysis.

In the earlier paper³ the foundations of our interpretation of the isotope effect of solvent deuterium oxide on the dissociation constants of acids were the following.

1. The effects are principally due to the differential zero point energy changes between initial and final states of the reaction in the two isotopic solvents.

2. Vibration changes of all isotopically substituted hydrogens must be accounted for. This involves primarily, besides all of the hydrogens of the reactants and products, those of the solvent molecules hydrogen bonded to them.

3. The stretching vibration frequency of a hydrogen donated from an oxygen acid to water for hydrogen bonding varies linearly with the acidity (pK_a) of the donor and of a hydrogen donated by water to an oxygen base varies linearly with the basicity (pK_b) of the acceptor.

4. Changes in frequencies of the librational and bending modes are relatively unimportant.

In addition a set of simple rules was formulated for the determination of the number of hydrogen bonds affected by the reaction.

The relation between the kinetic isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ and the relevant hydrogen stretching frequencies is

$$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = \text{antilog} \frac{\Sigma\nu_{\text{H}} - \Sigma\nu'_{\text{H}}}{12.53T}$$

where $\Sigma\nu_{\text{H}}$ and $\Sigma\nu'_{\text{H}}$ are the sum of hydrogen stretching frequencies (cm^{-1}) in the initial and transition states, respectively, and T is the absolute temperature.³ For estimating the stretching frequencies of the hydrogens of water donated to oxygen bases in aqueous solution we use the equation³

$$\nu (\text{cm}^{-1}) = 3040 + 22.9K_b$$

and for the hydrogen bonds donated by acids

$$\nu (\text{cm}^{-1}) = 2937 + 28.8pK_a$$

In this paper we restrict our discussion to reactions in which there is no primary deuterium isotope effect. The method of calculation which we have applied to equilibria cannot be applied to kinetic phenomena, unless certain assumptions are made with regard to the nature of the possible transition states. Following theory, we assume that the transition state is in equilibrium for all

(14) (a) A. R. Butler and V. Gold, *Proc. Chem. Soc.*, 15 (1960); *Chemistry and Industry*, 1218 (1960); (b) C. A. Bunton, N. A. Fuller, S. G. Perry and V. J. Shiner, *ibid.*, 1130 (1960).

(15) F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959).

displacements except that along the reaction coordinate and that in considering the secondary deuterium solvent isotope effect upon displacements orthogonal to this coordinate we need consider only changes in the stretching frequencies. This neglect of changes in bending and librational frequencies imposes a limit on the precision of our calculation as it does in consideration of equilibrium isotope effects.³ A detailed discussion by Swain and Bader¹⁶ suggests that these low frequency vibrations are of great importance in the understanding of deuterium isotope effects on the solubility of salts but are much less important for the dissociations of oxygen acids and bases.

For the purposes of calculation of secondary kinetic isotope effects we choose two extreme models for the representation of the partial single covalent bonds in the transition state. One of these considers the partial bonds at the reaction center to be fully covalent (represented by a dashed line) with the charge distribution and the hydrogen bonding which this implies. The other model considers this bond to be purely electrostatic (represented by a dotted line). Thus, in this model, electrostatic interactions between the partly bonded groups will leave the hydrogen bonding at other sites as it would be if this bond did not exist. Neither of these models is likely to correspond to reality, but choice of them makes for ease of calculation, and the values so obtained should bracket the correct one for any given mechanism. For a unimolecular dissociation or a bimolecular association we should then consider two possible structures for the transition state. For a bimolecular displacement four should be considered. The rules which were formulated for the availability of acceptor and donor sites in equilibria will also apply to kinetic systems. The values of pK_b for the weak oxygen bases used below are taken from the compilation of Paul and Long¹⁷ or estimated from the frequency shifts observed by Gordy and Stanford¹⁸ or from the empirical correlations of Branch and Calvin.¹⁹ In general the calculations are not sensitive to variations of one unit in the pK values.

This very simple model predicts the observed trends in secondary deuterium solvent isotope effects and can be summarized qualitatively in the following way. If, in a reaction, electronic displacements develop centers of high local acidity or basicity, there will be an increase in the strength of the hydrogen bonds which exist between these centers and the solvent water molecules (*i.e.*, a decrease in their stretching frequencies). This decrease in frequency, relative to the initial state, will increase the ratio k_{H_2O}/k_{D_2O} . These changes in stretching frequency are sufficiently large, in some reactions, for the secondary solvent isotope effects to be comparable in magnitude with those associated with primary deuterium isotope effects, and this general interpretation can be applied to reactions in acid, basic and neutral solution. As-

(16) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960).

(17) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

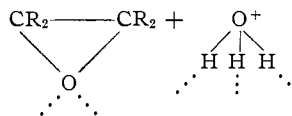
(18) W. Gordy and S. C. Stanford, *J. Chem. Phys.*, **9**, 204 (1941).

(19) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, Ch. VI.

sociated changes in the librational frequencies of the adjacent solvent molecules¹⁶ will give a (small) isotope effect in the same direction as the (large) effect which is governed by the changes in the stretching frequencies.

Acid Catalysis.—We illustrate our method for the acid hydrolyses of epoxides and carboxylic esters and summarize our results for these and other hydrolyses in Table I, which includes the generally accepted mechanism for each reaction. We choose the following models for the purpose of calculation: for an A-1 reaction we assume that in the transition state the leaving group is bound either covalently or by an electrostatic attraction. For the A-2 reactions we take the extreme model in which both the incoming and leaving groups are held covalently, and we show that this situation leads to small isotope effects (Table I). If we introduce electrostatic interaction between the reaction center and the incoming and leaving groups, we decrease the value of k_{H_2O}/k_{D_2O} and if both groups are considered to be held electrostatically, the isotope effect is very close to that calculated for the A-1 electrostatic model. This is reasonable, because a chemical distinction between these two models should not be made.

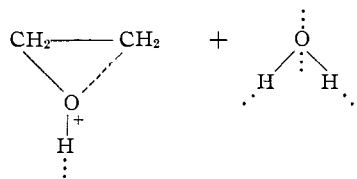
Hydrolysis of Epoxides.—The initial state is



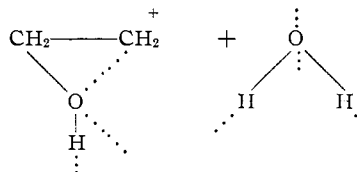
The "dangling" dotted lines refer to hydrogen bonds to or from solvent water molecules. Taking the pK_b of the epoxide to be 18.7, the sum of the stretching frequencies of the relevant protons in the initial state is

$$\Sigma\nu_{\text{H}} = 2 \times 3468 + 3 \times 2900 = 15,636 \text{ cm.}^{-1}$$

For the A-1 mechanism a covalently bound transition state is taken as one extreme model



An A-1 transition state having only electrostatic interaction (indicated by the dotted line) between the reaction center and the leaving group, would represent the other extreme



For the A-1 covalent transition state, using -4.7 as the pK_a of the conjugate acid of the epoxide

$$\Sigma\nu'_{\text{H}} = 4 \times 3400 + 2802 = 16,402 \text{ cm.}^{-1}$$

Thus

$$k_{H_2O}/k_{D_2O} = 0.63$$

(This number is identical with the calculated relative amounts of conjugate acid in D_2O and H_2O .)

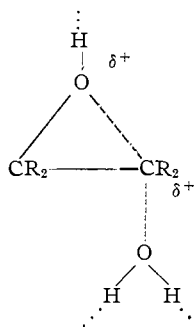
For the A-1 electrostatic transition state it is assumed that the hydrogen bonds to the hydroxyl group have the same frequency as in hydrogen bonded water and

$$\Sigma\nu_{\text{H}} = 6 \times 3400 - 3600 = 16,800 \text{ cm.}^{-1}$$

$$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.48$$

The figure of 3600 is deducted to allow for the fact that the transition state, in this formulation, has one extra acceptor site, and donation to it will accommodate one hydrogen of water which because of the excess of donors was not accepted in the initial state. (See Rule d, reference 3.) As indicated in the table, the value calculated for this model agrees well with the experimental one. The most probable mechanism should be intermediate between the two extremes just discussed; if this is so the calculated isotope effect is apparently a little too high, and this seems to be generally true for most estimates of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ by this method.

The transition state for the A-2 covalent model is formulated as



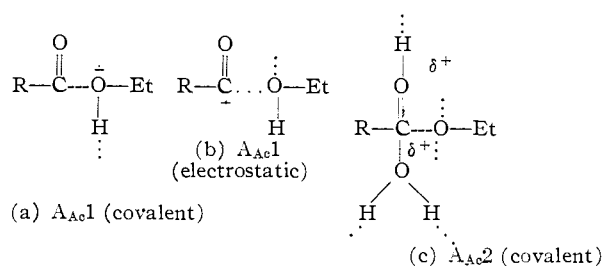
For an *extreme* estimate of the hydrogen bonding effects both bonds are considered to be fully covalent and both oxygen atoms are considered to carry a unit positive charge. Then

$$\Sigma\nu_{\text{H}} = 2802 + 2 \times 2900 + 2 \times 3600 = 15,802$$

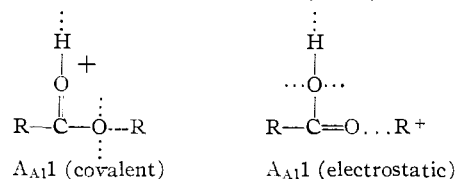
and $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.91$. In this model the strong covalent interaction at the reaction center increases the acidity of the two hydrogen atoms on the incoming water molecule; this will increase the ratio $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$. It is suggested that this spreading of the positive charge in the bimolecular transition state, which increases the number of acidic protons, is the probable reason for the ratio $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ being generally larger for A-2 than for A-1 reactions; an observation which has been discussed and extensively documented by Long²⁰ and his co-workers. With increase in the electrostatic character of the bonds the isotope effect for the A-2 model becomes close to that of the A-1 electrostatic model.

Carboxylic Esters.—The models used for the transition states for acid hydrolysis of carboxylic esters with acyl-oxygen fission are shown as (a), (b), (c). These three models are chosen because they fit the published chemical observations reasonably well; there is no reason to believe that they are unique in this respect. The problem of the mechanism of the acid hydrolysis of carboxylic esters with acyl-oxygen bond fission is so complex that it is not suggested that our calculated values given in the table favor any one formulation.

(20) J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 6008 (1956); **80**, 4162 (1958).

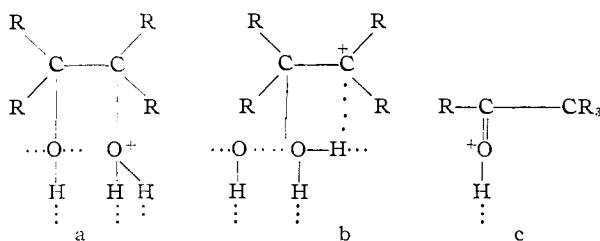


The models taken for A_{A1} hydrolysis are



Here, as in the hydrolysis of epoxides the electrostatic model gives the slightly better fit; however, the fact that one of the experimental values is for an aqueous dioxane solvent is a complicating factor. In making these calculations on ester hydrolyses the pK_b for a carboxylic ester was taken to be 19. Dioxane and other organic solvents have similar basicities to H_2O and their addition should not markedly affect the situation, except that because they may provide an excess of acceptor sites the values of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ should then be slightly larger.

Pinacol-Pinacone Rearrangement.—In this calculation we assume that the donor and acceptor frequencies for the hydroxyl group of a glycol are 3400 cm.^{-1} , the same as for water, corresponding to pK_a (per hydroxyl group) of 16. Three possible models for the transition state for the A-1 mechanism are



The covalent model "a" is close to the conjugate acid of the glycol and "c" to the conjugate acid of the ketone. For model "c" we take the pK_a for the conjugate acid of the ketone to be -5 . The results are:

Model	a	b	c	Exp. ²¹
$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$	0.77	0.53	0.62	0.53

The most reasonable model, b, gives agreement with experiment.

Nucleophilic Substitution by Hydroxide and Oxide Ions at Carbon. General Considerations.—We illustrate an application of our theory by first considering a bimolecular substitution by hydroxide ion, *e.g.*, on carbon. Several limiting models can be chosen for the structures of the transition state. They have the common feature that for the hydroxide ion to become a nucleophile, one of

(21) J. F. Duncan and K. R. Lynn, *Austral. J. Chem.*, **10**, 1 (1957); C. J. Collins, *Quart. Rev.*, **14**, 357 (1960).

TABLE I
SOLVENT ISOTOPE EFFECTS IN ACID-CATALYZED SOLVOLYSES INVOLVING ONLY SECONDARY ISOTOPE EFFECTS
The experimental values, unless otherwise specified, are taken from ref. 6.

Reaction	Class.	Obsd.	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$		
			A-2 (Covalent)	Calcd. A-1 (Covalent)	A-1 (Electrostatic)
Hydrolyses of epoxides	A-1	ca. 0.5 ^a	0.91	0.63	0.48
Hydrolyses of acetals	A-1	.37	.83	.59	.40
Inversion of sucrose	A-1	.49	.83	.59	.40
Hydrolysis of ethyl ortho- formate	A-1	.43	.91	.63	.35
Hydrolysis of ethyl acetate	AAc2	.63	.72	.67	.42
Hydrolysis of ethyl formate	AAc2	.73	.77	.68	.45
Hydrolysis of 4-methoxy diphenylmethyl acetate ^b	AA11	.53	.72	.62	.55
Hydrolysis of <i>t</i> -butyl acetate ^c	AA11	.50	.72	.62	.53

^a Ref.²⁰ ^b C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 3043 (1957). ^c D. Whittaker, unpublished results.

the hydrogen bonds donated to it, by water, must be broken. This is true whether we choose an "electrostatic" or "covalent" model for the transition state. The relevant hydrogen of a water molecule will change its stretching frequency³ from 3000 to 3400 cm^{-1} , leading to an isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ of 0.79 for model 1 (Table II). (This

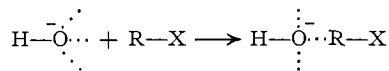
TABLE II

CALCULATED ISOTOPE EFFECTS IN LIMITING TRANSITION STATES FOR REACTIONS OF HYDROXIDE ION

Model	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$	Binding in transition state Incoming group	Leaving group
1	0.79	electrostatic	covalent
2	.54	covalent	covalent
3	.54	covalent	electrostatic ^a
4	.88	covalent	electrostatic ^b

^a Leaving group equal or less basic than water. ^b Leaving group with same basicity as hydroxide ion and possessing two acceptor sites.

effect should also be important when the hydroxide ion removes a proton attached to a carbon atom.) If the hydroxide ion becomes completely covalently bound and no group more basic than water is displaced, the frequencies associated with the OH group will change from $3 \times 3000 + 3600$, *i.e.*, 12,600 to 4×3400 , *i.e.*, 13,600. This gives $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.54$ (model 2). Values of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ of



ca. 0.75 are observed for many reactions in which OH^- attacks an electrophile or an acid in the rate-determining step. We should expect this value to be that for the deuterium "solvent" effect when there are no other strongly hydrogen bonding groups in the system and when the transition state is like the initial state or equivalent to model 1. This situation apparently obtains for many bimolecular substitutions at carbon.²² In discussing this model we have assumed that the leaving group X does not accept a hydrogen bond from water in the transition or initial states either because it is insufficiently basic or because it is covalently bonded to the reaction center in the transition state.

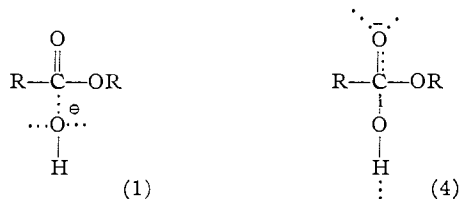
Hydrogen bonding between the leaving group and water should increase $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$. The pre-

(22) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

dicted effects are listed, Table II. These give a simple explanation of the apparent greater nucleophilicity of OD^- relative to OH^- , but the values are not very sensitive to mechanism and unfortunately are therefore of limited use in establishing mechanism.

For the $\text{S}_{\text{N}}2$ reaction of a hydroxide ion with an alkyl sulphonic ester $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.86$.²³ Model 1 Table II should be appropriate for this reaction. For the alkaline hydrolysis of epoxides $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.91$.²⁴ This is in reasonable agreement with values calculated for models 1 or 4, Table II.

For the alkaline hydrolysis of carboxylic esters a reasonable model for the rate-determining step is the displacement of a pair of π electrons toward the carbonyl oxygen atom; models 1 and 4, Table II.



The calculated value for (1) is in good agreement with the experimental value of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.75$.⁶

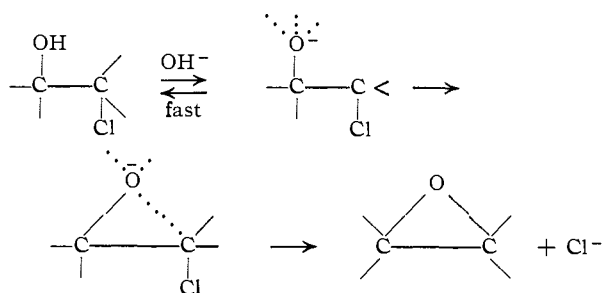
Reactions Involving Decomposition of the Conjugate Base.—Alkaline Hydrolysis of Chlorohydrins.—The slow step is the decomposition of the conjugate base,²⁵ and the over-all solvent isotope effect is $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.87$.

The frequency of the hydrogen bond accepted by the initial alkoxide ion should be 3030 cm^{-1} , (pK_b of -0.3). In forming the transition state one of these acceptors is lost, and the relevant hydrogen bond frequency becomes 3400 cm^{-1} . Thus on this electrostatic model for the transition state $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ (calcd.) = 0.80. Hydrogen bonding between water and the leaving chloride ion should increase this ratio toward unity.

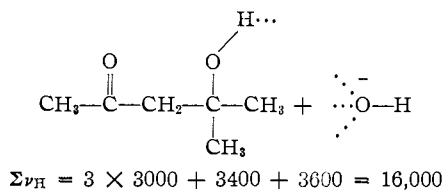
(23) Private communication from S. Hartman and R. E. Robertson. We are grateful to these authors for the prior communication of their results.

(24) J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 6008 (1956).

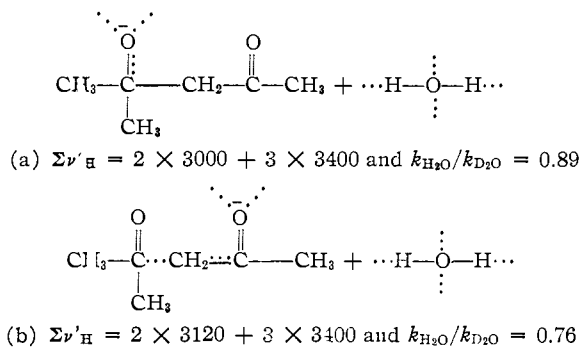
(25) P. Ballinger and F. A. Long, *ibid.*, **81**, 2347 (1959); C. G. Swain, A. D. Ketley and R. F. W. Bader, *ibid.*, **81**, 2353 (1959), and references cited therein.



Decomposition of Diacetone Alcohol.—It appears likely that this is another reaction in which an initial equilibrium proton transfer is followed by a slow breakdown of the conjugate base. The initial state is formulated as



For the transition state we consider two models (a) like the alcoholate ion and (b) like the enolate ion.



Either model agrees reasonably well with the experimental values of 0.82 and 0.68.²⁶

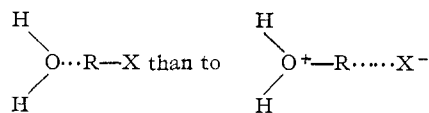
Solvolytic Nucleophilic Substitution at a Saturated Carbon atom.—Much of the experimental results comes from the extensive work of Robertson and his co-workers.²⁷ For many SN1 and SN2 reactions the value of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is consistently above unity. For alkyl halides and alkyl sulfonium salts we cannot predict the size of this effect because we do not know the stretching frequencies of the hydrogens of water accepted by bases such as halide ions and dialkyl sulfides. To the extent that these interactions exist our model would predict a small isotope effect in the direction observed.

Involvement of a water molecule in bonding to the reaction center, in the SN2 mechanism, will increase its acidity, lower its stretching frequency and hence increase the ratio $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$. The observed values of this ratio for SN2 solvolyses at a saturated carbon atom are close to unity, and this suggests that the water molecule is not strongly

(26) (a) W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 957 (1933); (b) J. C. Hornel and J. A. V. Butler, *ibid.*, 1361 (1936).

(27) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **34**, 1714 (1956).

covalently bonded to the reaction center in the transition state; e.g., the transition state should be closer to

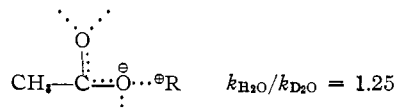
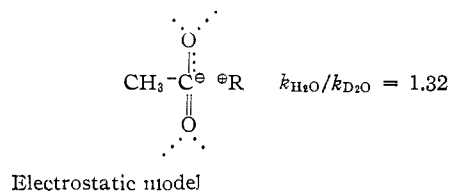


(cf. ref. 22.)

Because the SN1 reaction of an alkyl halide or sulfonic ester involves separation of ions a detailed explanation of the *small* solvent isotope effect must involve consideration of the librational or bending vibrations of the water molecules which solvate the transition state.¹⁶

For SN1 mechanisms we expect values of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ appreciably above unity only when the leaving group is more basic than water, as in the hydrolysis of carboxylic esters by mechanism B_{Al}1. For hydrolysis of 4-methoxydiphenylmethyl acetate at 100° in initially neutral aqueous dioxane, $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.87$.^{14b} The calculated values for models of transition states are

Akin to carbonium ion: (*i.e.* to final state)



The somewhat poor agreement in this example may indicate a limitation in applying our model at higher temperatures where it is known that the solvent structure is disturbed.

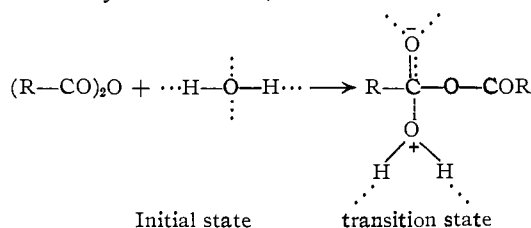
The neutral hydrolysis of β -propiolactone by the B_{Al}2 mechanism has a value of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.16$.^{14a} The water molecule is not strongly covalently bonded to the reaction center in the transition state, whose structure should be close to that of the highly strained initial state (cf. ref. 22). Thus we should not expect the ratio $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ to be much above unity.

Solvolytic Nucleophilic Substitution at Unsaturated Centers.—For these reactions there is an uncertainty as to the timing of the bond making and breaking processes, just as there is for the corresponding reactions in acidic or alkaline solution. An additional complication is that general nucleophiles (*i.e.*, other than the hydroxide ion) may catalyze the reactions. In these reactions there is usually considerable charge separation in the transition state, which leads to large solvent isotope effects.

Carboxylic Anhydrides.—The solvent deuterium isotope effect has been measured for the spontaneous hydrolysis and that catalyzed by pyridine and carboxylate ions; $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ is always greater than unity.¹⁴ Apparently all of these reactions proceed more rapidly than the concurrent oxygen

exchange with water so that if the mechanism involves addition of water prior to the elimination of some other group the transition state for the over-all reaction must be passed in the addition step.²⁸

A. Spontaneous Hydrolysis.—Two models are considered. In the first, if the incoming water molecule is only electrostatically bound and the π bond in the carbonyl group is largely intact, the isotope effect will be very nearly unity (*cf.* p. 3214). In the second, the incoming water molecule is largely covalently bound and the breaking π bond is only electrostatic, *i.e.*



$$\Sigma \nu_H = 13,600 \text{ cm.}^{-1}$$

$$\Sigma \nu_H' = 2 \times 2900 + 2 \times 3000 = 11,800$$

$$k_{H_2O}/k_{D_2O} = 3.0$$

In this calculation it is assumed that the negative oxygen function has a basicity like that of hydroxide and that the hydrogens on the positive oxygen have the acidity of the hydronium ion. This model gives good agreement with the experimental value of k_{H_2O}/k_{D_2O} of *ca.* 3,¹⁴ and the relatively low nucleophilicity of water makes it a reasonable one.

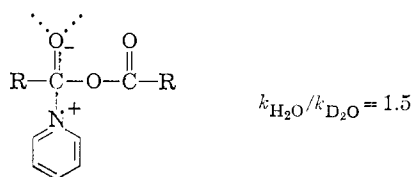
B. Formate Ion-catalyzed Hydrolysis of Acetic Anhydride.—The value of k_{H_2O}/k_{D_2O} for this reaction is 1.1, and the rate-determining step is believed to be formation of formic acetic anhydride.¹⁴ We should expect the deuterium isotope effect for this reaction to be close to unity because formate ion displaces the more basic acetate ion, with a consequent small decrease in the frequency of the hydrogen atoms of water which are hydrogen bonded to the oxygen atoms.

C. Pyridine-catalyzed Hydrolysis of Acetic Anhydride.—Tertiary amines are powerful catalysts for the hydrolysis of carboxylic anhydrides. For the pyridine-catalyzed hydrolysis of acetic anhydride $k_{H_2O}/k_{D_2O} = 5.7$.^{14a} The relation between pK and frequency of hydrogen bonds³ has been applied only to oxygen acids and bases, and there is therefore uncertainty as to the frequency of the hydrogen bond accepted by pyridine; for the purpose of this calculation we assume it to be the same as that of an oxygen base of the same pK . Possible models are shown as (1) and (2).

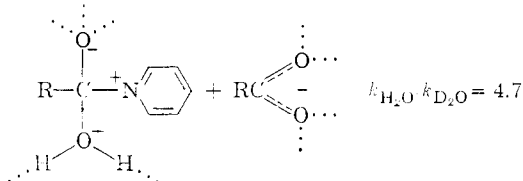
It is thought that the slow step of the reaction is the decomposition of the acetylpyridinium ion.^{14a} Our model "2" is in reasonable agreement with experiment, despite uncertainties in the frequencies; there may well be other models for the decomposition of the acetylpyridinium ion which are equally satisfactory.

D. Acetate-catalyzed Hydrolysis of Acetic Anhydride.—The mechanism of the acetate-catalyzed

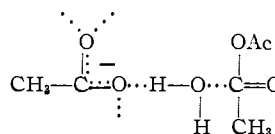
(1) The slow step is attack of pyridine upon the anhydride



(2) Attack of water upon the acetylpyridinium ion

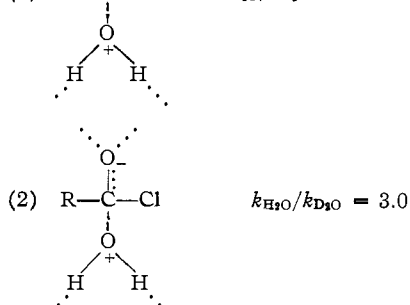
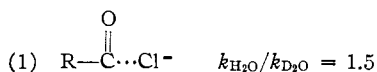


hydrolysis is uncertain. The acetate ion may act as a base, and through hydrogen bonding make a water molecule more nucleophilic, *e.g.*



This mechanism should give a value of $k_{H_2O}/k_{D_2O} > 1$, because the frequencies of the hydrogens involved in hydrogen bonding should be decreased. Because of the uncertainties of the mechanism quantitative calculations of the deuterium isotope effect are not included.

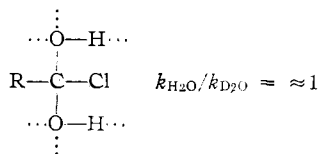
Acid Chlorides.—The solvent deuterium isotope effects for the spontaneous hydrolysis of acyl and sulfonyl chlorides are $k_{H_2O}/k_{D_2O} = 1.7$ ¹⁴ and 1.6,²⁷ respectively. In calculating the isotope effect we have neglected hydrogen bonding between the leaving chloride ion and water and the effect of a negatively charged halide upon the water structure.¹⁶ The effect should make our values of k_{H_2O}/k_{D_2O} too low, but the error should be small because chloride ions are insufficiently basic to form strong hydrogen bonds with water. In contrast we should expect the spontaneous hydrolysis of acyl (and alkyl) fluorides to show larger solvent deuterium isotope effects, because of strong hydrogen bonding to the fluoride ion. We consider only bimolecular transition states (the value of k_{H_2O}/k_{D_2O} for a unimolecular mechanism should be similar to that for alkyl halides, *i.e.*, *ca.* 1).



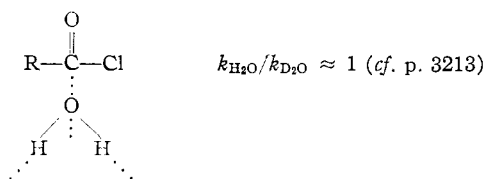
(28) C. A. Bunton, T. A. Lewis and D. R. Llewellyn, *Chemistry and Industry*, 1154 (1954); N. A. Fuller, unpublished results.

assuming $\nu_{\text{donor}} = 2900 \text{ cm.}^{-1}$, and $\nu_{\text{acceptor}} = 3000 \text{ cm.}^{-1}$

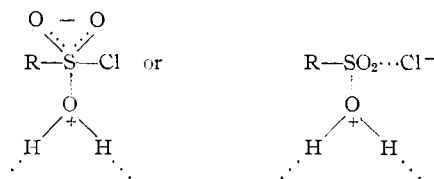
(3) Transition state akin to a tetrahedral intermediate



Transition state like initial state

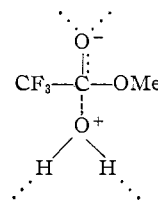


For the hydrolyses of sulfonyl chlorides



we arrive at values for $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ of 1.5, assuming $\nu_{\text{donor}} = 2900 \text{ cm.}^{-1}$. Although some of our models lead to calculated values in good agreement with experiment, we do not believe the calculations to be sufficiently precise for differentiation between various mechanisms.

Esters.—The spontaneous hydrolysis of many carboxylic esters is swamped by their acid and alkaline hydrolyses. The spontaneous hydrolysis of methyl trifluoroacetate can be followed, and $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.8$.^{14b} For the B_{Ac}2 mechanism we can postulate the transition state model shown. If we assume that the acceptor frequency is that of the conjugate base of trifluoroethanol, we estimate $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 2.7$. A transition state structure with



the negative charge on the leaving methoxide ion gives a similar value. The difference between the experimental and calculated values suggests that these models overestimate the polarity of the transition state.

Limitations of the Method.—Calculations of kinetic isotope effects require assumptions to be made about the structure of the transition state, just as does any discussion of mechanism. For calculation of secondary isotope effects our models are least satisfactory for reactions in which the initial and transition states cannot be approximately represented by classical structures, *e.g.*, the bimolecular hydrolysis of carboxylic esters with acyl-oxygen fission. This complication was noted also in the calculation of equilibrium isotope effects for dissociation of acids to mesomeric ions.³ As for equilibria (Part I³) our treatment of secondary isotope effects is here restricted to substrates containing oxygen. Extension to other compounds requires observation of the frequencies of the relevant hydrogen bonds and there is the further problem that reactions of such compounds may change the librational and bending frequencies of the adjacent water molecules. For many of the reactions in basic or neutral solution the isotope effects are close to unity and therefore uncertainties in the calculations are comparable with the observed effects. Despite this the direction of the isotope effect is generally predicted correctly, as are the trends in the change of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ with changes in the nature of the reactants, and we believe that this, rather than the numerical agreement, is the most significant part of this treatment.

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF INDIANA UNIVERSITY, BLOOMINGTON, INDIANA, No. 991, AND THE WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE, LONDON, ENGLAND]

Isotope Effects in Deuterium Oxide Solution. Part III. Reactions Involving Primary Effects

By C. A. BUNTON AND V. J. SHINER, JR.¹

RECEIVED NOVEMBER 10, 1960

The interpretation of secondary solvent deuterium oxide isotope effects in terms of hydrogen bonding interactions between solute and solvent molecules is applied to reactions which involve primary deuterium isotope effects attendant on rate-limiting proton transfer. The wide variations in magnitude of primary isotope effects are rationalized and correlated with transition state structure, and the treatment is shown to give reasonable calculated values for the secondary isotope effects.

In Part II² of this series reactions involving only secondary solvent deuterium isotope effects³ were treated; in this paper are considered reactions in solvent deuterium oxide which involve primary

isotope effects³ attendant on rate-determining proton transfers. Our method of calculation does not give any quantitative estimate of the primary isotope effect for transfer of a hydrogen atom or ion, but we can estimate the associated secondary effect. For some reactions, *e.g.*, the enolization of ketones, it is possible to measure the primary and secondary isotope effects separately, and in

(1) National Science Foundation Senior Postdoctoral Fellow and Alfred P. Sloan Research Fellow.

(2) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **85**, 3207 (1961).

(3) See part II for definitions of these terms.