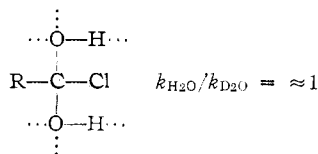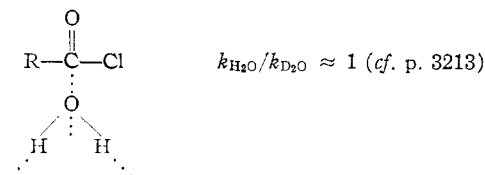assuming $\nu_{donor} = 2900$ cm.$^{-1}$, and $\nu_{acceptor} = 3000$ cm.$^{-1}$
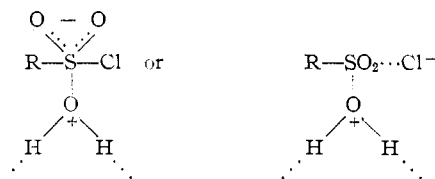
(3) Transition state akin to a tetrahedral intermediate

Transition state like initial state

For the hydrolyses of sulfonyl chlorides

we arrive at values for k_{H_2O}/k_{D_2O} of 1.5, assuming $\nu_{donor} = 2900$ 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 $k_{H_2O}/k_{D_2O} = 1.8$.[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 $k_{H_2O}/k_{D_2O} = 2.7$. A transition state structure with
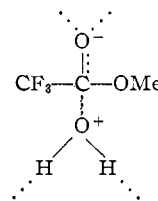
the negative charge on the leaving methoxide ion gives a similar value. The difference between the experimental and calculated values suggests that these models overestimate the polarity of the transition state.

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 I[3]) 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_{H_2O}/k_{D_2O} 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.

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

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

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 II[2] of this series reactions involving only secondary solvent deuterium isotope effects[3] were treated; in this paper are considered reactions in solvent deuterium oxide which involve primary

isotope effects[3] 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.

some cases the primary effect can be evaluated by reference to related reactions. For these examples the calculated and observed secondary effects can be compared. For others the over-all experimentally observed solvent isotope effect is used with the theoretically estimated secondary effect to determine the primary effect.

Variation of Primary Isotope Effect with Transition State Structure.—Melander[4] has given a theoretical explanation, in terms of potential energy surfaces, for conservation of the hydrogen stretching zero point energy in the transition state of a hydrogen transfer reaction. Transfer of a hydrogen atom, or ion, between two identical atoms or groups, should in general proceed through a transition state in which the zero point energy of the hydrogen is lost. This is because for a completely symmetrical transition state the symmetric stretching frequency, orthogonal to the reaction coördinate, does not involve motion of the hydrogen, and the asymmetric stretching motion represents the reaction coördinate. Conversely, if the transition state is very unsymmetrical in either sense, the zero point energy of the initial state will be largely conserved, and the rate effect of isotopic substitution will be very small. This is because the symmetric stretching largely involves motion of the hydrogen, while the asymmetric stretching or reaction coördinate largely involves motion of the heavier atoms.

Applying this idea to proton transfers, one would expect that if the proton is shared between two bases of largely unequal strength the position of the proton at the state of highest potential energy (the transition state) is nearer to the weaker base, and most of its stretching zero-point energy is therefore conserved. These expectations are qualitatively borne out by the examples analyzed in this paper. The same idea should apply to transfers involving hydrogen atoms, where the hydrogen atom is shared between two atoms or radicals and to hydride ion transfers. The isotope effect will tend to the maximum value when the bond strengths in the starting and final states are equal.[5] If the bond to be broken is stronger than the bond to be made, the configuration of maximum energy during the transfer will be attained when the hydrogen is nearer to its final state configuration; on the other hand if the breaking bond is the weaker the configuration of the transition state will be nearer that of the initial state. This correlates with the Hammond hypothesis[6] and allows a reconciliation of the correlations of Swain[7] and of Wiberg.[8] Swain and his co-workers found that stronger bases gave larger isotope effects in the enolization of ketones. This would be predicted by the present hypothesis, because all of the bases were weaker than the enolate ion produced by the proton abstraction, and increasing the strength of the attacking base therefore increased the transi-

tion state symmetry. Wiberg found that isotope rate effects in hydrogen atom abstractions increased with increasing activation energy. This would be predicted also, because all of the reagents studied bond more strongly to hydrogen, than do the radicals left behind. Decreasing the activity of the attacking agents (increasing the activation energy) makes the sharing of the hydrogen atom in the transition state more symmetrical, thereby increasing the isotope rate effect.

In proton transfer reactions we also recognize another cause of conservation of zero-point energy of the hydrogen. In mutarotation, as in many hydrogen transfers, the reaction coördinate involves motion of the other atoms attached to the reaction center. Therefore movement of the hydrogen along the straight line between the two oxygen atoms in the transition state is a component not only of the motion along the reaction coördinate but also orthogonal to it. We note here that it should be possible in special cases, for transfer of a proton between two identical atoms or groups to take place without complete loss of the zero point energy of the stretching vibration. This is illustrated by the following diagrams in which potential energy is plotted against the reaction coördinate for the exchange

$$\text{A—H} + \text{A}^* \rightleftarrows [\text{A----H---A}^*] \rightleftarrows \text{A} + \text{H—A}^*$$
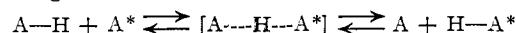
If hydrogen bonding between A and HA is unimportant, the situation is represented by the solid line in the figure. Here the initial and final states are "a" and "g," respectively, separated by the energy barrier for formation of the transition state "d." But if A and HA hydrogen bond strongly the symmetrical configuration is reduced in energy and two more energy barriers at "b" and "f" appear. If these are higher than "d," they now become the transition states for the hydrogen exchange. Thus the facile motion along the reaction coördinate from "c" to "e" does not involve the exchange reaction, and the stretching vibrations of hydrogen are conserved (in part) in the transition states "b" and "f." This argument can be extended to the extreme case, e.g., the exchange

$$\text{FH} + \text{F}^{-*} \rightleftarrows [\text{F----H---F}^*] \rightleftarrows \text{F}^- + \text{HF}^*$$
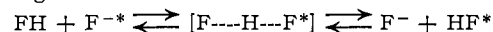
Here the symmetrical structure is in a deep potential energy well and is more stable than the initial and final structures.

Reaction coördinate
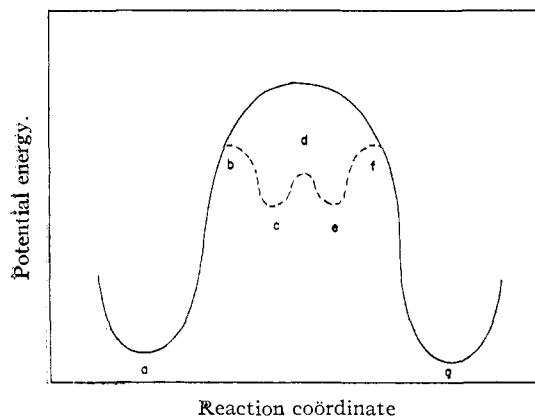
(4) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, p. 24.

(5) Or more precisely when the hydrogen is bound equally strongly to both centers in the transition state.

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

(7) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, ibid., **80**, 5885 (1958).

(8) K. Wiberg, Chem. Revs., **55**, 713 (1955), cf. ref. 9a, p. 202.

In our discussions of hydrogen transfers we have ignored changes in the bending and librational frequencies. These changes should in general be small, by comparison with those in the stretching frequencies, because neither of those vibrational modes are components of the reaction path,[9] and it is known that they are less affected by hydrogen bonding than are stretching vibrations. In some reactions, however, a libration in the initial state may change into a bending vibration in the transition state, or *vice versa*. For these reactions consideration of only the stretching vibrations will result in a somewhat poorer approximation to the isotope effect. The error so introduced would be at most a factor of antilog $(1400-700)/3760$ or 1.5.

Additions to Carbon–Carbon Double Bonds.—Hydration of Olefins.—It is known that the rate-determining step is, for simple olefins, the formation of a carbonium ion which is rapidly captured by water.[10]

We consider three models for the transition state for this reaction.

(a) Transition state similar to initial state
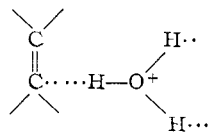
There will be some small change in the frequencies of the proton in the transition state which may be offset by the release of one acceptor site in the solvent. The net effect should be small and we expect a k_{H_2O}/k_{D_2O} ratio close to unity.

(b) A transition state in which the proton interacts electrostatically with both the water and the olefin ("free proton" model).
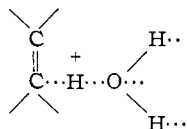
Here is convenient to separate the primary and secondary isotope effects for the purpose of calculation. For the secondary isotope effect (that due to all isotopic substitution except for the atom being transferred)

$$\Sigma\nu_H = 2 \times 2900 + 3600 = 9400 \text{ cm.}^{-1}$$

$$\Sigma\nu'_H = 3 \times 3400 = 10{,}200 \text{ cm.}^{-1}$$

Therefore, the secondary isotope effect upon k_{H_2O}/k_{D_2O} is antilog $-800/3760 = 0.61$. The maximum primary isotope effect will correspond to the loss of the frequency of one hydrogen bonded proton of the hydronium ion. *i.e.*, k_{H_2O}/k_{D_2O} ~6. Thus the maximum net effect will be k_{H_2O}/k_{D_2O}~6 × 0.61 or ~3.6. It is important to note that 3.6 is the maximum value of k_{H_2O}/k_{D_2O} to be expected for any slow proton transfer from a hydronium ion.

(9) (a) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, New York, 1959, p. 197; (b) V. J. Shiner, Jr., and M. L. Smith, *J. Am. Chem. Soc.*, **83**, 593 (1961).

(10) R. W. Taft, Jr., *ibid.*, **74**, 5372 (1952); R. W. Taft, Jr., E. L. Purlee, P. Reisz and C. A. DeFazio, *ibid.*, **77**, 1584 (1955).

(c) Transition state akin to the carbonium ion; *i.e.*, the proton covalently bound to the reaction center
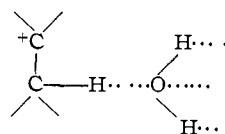
In this model the secondary isotope effect will be identical with that calculated for model "b." The CH stretching frequency in a carbonium ion should be expected to be close to that of an aliphatic CH, *ca.* 2900 cm.$^{-1}$, essentially the same as for CH in the hydronium ion. Thus this model should give a primary effect close to unity. A closer approximation can be obtained by using the principle of microscopic reversibility, and the known small primary isotope effect for the reverse reaction, elimination from a carbonium ion. For a tertiary amyl carbonium ion k_H/k_D is 1.8,[11] and because we assume similar frequencies for the hydrogen atom involved in the initial and final states, this should also be the isotope effect for proton addition. This value of k_H/k_D may be too high because values closer to unity are observed for elimination from other, less stable carbonium ions.[12] Therefore the limiting values for k_{H_2O}/k_{D_2O} are 1.8 × 0.61 or 1.1 and 0.61. The calculations of the deuterium isotope effect for these three models show that the maximum isotope effect for a slow proton transfer from a hydronium ion to an olefin (or to any other substrate) should not be expected to correspond to complete loss of the zero point energy of the hydrogen; *e.g.*, for model b $k_{H_2O}/k_{D_2O} = 3.6$ rather than ~6. They also show that a slow proton transfer from a hydronium ion may have a ratio of k_{H_2O}/k_{D_2O} close to unity, as is experimentally observed in the olefin hydration reaction.[13] As might be expected the deuterium isotope effect is close to unity for the two extreme models in which the zero point energy is conserved, *i.e.*, when the transition state is like the reactants or when the transition state is like the product, the carbonium ion. Analogy with the reverse reaction, elimination from a carbonium ion and the relative basicities of water and an olefin, suggests that this latter model is closest to reality.

Ketonization of Enols.—Long and Watson[14] have shown that in the neutralization of the enolate of methylacetylacetone by H_3O^+ the k_{H_2O}/k_{D_2O} ratio is 1.1 and is 5.6 for neutralization by acetic acid. For the reaction of the enolate with H_3O^+ the primary isotope effect is small and we consider a model in which the transition state is like the initial state.

For the same reasons outlined above for the hydration of olefins this model gives a k_{H_2O}/k_{D_2O} ratio near unity.

This result indicates that the transition state is similar to the initial state and can be rationalized in terms of the large difference in basicity between the enolate ion and water. This correlation is con-

(11) V. J. Shiner, Jr., *ibid.*, **75**, 2925 (1953).

(12) C. E. Boozer and E. S. Lewis, *ibid.*, **76**, 794 (1954).

(13) R. W. Taft, Jr., and E. L. Purlee, *ibid.*, **78**, 5807 (1956).

(14) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

firmed by comparison of the calculated values for the neutralization of the enolate ion by acetic acid. The "free proton" model gives a secondary effect of k_{H_2O}/k_{D_2O} = 1.3 and a primary effect *ca.* 6, *i.e.*, a net effect of *ca.* 8. The observed value of k_{H_2O}/k_{D_2O}, 5.6, is much closer to the value calculated for the "free proton" model in this reaction, because the basicities of acetate (pK_b 9.3) and enolate (pK_b 4.7) are closer than those of enolate and water (pK_b 15.74). However, they are not exactly the same, and the isotope effect is somewhat smaller than the calculated maximum for the free proton model. This trend is also illustrated by the value for the isotope effect for the hydration of an olefin, where in the transition state the proton is shared between a very weak base, the olefin, and a stronger base, water. This analysis thus indicates that the isotope rate effect is not an unambiguous mechanistic criterion for slow proton transfers between bases of markedly different strengths. In particular, because of the large associated secondary isotope effects, rate-determining proton transfers from hydronium ions to other substrates will show a maximum isotope effect near to a value of k_{H_2O}/k_{D_2O} of 3.6 only when the substrate is nearly equal in basicity to water, and less than this when the substrate is either a stronger base (*e.g.*, an enolate ion) or a weaker base (*e.g.*, an olefin).

Enolization of Ketones.—Acid Catalyzed.—These reactions, measured by uptake of bromine, proceed much more rapidly than the deuterium exchange of the ketone and are generally observed in the absence of a primary isotope effect. The initial state is
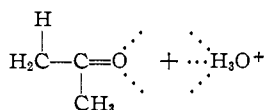

Assuming pK_b of acetone to be 19, we calculate $\Sigma\nu_H$ = 3 × 2900 + 2 × 3475 + 3600 = 19,250 cm.$^{-1}$. For the transition state we choose the free proton model because of the large primary isotope effect involved in the proton transfer.[8]
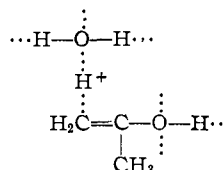
$\Sigma\nu'_H$ is 6 × 3400 or 20,400 cm.$^{-1}$ and the calculated secondary effect, k_{H_2O}/k_{D_2O} = 0.50 compares well with the experimental value, 0.488. The value calculated for the equilibrium formation of the conjugate acid of acetone is 0.63. For enolization of methyl acetylacetone catalyzed by H_3O^+ the calculated value of 0.50 is in poorer agreement with the experimental value of 0.71.[14] This discrepancy may be due to a lowering of the frequency of the enol hydrogen in the transition state by cyclic hydrogen bonding

Base Catalyzed.—The base-catalyzed enolization of ketones is subject to a large primary isotope effect which can be measured independently
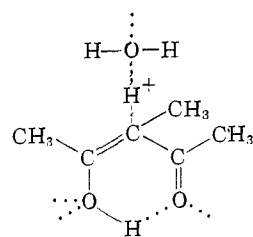
of the solvent secondary effects. The large primary effect[8] suggests that it should be reasonable to picture the proton as largely "free" in the transition state, and therefore our calculations of the secondary solvent isotope effect for catalysis by weak bases are based on our "free-proton" model.

A. Acetate Catalysis

1. Acetone
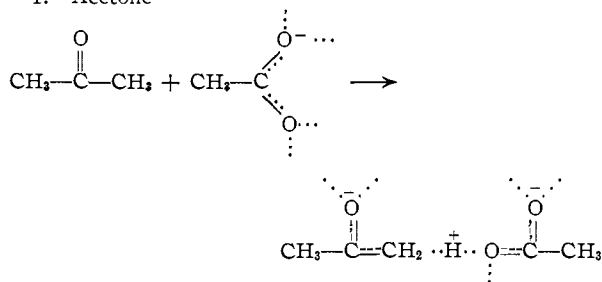
The pK_a of the enol is taken to be 10.5. Thus k_{H_2O}/k_{D_2O} = 1.3 calcd.; 1.13 experimental.[8]

2. For methyl acetylacetone the enol pK_a is 9.3, the calculated value is 1.7 and the experimental is 1.25.[14]

B. Water Catalysis.—

k_{H_2O}/k_{D_2O} = 1.4 calcd.; 1.37 experimental
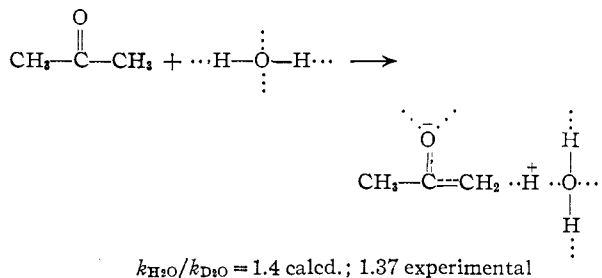
C. Catalysis by Hydroxide Ion.—

Acetone
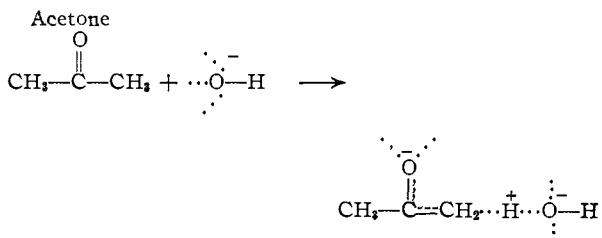
The attack of hydroxide ion on the α-hydrogen atom gives an isotope effect of 0.79 (Table II, Part II[2]); *i.e.*, OD$^-$ is more basic than OH$^-$. To the extent that negative charge develops upon the carbonyl oxygen atom our model predicts an isotope effect greater than this, *e.g.*, if unit negative charges were located on this atom k_{H_2O}/k_{D_2O} should equal 1.1. The experimental value is 0.69.[15] This comparison

(15) Y. Pocker, *Chemistry and Industry*, 1383 (1959).

suggests either that the free proton model is inapplicable to this reaction or more probably that we err in assuming that unit negative charge is located on the enolic oxygen atom in the transition state. Our models for enolization give high values of k_{H_2O}/k_{D_2O}. However, the predicted trends are as observed; the secondary effects being largest for water as the attacking base, intermediate for acetate ion and smallest for hydroxide ion. A reaction in which the free proton model is inapplicable and in which the zero-point energy of the transferred proton is largely conserved, is the neutralization of very basic carbanions by methanol or methanol-d.[8] This reaction is similar to the reverse of enolization by a strong base, and if the zero point energy of the hydrogen is conserved in the transition state in one direction, it must also be conserved in the reverse.

Cannizzaro Reaction.—The rate-determining step of this reaction is transfer of an hydride ion to an aldehyde; e.g.

$$\text{R-C-H} + \text{C-R} \longrightarrow \text{R-C} + \text{H-C-R}$$
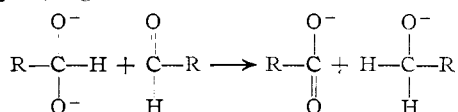
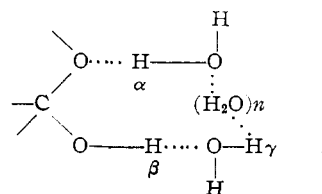The low primary isotope effect ($k_H/k_D = 1.24$ or 1.8)[8] is readily understandable, because the transition state should be reached with only a small C–H bond stretching and conservation of the zero-point energy of the hydrogen. This suggests that the primary isotope effect should depend upon the order with respect to hydroxide ion, i.e., upon the charge on the hydride donor.
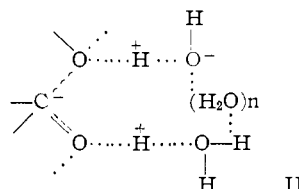
Reactions Involving Proton Transfers to and from Oxygen.—Typically, proton transfer is synchronous with making or breaking a carbon–oxygen covalency, e.g., the mutarotation of glucose, and the hydration of acetaldehyde. Both these reactions are catalyzed by acids and bases.[16] The solvent isotope effect k_{H_2O}/k_{D_2O} is always greater than unity,[17] but for the latter reaction (and probably for both), there is only a small equilibrium solvent isotope effect.

A plausible mechanism for the acid catalysis of, e.g., mutarotation, is one in which the conjugate acid is formed rapidly (with an equilibrium isotope effect $k_{H_2O}/k_{D_2O} < 1$), followed by a slow proton transfer with $k_{H_2O}/k_{D_2O} > 1$ and it has been shown that the deuterium isotope effects can be rationalized on this basis.[17b,c18] However, the mechanism cannot be written as proceeding through a pre-equilibrium proton transfer in both directions.[16b,19] It has been pointed out that there is no certainty that conjugate acids, or bases, are essential intermediates, and mechanisms involving

(16) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, 1941; (b) R. P. Bell, M. H. Rand and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956), and references cited.

(17) W. M. Hamill and V. K. LaMer, *J. Chem. Phys.*, **4**, 395 (1936); E. A. Moelwyn-Hughes, R. Klar and K. F. Bonhoeffer, *Z. physik. Chem.*, **A169**, 113 (1934); (b) B. C. Challis, F. A. Long and Y. Pocker, *J. Chem. Soc.*, 4679 (1957); (c) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

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

(19) (a) R. P. Bell and B. de B. Darwent, *ibid.*, **46**, 34 (1950). (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York, 1953, p. 689.

hydrogen bonding by both acids and bases to the substrate, followed by concerted proton transfer have been proposed.[20] Our treatment of solvent isotope effects in terms of hydrogen bonding interactions between reactants and the solvent matrix leads to the further point that the acidic and basic catalysts may themselves be interconnected through the solvent by a Grothuss chain. In other words the solvent acts as a source and a sink for protons and therefore for electrons, e.g., the water "catalysis" can be written as

$$\begin{array}{c} \text{O} \cdots \text{H} \longrightarrow \text{O} \\ \alpha \\ \text{—C} \qquad (H_2O)n \\ \text{O} \longrightarrow \text{H} \cdots \text{O—H}\gamma \qquad \text{I} \\ \beta \qquad \text{H} \end{array}$$

In this representation, I, water is acting as acid and base; a coupled shift of hydrogens α and γ counterclockwise gives a structure which represents attack of OH^-, upon the conjugate acid, whereas coupled shifts of hydrogen $\beta + \gamma$ counterclockwise and coupled through the chain, gives a structure which represents attack of H_3O^+ upon the conjugate base. It is clear that these structures are interconvertible by rapid hydrogen shifts through the Grotthus chain. This is also true for other uncharged catalysts. Proton transfers, synchronous with covalency changes in the carbon–oxygen bonds, will not involve complete loss of the hydrogen zero point energy. For reaction to occur there must also be movement of the heavy atoms. As the heavy atoms move, charges, and therefore sites of acidity and basicity, will be generated upon the oxygen atoms of the substrate and the two adjacent water molecules. This will lead to secondary deuterium isotope effects and, because the initial and final states are not very different in energy, the charge distribution of the transition state, II, could correspond to that of a structure having protons α and β approximately mid-way between the two oxygen atoms, e.g., to our "free-proton" model. This for transfers to and from carbon is associated with a large primary isotope effect, but in transfers to and from oxygen it may give conservation of zero-point energy because of strong hydrogen bonding.

$$\begin{array}{c} \text{O} \cdots \overset{+}{\text{H}} \cdots \text{O}^- \\ \text{—C} \qquad (H_2O)n \\ \text{O} \cdots \overset{+}{\text{H}} \cdots \text{O—H} \\ \text{H} \qquad \text{II} \end{array}$$

We assume that the frequency of the hydrogen bonds accepted by negatively charged oxygen atoms is that of the hydroxide ion, i.e., 3000 cm.$^{-1}$, (for a justification of this see Appendix). Thus formation of the transition state gives a frequency decrease of 1600 cm.$^{-1}$ and a secondary isotope

(20) (a) C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, **74**, 2534 (1952); (b) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt-Dryden, New York, N. Y., 1959, p. 542.

effect of 2.7. This leads to a primary effect (k_{H_2O}/k_{D_2O}) between 1.2 and 1.4. Models other than II can be written for the transition state, but it is very difficult to envisage any which do not involve charge separations, with consequent large secondary and small primary isotope effects. To the extent that we overestimate the charge separation we overestimate the secondary isotope effect; e.g., the model such as IIa which represents the attack of hydronium ion upon the conjugate base of the open chain structure should give a frequency decrease of 800 cm.$^{-1}$, and a secondary effect of 1.6 (and a primary effect ~2), as would other models having only two formal charges.

$$\begin{array}{c} \text{H} \\ | \\ \overset{..}{\underset{..}{\text{O}}}\text{--}\cdots\cdots\text{H}\text{----}\text{O} \\ -\text{C} \qquad\qquad (\text{H}_2\text{O})_n \\ \diagdown \\ \text{O}\cdots\cdots\overset{+}{\text{H}}\cdots\cdots\text{O---H} \\ | \\ \text{H} \quad \text{IIa} \end{array}$$
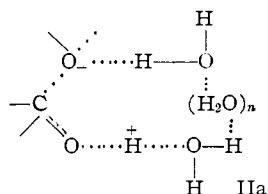
For hydronium ion catalysis the situation is different. The system has a net positive charge, and therefore in the transition state proton addition will have proceeded further than proton removal. Moreover the movements of the protons are not linked by a single Grothuss chain, because both functional groups of the conjugate acid act as hydrogen bonding donors, and we cannot write structures in which protons are conveyed through the water matrix as in II. The reaction can be written formally as

$$\begin{array}{c} \text{H} \\ | \\ \overset{+}{\text{O}} \\ \diagup \diagdown \\ \text{H} \quad \text{H} \\ -\text{O} \qquad\qquad \text{H} \quad \rightleftarrows \\ \diagdown \qquad\qquad\quad \diagup \\ \text{C---O---H}\cdots\text{O} \\ \diagup\diagdown \qquad\qquad \diagdown \\ \qquad\qquad\qquad \text{H} \\ \text{III} \end{array}$$

$$\begin{array}{c} \text{H} \\ | \\ \text{O} \\ \diagup\diagdown \\ \text{H} \quad \text{H} \\ \overset{+}{-} \; \text{O} \qquad\qquad \text{H} \quad \rightleftarrows \\ \diagdown\qquad\qquad\quad \diagup \\ \text{C---O---H}\cdots\text{O} \\ \diagup\diagdown\qquad\qquad \diagdown \\ \qquad\qquad\qquad\text{H} \\ \text{IV} \end{array}$$

$$\begin{array}{cc} \text{H} & \text{H} \\ | & | \\ \text{O} & \text{O} \\ \diagup\diagdown & \diagup\diagdown \\ \text{H}\quad\text{H} & \text{H}\quad\text{H} \\ -\text{O} & -\text{O} \\ \quad\rightleftarrows \\ \text{H} & \text{H} \\ \text{C}=\overset{+}{\text{O}}\text{---H}\cdots\text{O} & \text{C}=\overset{+}{\text{O}}\cdots\text{H---}\overset{+}{\text{O}} \\ \diagup\diagdown\quad\diagdown & \diagup\diagdown\quad\diagdown \\ \quad\text{H} & \quad\text{H} \\ \text{V} & \text{VI} \end{array}$$
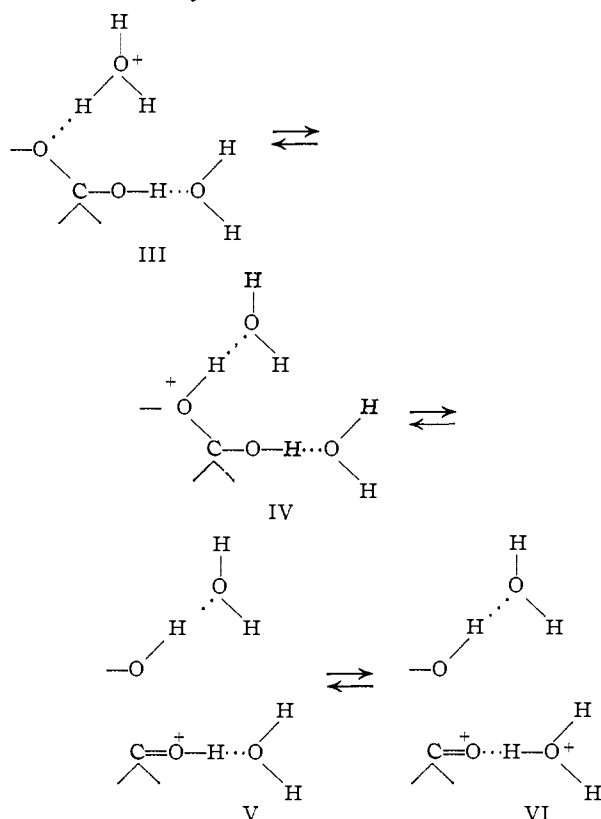
However these steps cannot be discrete (cf. refs. 16b, 19). The transition state must correspond

closely to the second step, but coupled with this must be some proton motion, here formally indicated as occurring in the first and third steps. For purposes of estimating the secondary isotope effect charge distributions corresponding to either IV or V are assumed. Thus in forming the transition state two protons of the hydronium ion are converted into two protons of water, and $\Sigma\nu_H$ increases by 1000 cm.$^{-1}$, and $k_{H_2O}/k_{D_2O} = 0.54$. The over-all solvent isotope effect is ca. 1.3,[17] and the calculated primary isotope effect is thus ca. 2.4. This low primary effect we believe is due to strong hydrogen bonding in the transition state, as already discussed for the water-catalyzed reaction. We note that these numbers are consistent with the pre-equilibrium mechanism,[18] but the treatment for both hydronium ion and water-catalyzed reactions shows that these deuterium isotope effects can be interpreted without assuming the existence of such pre-equilibria. Consideration of mutarotation catalyzed by acetic acid and acetate ions leads to secondary isotope effects of ca. 1.5 and comparatively small primary isotope effects (cf. ref. 18).

Limitations.—The limitations discussed in Parts I and II apply to these calculations. There is the additional problem of the extent of hydrogen transfer in the transition state, e.g., Bell[21] has suggested, from consideration of variation of the Brönsted exponent α, that the extent of this transfer will depend upon the reactivity of the reagent. This leads to uncertainties in charge distribution, particularly for the "free proton" model, although consideration of the basicities of F^- and HF_2^- (Appendix) shows that they are less serious than might be thought at first sight. For proton transfers between oxygen atoms, e.g., in the mutarotation of glucose, it is difficult to give precise definitions of primary and secondary isotope effects, although these remain convenient distinctions. The models which we use are put forward for the purpose of estimating limits to the extent of secondary isotope effects and bear no more relation to reality than do the classical structures of a mesomeric molecule; this is true for any mechanistic approach to problems of reaction.

Conclusions

Our treatment stresses the importance of hydrogen bonding interactions between solvent molecules and the initial and transition states, in determining the solvent deuterium isotope effects in reactions of oxygen compounds. It shows how these interactions depend upon the generation or destruction of acidic or basic centers frequently associated with charges. In so far as hydrogen bonding is an interaction between acids and bases, it is not surprising that some reactions in which strong hydrogen bonds are formed with solvent molecules show various facets of behavior typically associated with slow proton transfers, e.g., not only values of k_{H_2O}/k_{D_2O} greater than unity, but also catalysis by general bases[22] which may hydrogen bond to the charged centers in the transition state.

(21) Ref. 16a, pp. 93 and 172; ref. 9a, p. 162.
(22) See e.g., M. Kilpatrick, J. Am. Chem. Soc., 50, 2891 (1928); and private communication, W. P. Jencks.

For reactions involving primary deuterium isotope effects, we show how the zero point energy of the hydrogen may be conserved in the transition state, either because of asymmetry about the hydrogen or because of strong hydrogen bonding in proton transfers between electronegative atoms.
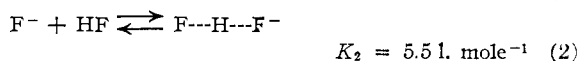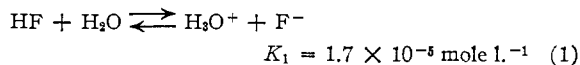
Reaction rate theory requires that any transition state for a solution reaction be in solvation equilibrium. Therefore if this theory is accepted it must be concluded that isotope effects, like any kinetic method, cannot provide proof of the existence of any equilibrium involving solvent molecules preceding the formation of the transition state.[23] The fact that an observed isotope effect may be explained in terms of a pre-equilibrium proton transfer should not lead us to accept this formulation if it is not conveniently consistent with other chemical behavior. However, postulation of conjugate acids and bases as intermediates in equilibrium with reactants, provides a very useful basis for discussion and classification when chemical species which are structurally analogous to these intermediates are well-known.

Appendix

Justification of Free Proton Model.—In the "free-proton" model we assume that the strengths of H-bonds to the bases, which in the transition state share the proton, are the same as in the absence of the proton. Our working hypothesis is therefore that the basicities of these atoms are

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

not influenced markedly by the presence of the proton shared between them in the transition state. Some justification for this view can be drawn from a consideration of the basicity of HF_2^- compared to F^-. The equilibria involved are

$$HF + H_2O \rightleftarrows H_3O^+ + F^-$$
$$K_1 = 1.7 \times 10^{-5} \text{ mole l.}^{-1} \quad (1)$$

$$F^- + HF \rightleftarrows F\text{---}H\text{---}F^-$$
$$K_2 = 5.5 \text{ l. mole}^{-1} \quad (2)$$

The basicity of FHF^- is measured by the equilibrium constant of reaction 3. This constant

$$FHF^- + H\text{---}O\text{---}H \rightleftarrows HF + HF + OH^-$$
$$K_3 = \frac{[HF]^2[OH^-]}{[FHF^-]} \quad (3)$$
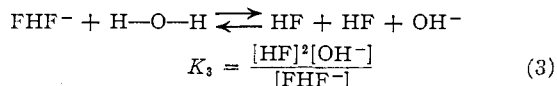
can be evaluated from K_w, K_1 and K_2.

$$K_3 = \frac{K_w}{K_1 K_2} = \frac{[H_3O^+][OH^-][HF][F^-]}{[FHF^-]} \cdot \frac{[HF]}{[H_3O^+][F^-]}$$
$$= \frac{10^{-14}}{1.7 \times 10^{-5} \times 5.5} = 1.1 \times 10^{-10}$$

The basicity of the fluoride ion is $K_w/K_1 = 5.9 \times 10^{-10}$. Thus the basicity of fluoride ion in HF_2^- is not largely affected by the proton which is shared apparently equally between it and another fluoride. The transition states for proton transfers will generally not be bound by any H-bonds nearly so strong as the one in HF_2^-, and the bases involved should therefore show essentially the same basicity as they do in the absence of the proton.

Isotope Fractionation at the Methyl Carbon in the Reactions of Cyanide Ion with Methyl Chloride and Methyl Bromide

BY K. R. LYNN AND PETER E. YANKWICH*
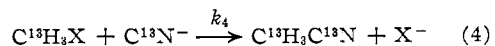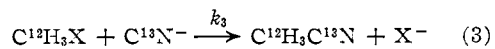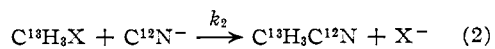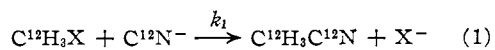
The C^{13} isotope effect for isotopy at the methyl carbon atom has been measured in the cyanizations of methyl chloride and methyl bromide in water solution between 11.4 and 55.5°. In contrast with results previously reported for the iodide reaction, the chloride and bromide systems exhibit relatively large temperature dependence, indicative of the greater importance of bond rupture than bond forming in the reaction coördinate motion. Simple three particle models for the reaction seem incapable of reproducing the experimental values of both the temperature-dependent and temperature-independent factors in the isotopic rate constant ratios. The situation with respect to the latter is especially grievous. Some improvement in calculation of the temperature-dependent factors is available in the consideration of the changes which occur upon activation in the configuration of the methyl hydrogens. The possibility of significantly different reaction coördinate motions in the three cases is considered but does not seem particularly fruitful.

Introduction

Four isotopic reactions occur when cyanide ions react with a methyl halide

$$C^{12}H_3X + C^{12}N^- \xrightarrow{k_1} C^{12}H_3C^{12}N + X^- \quad (1)$$

$$C^{13}H_3X + C^{12}N^- \xrightarrow{k_2} C^{13}H_3C^{12}N + X^- \quad (2)$$

$$C^{12}H_3X + C^{13}N^- \xrightarrow{k_3} C^{12}H_3C^{13}N + X^- \quad (3)$$

$$C^{13}H_3X + C^{13}N^- \xrightarrow{k_4} C^{13}H_3C^{13}N + X^- \quad (4)$$

In recent publications from this Laboratory results have been reported for isotope fractionation at the

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cyanide carbon[1] and at the methyl carbon[2] in the reaction of cyanide ion with methyl iodide; the data were obtained from experiments in which the reagents were present at very different concentrations (complete reaction of the minor reagent corresponding to approximately 3% reaction of the major)[3] and checked through experiments in which they were present at the same concentration.[2] The present extension of these investigations to isotope fractionation at the methyl carbon in the reactions of methyl chloride and bromide with cyanide ion was in-

(1) K. R. Lynn and P. E. Yankwich, *J. Am. Chem. Soc.*, **83**, 53 (1961).

(2) K. R. Lynn and P. E. Yankwich, *ibid.*, **83**, 790 (1961).

(3) K. R. Lynn and P. E. Yankwich, *Chemistry and Industry*, 117 (1960).