Solvent Deuterium Isotope Effects on Acid-Base Reactions

Part I. Thermodynamic Theory and Its Simplifications

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Exact thermodynamic equations that describe the dependence of acid-base equilibrium constants and rate coefficients of acid- or base-catalyzed reactions in the $H_2O - D_2O$ solvent system are derived. The assumptions which reduce these general equations to those introduced in an earlier extension of the so-called equilibrium theory of solvent deuterium isotope effects are critically examined as to their validity. These assumptions concern (a) the operational form of the hydrated hydrogen ion in its isotopic exchange reactions; (b) the applicability of the postulate of the geometric mean (PGM) to the isotopic disproportionation equilibria involved; (c) the independence of the isotope exchange equilibria of solvent composition in the $H_2O - D_2O$ system; (d) the independence of the protolytic equilibria of the medium in the isotopically different waters.

It is concluded that there actually is at present some experimental justification for most of the above-mentioned assumptions; the serious exception is the last-mentioned one and, perhaps also, to a minor degree, that concerning the application of PGM to various polybasic acid species involved, including the different lyonium ions present. Some experimental methods for further testing the validity or invalidity of these assumptions are outlined.
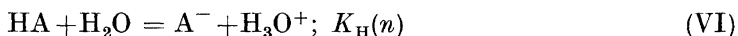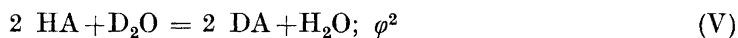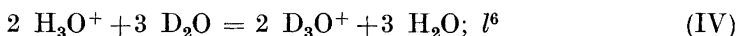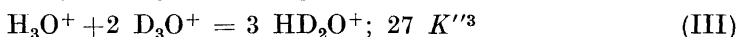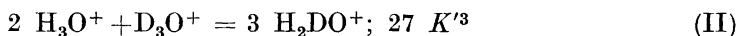
T he study of solvent deuterium isotope effects on acid-base reactions, on both equilibria and kinetics, was initiated three decades ago, mainly by LaMer and Gross and their coworkers.[1] Apart from the interest focused on the newly detected isotope effects themselves, one question that arose was the extent to which investigations in the $H_2O - D_2O$ solvent system could give information on the mechanisms of reactions that involve proton transfers. The renewed interest in the field [1] was stimulated by the study of Purlee,[2] in which he not only updated the values of some of the parameters that appear in the theory, but also made numerous applications to existing experimental data. A more general form of the theory was presented by Salomaa, Schaleger and Long,[3a] who derived equations for several proton transfer schemes, includ-

ing protolytic equilibria of polybasic acids and various mechanisms of acid-base catalysis.*

The primary aim of this series of papers is to present new experimental data which allow a critical re-examination of some of the assumptions and simplifications that were incorporated in the earlier theory. It will be shown that certain assumptions on which the earlier equations were based are, indeed, quite satisfactorily supported by experimental data, whereas some others are generally not, and thus necessitate refinement of the theory.

GENERAL DISCUSSION

Variation of acidity constants with the hydrogen isotope composition of water. As the simplest possible example, let us first consider the equilibria among the various species present in a dilute solution of a monobasic acid HA (with no isotopically exchangeable protons except the acid proton) in water of arbitrary deuterium content (deuterium atom fraction$=n$). The prevailing equilibria and their equilibrium constants may be written as follows:

$$H_2O + D_2O = 2 \ HDO; \ 4 \ K^2 \ (= K_1) \tag{I}$$

$$2 \ H_3O^+ + D_3O^+ = 3 \ H_2DO^+; \ 27 \ K'^3 \tag{II}$$

$$H_3O^+ + 2 \ D_3O^+ = 3 \ HD_2O^+; \ 27 \ K''^3 \tag{III}$$

$$2 \ H_3O^+ + 3 \ D_2O = 2 \ D_3O^+ + 3 \ H_2O; \ l^6 \tag{IV}$$

$$2 \ HA + D_2O = 2 \ DA + H_2O; \ \varphi^2 \tag{V}$$

$$HA + H_2O = A^- + H_3O^+; \ K_H(n) \tag{VI}$$
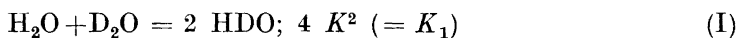
Any other equilibrium that might be written is not an independent one and can be represented by some combination of those given. The above notation is used for the equilibrium constants to simplify the equations that result. When writing down the equilibrium expressions for reactions (I)—(VI) in terms of the respective activities, we choose mole fraction units for the waters and molarity units for the other species, following the common usage for acid-base equilibria in ordinary water. The only assumption made thus far, and which will be discussed later in more detail, is that the molecular form of the lyonium ion in its isotopic exchange reactions in water can be written as L_3O^+ (L=H, D).

Inspection of equilibria (I)—(VI) reveals that these may be divided into three categories; the same also applies to more complicated acid-base reactions such as those involving polybasic acids. First, there are isotopic disproportionation equilibria like those illustrated by eqns. (I)—(III) between the isotopically different species that contain more than one exchangeable hydrogen. Second, isotopic exchange, or fractionation, equilibria between the dissolved species and the solvent, as exemplified by eqns. (IV) and (V). Third, there are the acid-base equilibria themselves, like that represented by eqn.

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* *Added in proof.* Quite recently, Gold [3b] has reviewed new developments of the theory, with particular emphasis in its kinetic applications in mixed H_2O-D_2O solvents. The writer is grateful to Dr. Gold for forwarding a preprint of this article.

(VI). Any strict thermodynamic application of the solvent deuterium isotope effects to acid-base equilibria and kinetics thus requires, in addition to a knowledge of the thermodynamic values of the different equilibrium constants in question (pertaining to some reference states chosen as the standard states), detailed information about the changes in the activity coefficient ratios involved in equilibria of types (I)—(VI), when one changes the isotopic composition of the solvent.

When working with very dilute solutions in a given water of deuterium atom fraction n, or, as is the more common usage, when extrapolating the experimentally measured values to infinite dilution in this solvent, the electrolyte effects on the activity coefficients are eliminated. The apparent acidity constant K_n referring to dilute solution in this solvent is then given by

$$K_n = \frac{[A^-] \sum [L_3O^+]}{\sum [LA]} \tag{1}$$

in which the summations refer to the various isotopic forms present. The experimental acidity constant which is measured in a solvent of deuterium atom fraction n is that given by eqn. (1), when its value has been extrapolated to infinite dilution.

Let us denote the concentration equilibrium constants of reactions (I)—(VI) in a solvent of deuterium atom fraction n by $4\,K^2(n)$, $27\,K'^3(n)$, etc. Their relations to the corresponding thermodynamic quantities associated with some chosen standard states of unit activities are given by

$$4\,K^2(n) = 4\,K^2(f_{H_2O}\,f_{D_2O}/f_{HDO}^2)_n$$
$$27\,K'^3(n) = 27\,K'^3(f_{H_3O^+}^2\,f_{D_3O^+}/f_{H_2DO^+}^3)_n \tag{2}$$
$$\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots\vdots$$
$$K_H(n) = K_H(f_{HA}\,f_{H_2O}/f_{A^-}\,f_{H_3O^+})_n$$

in which the subscripts n refer to the solvent in question. Denoting by K_{H_2O} the dilute solution value of the acidity constant of the acid HA in pure light water and computing the concentrations of the various isotopic species from equilibria (I)—(VI), one obtains the expression (3) for the relative solvent deuterium isotope effect associated with the change in the solvent from ordinary water to one with deuterium atom fraction n

$$\frac{K_{H_2O}}{K_n} = \frac{[H_2O]^{\frac{1}{2}} + \varphi(n)[D_2O]^{\frac{1}{2}}}{S\,(n)} \times \left\{\frac{f_{HA}\,f_{H_2O}}{f_{H_3O^+}\,f_{A^-}}\right\}_{H_2O} \times \left\{\frac{f_{H_3O^+}\,f_{A^-}}{f_{HA}\,f_{H_2O}}\right\}_n$$

$$S(n) = [H_2O]^{\frac{3}{2}} + 3\,l(n)K'(n)[H_2O][D_2O]^{\frac{1}{2}} + 3\,l^2(n)\,K''(n)[H_2O]^{\frac{1}{2}}[D_2O] \tag{3}$$
$$+ l^3(n)[D_2O]^{\frac{3}{2}}$$

in which the concentrations of the waters are in mole fraction units in a solvent of deuterium atom fraction n, and the values of the parameters φ, l, K', and K'' refer to this same solvent. It should be emphasized that, at this stage, no assumptions have been made except that concerning the molecular form of the hydronium ion in its isotopic exchange reactions.

For the "pure solvent isotope effect", that is, for the relative effect when going from H_2O to D_2O, one obtains from eqn. (3)

$$\frac{K_{H_2O}}{K_{D_2O}} = l^{-3}(1) \times \varphi(1) \times \left\{ \frac{f_{HA}\, f_{H_2O}}{f_{H_3O^+}\, f_{A^-}} \right\}_{H_2O} \times \left\{ \frac{f_{H_3O^+}\, f_{A^-}}{f_{HA}\, f_{H_2O}} \right\}_{D_2O} \qquad (4)$$

One thus notes that this effect is made up of two kinds of factors, *viz.* the limiting values of the concentration equilibrium constants of the isotopic fractionation equilibria (IV) and (V) when pure deuterium oxide is approached, and the changes in the activity coefficients of the species participating in equilibrium (VI) when going from H_2O to D_2O. Alternatively, eqn. (4) may be thought to be composed of the concentration equilibrium constants of the following reactions, many of which are hypothetical in the sense that there are no methods for studying them individually:

$$
\begin{aligned}
&HA(H_2O) = A^-(H_2O) + H_3O^+(H_2O); \quad K_{H_2O}\\
&DA(D_2O) = A^-(D_2O) + D_3O^+(D_2O); \quad K_{D_2O}\\
&HA(H_2O) = HA(D_2O); \quad (f_{HA})_{H_2O}/(f_{HA})_{D_2O}\\
&H_3O^+(H_2O) = H_3O^+(D_2O); \quad (f_{H_3O^+})_{H_2O}/(f_{H_3O^+})_{D_2O}\\
&A^-(H_2O) = A^-(D_2O); \quad (f_{A^-})_{H_2O}/(f_{A^-})_{D_2O}\\
&H_2O(H_2O) = H_2O(D_2O); \quad (f_{H_2O})_{H_2O}/(f_{H_2O})_{D_2O}\\
&HA\ (D_2O) = DA(D_2O) + \tfrac{1}{2}\, H_2O(D_2O); \quad \varphi(1)\\
&H_3O^+(D_2O) = D_3O^+(D_2O) + \tfrac{3}{2}\, H_2O(D_2O); \quad l^3(1)
\end{aligned} \qquad (VII)
$$
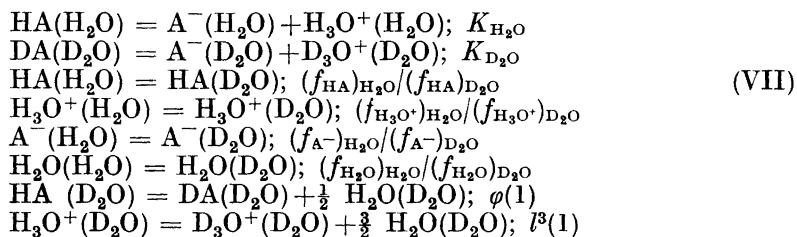
Although the above derivation of eqns. (3) and (4) was made for a monobasic acid reacting according to the scheme (VI), its generalization to more complex acid-base reactions, such as those of polybasic acids, is straightforward and need not be discussed in detail here. The activity coefficient terms corresponding to those of eqns. (3) and (4) are now composed of the activity coefficients of the participants of the acid-base equilibrium in question (*cf.* eqn. VI), and for each multiprotic species a term is introduced which is formed in the same way as the $S(n)$ term for the hydronium ion in eqn. (3), using the appropriate fractionation factors and the equilibrium constants of the respective isotopic disproportionation reactions.

Simplifications of the general equations. In addition to the molecular form of the lyonium ions in water in their isotopic exchange reactions, three additional assumptions are needed to reduce the above equations to those of the equilibrium theory of the solvent deuterium isotope effects.[1] These assumptions are:

(A) The postulate of the geometric mean (PGM). According to PGM, the constants for the isotopic disproportionation equilibria, like those represented by eqns. (I)—(III), have already at ordinary temperatures reached their classical values, *viz.*, 4, 27, and 27 (or $K = K' = K'' = 1$), which are determined by symmetry considerations alone.

(B) All isotopic exchange equilibria (including, of course, the disproportionation equilibria) are solvent-independent in the H_2O-D_2O system. Thus the activity coefficient ratios involved in equilibria (I)—(V) are considered to remain unchanged when one goes from ordinary water to a water of arbitrary deuterium content.

(C) The proton transfer equilibrium (VI) itself is solvent-independent in the system under study, so that the products of the last two terms in eqns. (3) and (4) reduce to unity.

In particular, assumptions (A) and (B) lead to very simple expressions for the concentrations (in mole fraction units) of the different waters in terms of the deuterium atom fraction n of the solvent:

$$[H_2O] = (1-n)^2, \quad [HDO] = 2n(1-n); \quad [D_2O] = n^2 \tag{5}$$

With the above assumptions, eqns. (3) and (4) reduce to the earlier simpler forms (3') and (4'), the Gross equations, in which the fractionation factors l and φ are true constants that do not depend on the isotope composition of the solvent water.

$$\frac{K_{H_2O}}{K_n} = \frac{1-n+n\,\varphi}{(1-n+n\,l)^3} \tag{3'}$$

$$K_{H_2O}/K_{D_2O} = l^{-3}\,\varphi \tag{4'}$$

In the following, the experimental justification of these assumptions is discussed. More detailed information will be given in the subsequent papers of this series.

The postulate of the geometric mean (PGM). The quantum statistical foundations of the PGM were laid down by Bigeleisen,[4] who derived expressions (6), (7), and (8) for isotopic disproportionation equilibria of the general type (VIII). Here Y and Y' are different

$$\Delta G^\circ/RT = s\,\ln\,(\sigma_{XY_s}/\sigma_{XY_{s-z}Y_{z'}}) = -\ln K_{YY'} \tag{6}$$

$$\Delta S^\circ/R = -s\,\ln\,(\sigma_{XY_s}/\sigma_{XY_{s-z}Y_{z'}}) \tag{7}$$

$$\Delta H^\circ = \Delta C_p^\circ = 0 \tag{8}$$

$$s\,XY_{s-z}Y_z' = (s-z)\,XY_s + z\,XY_z'; \quad K_{YY'} \tag{VIII}$$

isotopes of the same element, and σ's are the symmetry numbers of the species involved in equilibrium (VIII). It was shown that PGM can be expected to hold accurately for molecules with a harmonic potential function and for relatively small values of the vibrational frequencies. In the case of the isotopes of hydrogen, when one chooses the extreme example, the latter conditions are least satisfactorily fulfilled for the participants of the reaction $H_2 + D_2 = 2\,HD$, and thus its equilibrium constant at 25°C is only 81 % of its PGM-value of 4. In contrast, protium-deuterium disproportionation reactions involving heavier molecules than these seem to obey fairly well the PGM. This was recently shown experimentally by Pyper and Long,[5] who found that the equilibrium constant of the reaction $C_2H_2 + C_2D_2 = 2\,C_2HD$ has the value 3.95 ± 0.10 over the temperature range from 5° to 85°C.

In particular, knowledge of the exact value of the equilibrium constant of reaction (I) is of utmost importance for the theory of solvent deuterium isotope effects. During recent years, this problem seems to have been the subject of a serious controversy. Whereas calculations based on the latest and most accurate spectroscopic data led to values of the equilibrium constant

as low as 3.4 at 25°C,[6,7] indirect experimental data seemed to favor a PGM value close to 4 at ordinary temperatures.[5] This discord seems, however, to have been resolved by Friedman and Shiner,[8] who were able to overcome the difficulties encountered in the direct experimental determination of this equilibrium constant. Their values, measured by a refined mass-spectrometric technique, are 3.74 ± 0.02 at 0°C, 3.76 ± 0.02 at 25°C, and 3.80 ± 0.04 at 75°C.

The above values of the equilibrium constant of reaction (I) refer to the gaseous phase. However, when the latest and most accurate values of the relative vapor pressures of H_2O, D_2O, and HDO reviewed by Narten [6] are used, it is found that the equilibrium constants have almost the same values in the liquid phase. Thus, for example, the value 3.77 ± 0.02 can be computed for reaction (I) in the liquid state at 25°C.

A point of interest in this context is the observation that the equilibrium constant of reaction (I) and its temperature dependence, measured by Friedman and Shiner,[8] can be shown to be in accord with the experimentally determined heat of mixing of light and heavy water, which was first measured by Doehlemann and Lange [9] three decades ago. Their calorimetric values (at 25°C) could be wholly accounted for by assuming the solvent system $H_2O - D_2O - HDO$ to behave ideally and thus ascribing the enthalpy effects solely to those of reaction (I). In this way, they derived a value of $+32$ cal (per two moles of HDO formed) for the heat of reaction (I). The value 33.4 ± 1.0 reported later by Skripov and Povyshev [10] is in good agreement with this value. When one now writes the equilibrium constant of reaction (I) in terms of the enthalpy and entropy changes in the reaction, it is most likely that deviations from PGM arise solely from the circumstance that the enthalpy factor, $\exp(-\Delta H^\circ / RT)$, has not reached its classical value of unity at ordinary temperatures, i.e., the zero-point energy difference between two moles of HDO and one mole of H_2O and D_2O divided by RT is not satisfactorily close to its high-temperature limit of zero. Thus, taking for the entropy term its statistical value, which can be calculated from eqn. (7), and adopting the value 3.77 ± 0.02 for the equilibrium constant of reaction (I) in the liquid

Table 1. Calculated values for the solvent deuterium isotope effect on the dissociation of monobasic acids in $H_2O - D_2O$ mixtures taking different values for the equilibrium constant, K_1, of the reaction $H_2O + D_2O = 2HDO$. $n =$ deuterium atom fraction of the solvent, $\varphi =$ fractionation factor relating to the undissociated acid, $l = 0.69 =$ fractionation factor relating to the lyonium ions (see eqns. 3 and 3′).

		$\varphi = 0.5$				$\varphi = 1.0$	
		K_{H_2O}/K_n				K_{H_2O}/K_n	
n	$K_1 = 4$	$K_1 = 3.77$	$K_1 = 3.48$	n	$K_1 = 4$	$K_1 = 3.77$	$K_1 = 3.48$
0	1	1	1	0	1	1	1
0.2	1.0950	1.0814	1.0697	0.2	1.2117	1.2035	1.1929
0.4	1.1901	1.1737	1.1529	0.4	1.4876	1.4685	1.4441
0.6	1.2979	1.2783	1.2538	0.6	1.8541	1.8243	1.7870
0.8	1.4109	1.3957	1.3764	0.8	2.3515	2.3206	2.2814
1.0	1.5220	1.5220	1.5220	1.0	3.0441	3.0441	3.0441

phase at 25°C, we obtain the value $+35\pm3$ cal for $\Delta H°$, which is in excellent agreement with the calorimetric values. Moreover, the temperature dependence of the equilibrium constant determined by Friedman and Shiner [8] is in accord with an enthalpy change of this magnitude, although a direct calculation of the enthalpy change from equilibrium constants measured at different temperatures is in this case less accurate.

Turning to acid-base equilibria in the H_2O-D_2O solvent system, one might ask if the deviation from PGM in the case of equilibrium (I) is serious enough to have an influence upon the results. Table 1 contains results of some numerical calculations illustrating this point. As examples, two monobasic acids with φ values of 0.5 and 1.0 have been chosen (corresponding to values of K_{H_2O}/K_{D_2O} of about 1.5 and 3.0), as the values for most monobasic acids are inside this range. In the calculations it is, of course, assumed that the other simplifications that reduce the general eqns. (3) and (4) to eqns. (3') and (4') are justified, including the applicability of PGM to the lyonium ion species, which simplifications are dealt with in later paragraphs.

From Table 1 it is seen that when one uses the value 4 for K_1 instead of its experimental value of 3.77, the maximum differences between the values calculated for K_{H_2O}/K_n are about 1.5 %. Therefore, it seems unnecessary to alter the previous treatment in this respect, unless the experimental accuracy is essentially improved. Moreover, possible small deviations from PGM in the case of the lyonium ions would have an effect in the opposite direction and would thus smooth out the combined influence of these deviations. The table also gives results based on the value $K_1=3.48$, which is close to that derived from spectroscopic data. In this case, the maximum deviations of K_{H_2O}/K_n from those calculated with $K_1=4$ are about 4 %, which should be experimentally detectable. The fact that systematic deviations of this kind have not been detected in earlier applications of the theory is consistent with the conclusion that K_1 does not significantly differ from its statistical value of 4.

Up to the present, there has been no *direct* experimental verification of the applicability of PGM to the lyonium ions in the H_2O-D_2O system. The same is the case for other polybasic acid species dissolved in isotopically different waters. From the theoretical standpoint, as was mentioned above, one should expect the PGM to hold the better the smaller the zero-point energy of the $X-Y$ bond (see eqn. VIII). As the $O-H$ stretching force constant decreases in going from H_2O to H_3O^+,[11] one might well argue that PGM governs the lyonium ions more satisfactorily than the solvent waters themselves, the same also applying to ordinary polybasic acids since, as shown by their higher acidity, their protons are bound less tightly than those of water. One piece of indirect evidence for PGM in the case of the lyonium ions comes from the fact that, when one applies it to the calculation of l, similar values ($l=0.69$) can be derived from experiments made in solvents of intermediary deuterium content [12-14] as from those in the both pure waters, H_2O and D_2O.[15]

The molecular structure of the hydronium ion in its isotope exchange reactions. This structure has been extensively discussed recently by Gold,[16] and therefore only the main points of interest are presented here. Although there is compel-

ling evidence for a relatively stable $H_3O^+(H_2O)_3$ complex in water solutions of strong acids,[17-19] the results of different independent studies of isotopic distribution of hydrogen in the lyonium ions lead to the same value, *viz.*, on average $l = 0.69$ at 25°C, only when the formula H_3O^+ is adopted for the hydrated proton. This does not, however, imply any controversy between the two sets of experimental data. It merely shows that the structure of the lyonium ion in its isotope exchange reactions is best described as L_3O^+, *i.e.*, that the isotopic composition of the water molecules present in the hydration shell of L_3O^+ is virtually the same as in the bulk of the water. Further experimental evidence supporting this formula is cited in Ref. 1.

The influence of solvent on isotope exchange equilibria in the H_2O-D_2O system. The participants in isotope exchange equilibria, like those in reactions (I)−(V), are chemically very similar and differ only in their isotopic composition. Therefore, one might expect the influence of the outer medium on these equilibria to be, if detectable, rather small. Although the assumption of the independence of isotope exchange equilibria of the medium thus seems quite reasonable and was tacitly made already in the earlier phases of the development of the theory,[1] examples of its experimental verification have not been presented until recently.

Gold and Kessick [16,20] studied kinetically the lyon transfer from L_3O^+ ions to olefins in H_2O-D_2O mixtures and measured, in addition to the kinetic isotope effect, the deuterium abundance in the reaction products. The latter made it possible to calculate separately the equilibrium constant for the isotope exchange reaction:

$$2(X-H^{\ddagger})^+ + D_2O = 2(X-D^{\ddagger})^+ + H_2O \qquad (IX)$$
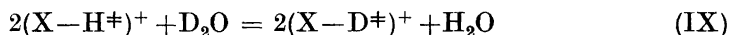
in which $(X-L^{\ddagger})^+$ is the transition state of the reaction. Of course, reaction (IX) is fundamentally similar to reaction (V), the acid now being a transition state instead of an ordinary acid. The values obtained in this way for $1/\varphi$ (using the notations of eqn. V) for the transition state derived from isobutene were 3.9 ± 0.2 in solvents of deuterium atom fractions 0.16 to 0.93, and exhibited no detectable change with solvent composition. Results of similar measurements of the deuterium abundance in reaction products have been reported by Kreevoy and coworkers,[21] who studied the lyonium ion-catalyzed cleavage of vinylmercuric and allylmercuric iodides in H_2O-D_2O mixtures of varying isotopic composition. For example, the values obtained for $1/\varphi$ for the former reaction were constantly 7.30 ± 0.09. On the other hand, these data also support the assumption of the nearly ideal behavior of the solvent system itself, since otherwise the concentration equilibrium constants of the isotope exchange reactions would exhibit a detectable trend with the isotopic composition of the solvent.

The influence of solvent on the acid-base equilibria in the H_2O-D_2O mixtures. The assumption of a solvent-independence of these equilibria, *e.g.*, equilibrium (VI), implies a cancellation of the last two activity coefficient quotients in equations (3) and (4). First, it should be emphasized that in the case of these equilibria the reactants and products are chemically quite different species and that the situation thus greatly differs from that in the isotope exchange

reactions discussed above.* Many of these equilibrium reactions involve the formation of ions from neutral molecules. The assumption that the free energies of transfer of these species from light water to a mixed H_2O-D_2O solvent or to pure D_2O would be generally zero, or, at least would cancel, is not *a priori* reasonable. On the contrary, it is a well-known fact that the standard free energies of transfer of electrolytes and nonelectrolytes from light to heavy water have definite values differing from zero. For instance, when one transfers one mole of potassium chloride from its dilute solution in H_2O to D_2O to give the same molar concentration, $\Delta G° = +219$ cal at 25°C,[15] which corresponds to an about 45 % increase in the molar activity coefficient of the salt.

When one considers the free energies of transfer of the individual species involved in equilibria of type (VI), one might well argue that the standard free energies associated with the transfer of water within this system can be set equal to zero, *i.e.*, the activity coefficients of water in eqns. (3) and (4) cancel out. This follows from the nearly ideal behaviour of the solvent mixtures under study, as discussed above. Additional, indirect experimental evidence having bearing on this point comes from electrochemical studies,[15] in which it was shown that conforming values could be derived for the standard transfer free energy of potassium chloride both from cells with and without liquid junction, the former cells involving transfer of H_2O to D_2O across the boundary and *vice versa*. Another assumption, which in this context seems quite plausible, is that the transfer free energy of the hydronium ion can be also neglected owing to the fact that this ion does not effect significant disturbances in the structure of the surrounding water,[23] and moreover, irrespective of the deuterium content of the water, this ion forms hydrogen bonds to isotopically similar atoms, that is, to the oxygen atoms of the closest water molecules. It can therefore be concluded that the solvent influence on the acid-base equilibria under study must be mainly due to the circumstance that the activity coefficients of the acid and its conjugate base do not vary similarly when the medium is changed.

The effect of ignoring the medium dependence of the activity coefficients of the participants in acid-base equilibria may be quite serious when the acid and its conjugate base differ in charge type, *e.g.*, in the dissociation of ordinary inorganic acids. On the other hand, in many kinetic studies of acid-base catalysis of organic reactions, we deal with acidic or basic transition states the activity coefficient variation of which can be considered to be relatively small in the H_2O-D_2O system and, moreover, to be largely eliminated by the variation of the activity coefficient of the reactant, which operates in the opposite direction. Let us take an A-1 reaction as an example. The acid-base reaction corresponding to (VI) is in this case

$$X-H^+ + H_2O = B + H_3O^+ \tag{X}$$
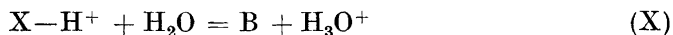
* This point seems to have been misunderstood in a discussion of solvent deuterium isotope effects,[22] where some preliminary, unpublished results of this writer were referred to. Actually, to the writer's knowledge, there is no experimental evidence that would support the conclusion that *isotope exchange equilibria* in this solvent system varied with n and that the solvent system itself showed detectable deviations from the ideal behavior.

in which B is the substrate molecule and $X-H^+$ is the acidic transition state formed from the conjugate acid of the substrate, BH^+, in the rate-determining stage of the reaction. The free energies of transfer of uncharged organic molecules from H_2O to D_2O (with standard states in molar units) are very small in magnitude [24] in comparison with those of inorganic electrolytes. Thus, even if the standard free energy of transfer of B within this solvent system (which can be independently studied, *e.g.*, by solubility measurements) cannot be set equal to zero, it may be assumed with a modicum of confidence that most of its influence is cancelled out by that of $X-H^+$, which is mainly composed of similar molecular constituents having similar individual structure-making or structure-disturbing effects on the surrounding water structure. A similar situation does not, of course, prevail in cases of acid-base catalysis where the initial reactants are electrically neutral and the attainment of the transition state involves considerable separation of opposite charges.

Experimental methods. Our next duty is to consider what possibilities there are to obtain experimental information about the possible influence of changes in the activity coefficients relating to the acid-base reaction under study, *e.g.*, reaction (VI). A direct determination of changes in the individual activity coefficients is possible only for the conjugate base of the acid in cases where this base is a neutral molecule that has no hydrogen atoms exchangeable with those of the solvent. This situation prevails in many kinetic studies of acid catalysis in which the substrate is a neutral molecule. Generally, at least the following three methods can be designed for studying the overall influence of the activity coefficient term in question. First, one might use the simplified theory to calculate values of K_{H_2O}/K_n and to compare them with those directly measured in order to see whether systematic deviations can be detected; *e.g.*, one might calculate φ from eqn. (4') and, using this value, calculate the relative acidity constants in the mixed solvents from eqn. (3'). Second, one could determine separately the equilibrium constants for all the relevant isotope exchange equilibria with the solvent (like that of reaction V), whereupon an application of equations of type (3) and (4) to the experimental values of K_{H_2O}/K_n and K_{H_2O}/K_{D_2O} permits the calculation of the variation of the activity coefficient term in question. Third, one might in certain special cases eliminate the terms in the general equations that contain isotope exchange equilibrium constants of unknown magnitude by combining the results of different sets of measurements on different acid-base equilibria involving the same species (see below).

The first of these three methods can be generally considered to be the most unsatisfactory. It has been pointed out earlier [1,3] that usually the simple expressions for K_{H_2O}/K_n in H_2O-D_2O mixtures are too insensitive to reveal experimentally detectable deviations. This does not, however, prove the medium-independence of the activity coefficient term under discussion. More strictly, the empirical fractionation equilibrium constant φ that is calculated from eqn. (4') also includes the activity coefficient terms shown in eqn. (4), which circumstance leads to a substantial smoothing of the values calculated for the relative acidity constants from eqn. (3'). A particular example, *viz.* the dissociation of periodic acid,[25] has been reported in which marked deviations from the simplified theory can be detected in this way.

This is due to the rather peculiar circumstance that periodic acid itself is in water a five-basic acid with five equivalent protons, $IO(OH)_5$, whereas its monoanion is substantially in the form IO_4^-. Another example, relating to kinetics of acid-base catalysis, has been recently reported by Goodall and Long,[26] who showed that the simple theory could not account for the protonation of nitroalkane anions by acetic acid in H_2O-D_2O mixtures.

The second of the methods mentioned above is the most satisfactory in principle and would lead to the most convincing results. Its general use is at present limited by experimental difficulties encountered in accurate studies of isotope exchange equilibria in the water system. These are illustrated, e.g., by the difficulties which have been met in determining the equilibrium constants of reactions (I) and (IV), discussed above. Some kinetic applications seem to be very amenable in this respect and allow a determination of the exchange equilibrium constant relating to a particular hydrogen in the transition state, where it becomes trapped and its deuterium abundance can be analyzed in the reaction product.[20,21]

The third method is illustrated by equilibria of the type (XI) and (XII), in which A (and hence also AO^{2-}) does not contain hydrogens that could be exchanged with those of the solvent. When one

$$A + 2\ H_2O = A(OH)^- + H_3O^+;\ K_I \qquad\qquad (XI)$$
$$A(OH)^- + H_2O = AO^{2-} + H_3O^+;\ K_{II} \qquad\qquad (XII)$$
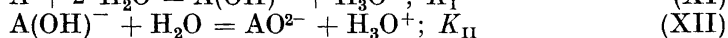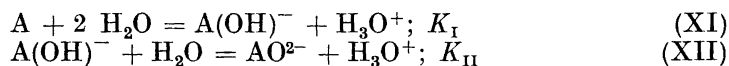
now applies the general equations separately to equilibria (XI) and (XII) and then forms the product of $(K_I)_{H_2O}/(K_{I_n})$ and $(K_{II})_{H_2O}/(K_{II})_n$ it is easily seen that the terms containing the fractionation factor of $A(OH)^-$ are cancelled out, the product being composed only of a term associated with the fractionation equilibrium of the hydronium ion and of that relating to the changes in the activity coefficients involved. The latter may be then calculated separately with the use of the known value for l. Examples of experimental applications of this type will be given in the second part of this series of papers.[27]

Concluding remarks. It may be concluded that most of the assumptions that were made in the earlier equilibrium theory of the solvent deuterium isotope effects lie on a sound theoretical basis and, moreover, that they have found some support from recent experimental data. It may well be that, when the experimental technique has been essentially improved, minor refinements, e.g., those arising from possible small deviations from PGM, will become necessary. The only really serious simplification which was incorporated in the earlier theory and which cannot be generally justified either by theoretical arguments or by experimental data, is that concerning the medium-independence of the acid-base equilibria themselves in the solvent system H_2O-D_2O. Further aspects and experimental applications of the theory will be treated in subsequent articles of this series.

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