PHYSICAL AND INORGANIC CHEMISTRY

### Solvent Deuterium Isotope Effects on Acid–Base Equilibria[1]

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The glass electrode affords precision measurements of acidities in mixed H_2O–D_2O solvents. Using electrodes standardized for H_2O solutions, the pL, the generalized equivalent of pH (where L includes all the isotopically different hydrogen ions), in solvent of deuterium atom fraction n is given by pL = (meter reading) + $0.3314n + 0.0766n^2$. Ionization constants in the mixed solvents have been determined for phosphoric and arsenic acids and for the aqueous solvent itself. For water, $pK_D - pK_H = 0.663n + 0.146n^2$. The apparent failure of the Gross equation to fit the data in these cases is shown to be due to the fact that the simple equation does not hold for polybasic acids. General equations, depending on the number and character of exchangeable protons in the acid and conjugate base, are derived with the aid of the rule of the geometric mean and without added assumptions about fractionation factors. Equations in which the solvated lyon is treated as L_3O^+ and which employ a value of the exchange constant of L = 11.0 satisfactorily fit all available data, whereas the "linear" equation for unspecified solvation fails in the case of the ionization of water. Several kinetic applications of mixed solvent studies are discussed, including acid-catalyzed ester hydrolysis.

Introduction

The equilibrium theory of solvent isotope effects in mixtures of light and heavy water, developed mainly by Gross and co-workers in 1936,[3-5] has been thoroughly re-examined in recent years. In Purlee's 1959 review,[6] the exchange constants 4.0[7,8] and L = 11.0 for reactions 1 and 2, respectively, were introduced. Gold[9] derived an equation

$$H_2O + D_2O = 2HDO \qquad (1)$$

$$2D_3O^+ + 3H_2O = 2H_3O^+ + 3D_2O, L \qquad (2)$$
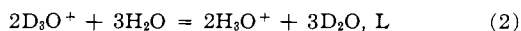
to be applied to the kinetics of slow proton-transfer reactions in H_2O–D_2O mixtures. Swain, Bader, and Thornton[10] derived a value of 8.2 for L from spectroscopic considerations. More recently, Halevi, Long, and Paul[11] have expressed reservations about the state of solvation of the proton and the neglect of medium effects. It was shown that an equation in which the solvation of the proton was unspecified, the so-called "linear" formulation, led to good fits for equilibrium data in several cases. This was also true of an equation derived on the assumption that the variation of the acid ionization constant with atom fraction of deuterium could be ascribed entirely to medium effects. Recently Swain and Thornton[12,13] have further

(1) The support of the Atomic Energy Commission is gratefully acknowledged.

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(3) P. Gross, H. Steiner, and F. Krauss, *Trans. Faraday Soc.*, **32**, 877 (1936).

(4) P. Gross and H. Wischler, *ibid.*, **32**, 879 (1936).

(5) P. Gross, H. Steiner, and H. Suess, *ibid.*, **32**, 883 (1936).

(6) E. L. Purlee, *J. Am. Chem. Soc.*, **81**, 263 (1959).

(7) H. C. Urey, *J. Chem. Soc.*, 562 (1947).

(8) J. Bigeleisen, *J. Chem. Phys.*, **23**, 2264 (1955).

(9) V. Gold, *Trans. Faraday Soc.*, **56**, 255 (1960).

(10) (a) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960); (b) C. G. Swain, R. F. W. Bader, and E. R. Thornton, *ibid.*, **10**, 200 (1960).

(11) E. A. Halevi, F. A. Long, and M. A. Paul, *J. Am. Chem. Soc.*, **83**, 305 (1961).

(12) C. G. Swain and E. R. Thornton, *ibid.*, **83**, 3884 (1961).

(13) C. G. Swain and E. R. Thornton, *ibid.*, **83**, 3890 (1961).

analyzed applications of the theory to kinetics problems.

The present work was undertaken in the hope that further accurate measurements in H_2O–D_2O mixtures of the dissociation constants of acids might cast some light on the general theory of solvent deuterium isotope effects and, in particular, on the importance of medium effects and the state of solvation of the proton.

Experimental

Materials.—Reagent grade chemicals were used throughout. Deuterium oxide was supplied by the U. S. Atomic Energy Commission. Density measurement in a 25-ml. pycnometer showed that it contained 99.0% D_2O. All water used for making up the various solutions was freed from carbon dioxide by boiling.

For the glass electrode measurements in solutions of strong acids, stock solutions 0.01 and 0.1 M in hydrochloric acid and 0.01 M in perchloric acid were prepared in both waters. The acid solutions in the solvent mixtures of light and heavy water were then prepared by mixing the corresponding stock solutions in the pure waters in the ratio required.

The appropriate buffer solutions used for the determination of the dissociation constants of weak acids were made up in a similar way by first preparing "stock buffers" in both waters using a solution of the weak acid in question along with a solution of a strong base, *viz.*, NaOH or NaOD. A solution of the latter in D_2O was prepared by allowing metallic sodium in toluene to react with heavy water in a separatory funnel. In the final buffer mixtures the concentrations of the acid and its conjugate base were each about 0.02 M. Most of the pH measurements were run at five different ionic strengths, varying from 0.02 to 0.10, and adjusted by adding the necessary amount of sodium chloride to the buffer solutions.

Potentiometric Measurements.—The pH measurements were carried out using a Radiometer potentiometer (Type pH 22) with a scale expander (Type pHA 630 P). The glass and reference electrodes employed were of the combined type (Radiometer GK 2021 C). The scale expander was found to be very useful for the present measurements, in which the relative acidities in a series of solvents are required. The estimated reproducibility of the pH readings was better than ±0.004 pH unit. The standardization of the pH meter in water solutions was made with conventional buffer solutions of appropriate acidity. All measurements were made at 25 ± 0.1°.

The pK values, *i.e.*, negative logarithms of the thermodynamic dissociation constants, were computed from the equation

$$pK = \text{meter reading} + \Delta pH + \log \frac{[LA] - [L^+]}{[A^-] + [L^+]} - \log f_\pm$$
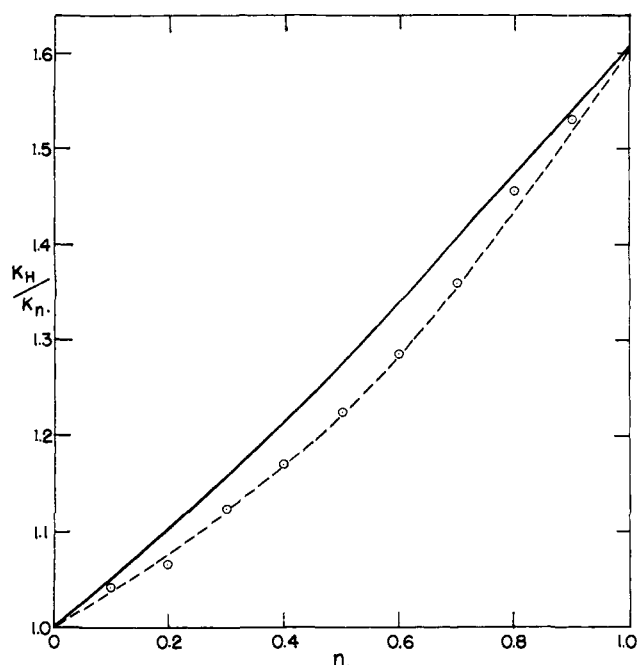
Fig. 1.—Ionization of phosphoric acid in H_2O–D_2O mixtures at 25°: ————, Gross equation; – – – –, eq. 6.

In this equation, ΔpH is a correction derived from calibration measurements on strong acids (vide infra) that is to be added to the pH meter reading in a mixed solvent to convert it to $-\log \Sigma [L_i^+]f_{\pm i}$, in which the sum is taken over all isotopically different hydrogen ions. The concentrations [LA] and [A⁻] refer to the total concentrations of the acid and its anion including the different isotopic species, and $f_\pm$ is the mean activity coefficient of the dissociated acid. The latter was estimated from the Debye–Hückel approximation

$$- \log f_\pm = 0.51\sqrt{I}/(1 + \sqrt{I})$$

where I is the ionic strength. It is to be noted that small errors in estimating the activity coefficients substantially cancel out in the values of relative dissociation constants for a given acid in a series of solvent mixtures.

An idea of the accuracy of the present procedure can be gained from the following typical results for phosphoric acid in a solvent of deuterium atom fraction of 0.891. Measurements were made on five buffer solutions with ionic strengths varying from 0.025 to 0.097. The calculated pK values were 2.343, 2.336, 2.324, 2.325, and 2.321 with an average value of 2.330 ± 0.004 (standard deviation of the mean).

The ionic product of water, K_w, was determined by making measurements on approximately 0.01 M solutions of barium hydroxide in H_2O–D_2O mixtures. The pK_w values were calculated from the equation

$$pK_w = \text{meter reading} + \Delta pH - \log[OL^-] - \log f_\pm$$

in which the mean activity coefficient was calculated from the approximate Debye–Hückel formula. These experiments led to a value of pK_w = 14.00 for pure water at 25° and to the results of Fig. 2 for pK_w values in the mixed solvents.

Calibration of Glass Electrode.—pH meter readings using the standard electrodes were made on solutions 0.01 and 0.1 M in hydrochloric acid and 0.01 M in perchloric acid in various solvent mixtures of light and heavy water ranging from pure water up to a solvent of deuterium atom fraction of 0.990. The results are listed in Table I as a function of n, the atom fraction of deuterium in the solvent. All of the values given are averages of several determinations, the standard deviations of which were 0.002–0.003 pH unit.

It is seen that there are no systematic differences between the three sets of data, the small variations being entirely random. Thus the use of glass electrodes, standardized for use in H_2O, to read acidities in the mixed solvents seems to be substantially independent of the particular acid concentration used. A closely similar result for the pure waters was obtained by Glasoe and Long.[14]

The ΔpH values measured at 25° for various solvent mixtures of H_2O and D_2O obey the empirical equation

$$\Delta pH = 0.3314n + 0.0766n^2 \tag{3}$$

derived from the data by the method of least squares. This can

(14) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

TABLE I[a]

n	0.1 M LCl	0.01 M LCl	0.01 M LClO₄	ΔpH (eq. 3)
		ΔpH_{obsd}		
0.099	0.037	0.034	0.039	0.034
.197	.069	.070	.078	.068
.296	.110	.102	.107	.105
.395	.137	.142	.143	.143
.494	.190	.186	.184	.182
.593	.227	.223	.224	.224
.692	.264	.269	.274	.266
.792	.305	.308	.312	.310
.891	.347	.352	.357	.356
.990	.400	.405	.404	.403
(1.000)				(.408)

[a] ΔpH = (meter reading in H_2O) − (meter reading in mixed solvent) for relative readings of a glass electrode at 25° in solutions of strong acids in solvent mixtures of H_2O and D_2O.

be seen from the values of the last column of Table I, which were computed from this equation. This basic calibration equation has been used for all determinations of the dissociation constants for weak acids from the pH meter measurements.

TABLE II

COMPARISON BETWEEN THE GLASS ELECTRODE AND CONDUCTOMETRIC METHODS FOR DETERMINATION OF RELATIVE IONIZATION CONSTANTS OF ACETIC ACID IN H_2O–D_2O MIXTURES AT 25°

	0.284	0.484	0.771	0.930	1.000
			n		
K_H/K_n (glass electrode)	1.32	1.67	2.41	3.04	3.33
K_H/K_n (conductivity)	1.36	1.69	2.48	3.03	3.32

Experimental Results for Weak Acids.—In order to test the reliability of the glass electrode procedure in H_2O–D_2O mixtures the method was applied to acetic acid, for which precise conductimetric data are available.[15] Table II compares our values for the relative dissociation constants, K_H/K_n, of this acid with those obtained by the conductivity method. The agreement is quite satisfactory. Similar agreement is found when the present results for phosphoric acid are compared with those obtained by the conductivity method.[16] Another, equally satisfactory, comparison between the glass electrode and other methods is made in connection of the ion product constant of water (section D). It seems safe to conclude that the glass electrode offers a reliable and precise method for determining acidities in mixed H_2O–D_2O solvents.[16b]

Table III gives the results obtained for the first dissociation constants of phosphoric and arsenic acids in H_2O–D_2O solvent mixtures.

TABLE III

pK VALUES FOR THE FIRST DISSOCIATION OF PHOSPHORIC AND ARSENIC ACIDS IN H_2O–D_2O MIXTURES AT 25°

n	H_3PO_4	H_3AsO_4	n	H_3PO_4	H_3AsO_4
0.000	2.145	2.301	0.593	2.254	2.461
.099	2.163	2.315	.692	2.278	2.493
.197	2.172	2.335	.792	2.310	2.521
.296	2.196	2.366	.891	2.330	2.559
.395	2.213	2.393	.990	2.348	2.593
.494	2.233	2.421	1.000[a]	(2.350)	(2.596)
K_H/K_D	1.603	1.97			

[a] Extrapolated values.

Kinetics of Ester Hydrolysis.—Ethyl formate was purified by distillation through a 36-in. packed column; a 53.5° cut was used in all kinetic runs. Methyl acetate was purified[17] by refluxing with acetic anhydride and twice distilling through a 36-in. packed column; b.p. 55.5–56.5°, $n^{20}D$ 1.3613. Approximately 6 M hydrochloric acid-d was prepared by passing dry hydrogen chloride gas into heavy water (99+%) with cooling. A stock solution of DCl was then made up by diluting with the requisite amount of heavy water. Kinetics were followed titrimetrically in the usual manner. Pseudo-first-order rate constants were calculated by

(15) V. K. La Mer and J. P. Chittum, *J. Am. Chem. Soc.*, **58**, 1642 (1936).

(16) A. O. McDougall and F. A. Long, unpublished data.

(16) (a) Additional data for ionization of weak acids in the mixed solvents, obtained by the same procedures, are reported in a parallel publication[16b]. (b) P. Salomaa, L. L. Schaleger, and F. A. Long, to be published.

(17) L. F. Fieser, "Experiments in Organic Chemistry," Third Edition, D. C. Heath and Co., Boston, Mass., 1955, p. 287.

the method of averages,[18] using infinity points calculated from the initial ester concentrations (usually about 0.2 M). Second-order rate constants were calculated from the relation, $k_2 = k_1/[L^+]$.

Acid–Base Equilibria

A. Dissociation of Phosphoric Acid.

—It was noted earlier that the "linear" and Gross formulations for acid ionization constants differed significantly only when K_H/K_D was less than about two.[11] Since the first dissociation of phosphoric acid shows a value of $K_H/K_D = 1.6$, the lowest hitherto discovered, it seemed particularly favorable for a more detailed study. The measured values of the K_H/K_n ratios for this acid are plotted against the deuterium atom fraction n of the solvent in Fig. 1. The solid curve drawn in the figure is that calculated from the Gross equation

$$\frac{K_H}{K_n} = \frac{1 - n + n\varphi}{(1 - n + nl)^3}, \quad \varphi = l^{-3}\frac{K_H}{K_D} \qquad (4)$$

whereas the broken line is based on a more general equation derived below. In the calculations we have used a value of 0.67 for l ($= L^{-1/6}$) which corresponds to the value $L = 11.0$ given by Purlee[6] for the equilibrium constant of reaction 2. It can be seen from the figure that the Gross treatment fails in this case, the differences exceeding experimental error. Moreover, it has been shown[5,9] that the Gross plot is relatively insensitive to the particular choice of the value for l, so that in the present case an essentially better fit cannot be obtained without a drastic adjustment of this parameter.

The above emphasizes the limited applicability of the original Gross equation. However, it does not necessarily invalidate the Gross theory of solvent deuterium isotope effects itself. Equation 4 is, in fact, derived for a monobasic acid and, as shown below, the equations for polybasic acids take a different form. Unfortunately, the presence of more than one exchangeable hydrogen has been overlooked in many earlier applications of the solvent isotope effects to acid–base equilibria and kinetics of acid-catalyzed reactions.

Let us consider a solution of phosphoric acid in a mixed water–deuterium oxide solvent. There are four different undissociated species (H_3PO_4, H_2DPO_4, HD_2PO_4, and D_3PO_4), and three different types of monoanions ($H_2PO_4^-$, $HDPO_4^-$, and $D_2PO_4^-$). Define the deuterium fractionation factors φ_1 and φ_2 for the undissociated acid and its monoanion, respectively, by means of the equilibria

$$2D_3PO_4 + 3H_2O = 2H_3PO_4 + 3D_2O, \quad K_1$$

$$2D_2PO_4^- + 2H_2O = 2H_2PO_4^- + 2D_2O, \quad K_2$$
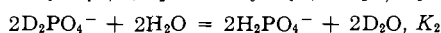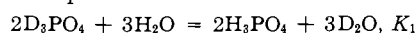
$$\varphi_1 = K_1^{-1/6} = \left(\frac{[D_3PO_4]}{[H_3PO_4]}\right)^{1/3}\left(\frac{[H_2O]}{[D_2O]}\right)^{1/2} = \left(\frac{[D_3PO_4]}{[H_3PO_4]}\right)^{1/3}\frac{1-n}{n}$$

$$\varphi_2 = K_2^{-1/4} = \left(\frac{[D_2PO_4^-]}{[H_2PO_4^-]}\right)^{1/2}\left(\frac{[H_2O]}{[D_2O]}\right)^{1/2} = \left(\frac{[D_2PO_4^-]}{[H_2PO_4^-]}\right)^{1/2}\frac{1-n}{n}$$

the concentrations of the waters having been calculated from the known value $K = 4.0$ of the equilibrium constant of reaction 1. If it can be assumed that the activity coefficients of the various isotopic species are the same in a given solvent, their relative concentrations can then be readily expressed in terms of the fractionation factors and the solvent composition with the aid of the rule of the geometric mean.[8] This derivation, which in principle is the same as applied by Gold[9] and by Purlee[6] to the various lyonium ions, gives for the total concentration of the undissociated acid

$$\Sigma[L_3PO_4] = [H_3PO_4]\left(1 + \frac{\varphi_1}{1 - n}\right)^3$$

(18) R. Livingston, in S. L. Friess and A. Weissberger, Ed., "Technique of Organic Chemistry," Vol. VIII, Interscience Publishers, Inc., New York, N. Y., 1953, p. 190.

and for that of the monoanions

$$\Sigma[L_2PO_4^-] = [H_2PO_4^-]\left(1 + \frac{n\varphi_2}{1 - n}\right)^2$$

The operationally meaningful dissociation constant K_n in a mixed solvent, i.e., that which is accessible to experimental measurement, is made up of the total concentrations of the various isotopic species involved. If we assume the model of the monohydrated proton, as in the Gross theory, K_n is given by

$$K_n = \frac{\Sigma[L_3O^+]\Sigma[L_2PO_4^-]}{\Sigma[L_3PO_4]\Sigma[L_2O]} \qquad (5)$$

in which the sum of the concentrations of the waters in the denominator reduces to unity if expressed in mole fraction units.

Let us now define an auxiliary, hypothetical dissociation constant $K_{H(n)}$ as

$$K_{H(n)} = \frac{[H_3O^+][H_2PO_4^-]}{[H_3PO_4][H_2O]} = \frac{[H_3O^+][H_2PO_4^-]}{[H_3PO_4](1 - n)^2}$$

Introducing the expressions for the total concentrations of the acid and its monoanion into eq. 5, and the corresponding expression for the total lyonium ion concentration

$$\Sigma[L_3O^+] = [H_3O^+]\left(1 + \frac{nl}{1 - n}\right)^3$$

in which the fractionation factor l is $L^{-1/6}$, we obtain

$$K_n = K_{H(n)}\frac{(1 - n + nl)^3(1 - n + n\varphi_2)^2}{(1 - n + n\varphi_1)^3}$$

If it can be assumed that the activity coefficient ratio $f_{H_3O}\cdot f_{H_2PO_4}^-/f_{H_3PO_4}f_{H_2O}$ remains constant as n is varied, $K_{H(n)}$ can be replaced by its known value K_H for the solvent water and eq. 6 is obtained.
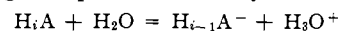
$$\frac{K_H}{K_n} = \frac{(1 - n + n\varphi_1)^3}{(1 - n + nl)^3(1 - n + n\varphi_2)^2} \qquad (6)$$

If the value of l is known, this equation contains one adjustable parameter because φ_1 and φ_2 are related to each other by

$$K_H/K_D = l^{-3}\varphi_1^3\varphi_2^{-2} \qquad (7)$$

The parameters of eq. 6 can be computed from the value of K_H/K_D, and from that of K_H/K_n measured for an intermediate solvent composition, e.g., for that of deuterium atom fraction of 0.5. When applied to the present data such a calculation gives $\varphi_1 = 0.77$ and $\varphi_2 = 0.98$. The broken line of Fig. 1 is based on these values of the fractionation factors. As discussed in section E, there is an indication that φ usually increases with decreasing acid strength, and in this respect the above values are quite reasonable. Moreover, similar calculations on arsenic acid lead to the values $\varphi_1 = 0.83$ and $\varphi_2 = 0.98$. These are consistent with the fact that arsenic is the weaker acid.

B. General Equations.

—Consider the first dissociation constant of an i-basic acid H_iA of any charge type. If the i hydrogens are equivalent, then eq. 8–9, corresponding to eq. 6–7, are easily deduced by inspection.

$$H_iA + H_2O = H_{i-1}A^- + H_3O^+$$

$$K_H/K_D = l^{-3}\varphi_1^i\varphi_2^{-i+1} \qquad (8)$$

$$\frac{K_H}{K_n} = \frac{(1 - n + n\varphi_1)^i}{(1 - n + nl)^3(1 - n + n\varphi_2)^{i-1}} \qquad (9)$$

If the dissociation scheme differs from that above, a derivation of the appropriate equations involves raising the terms referring to the acid and its corresponding base to powers that are determined by the numbers of exchangeable (and equivalent) hydrogens in these species. The utility of this procedure becomes evident when application is made to the kinetics of acid-catalyzed reactions (sections F and G).
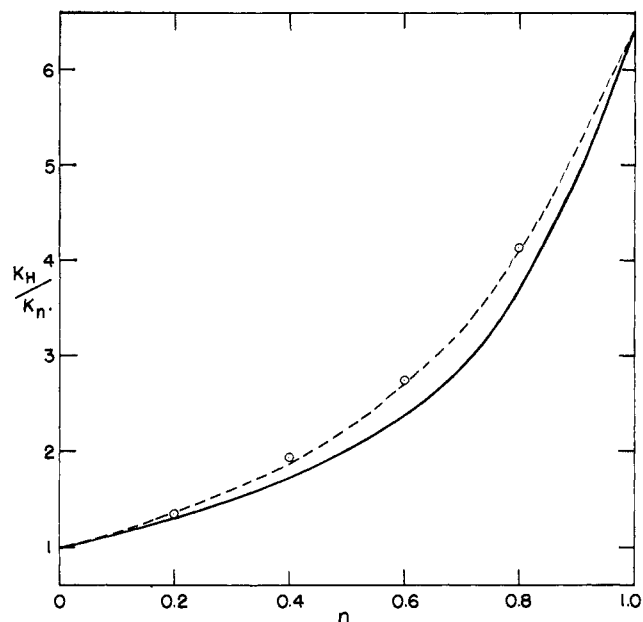
Fig. 2.—Ionic product of H_2O–D_2O mixtures at 25°: ————, "linear" equation; – – – –, "cubic" equation.

More complicated situations may arise in cases in which the acid and its conjugate base in question contain exchangeable hydrogens that are not equivalent. If one group of these hydrogens is much more acidic than the others a considerable simplification is possible, because only anions that are formed by proton removals from the most acidic groups can be present in appreciable concentrations. For instance, in the case of glycolic acid there are only anions of the type $HOCH_2COO^-$. It is further reasonable to assume that the deuterium fractionation factors for the hydroxylic groups of the undissociated acid and its anion will not be significantly different,[19] so that in this case the equation will reduce to the "monobasic" Gross equation. Similarly, in a general case of a polybasic acid having a group of hydrogens of greater acidity than the other exchangeable hydrogens present, only the former are to be considered when deriving the appropriate equation. This situation prevails especially for certain kinetic applications to polyhydroxy compounds, e.g., the inversion of sucrose and the mutarotation of glucose.

Equations corresponding to those presented above many be derived in a similar way for any assumed degree of proton solvation, differing from each other only by the exponents of the l terms in the denominators.

C. **Medium Effects.**—In the above derivations it is assumed that first, the fractionation factors l, φ_1, and φ_2 and, second, the dissociation constants $K_{H(n)}$ are independent of medium in the solvents under study. There is much more justification for the first assumption than for the second, because in the fractionation equilibria the reactants and products differ only isotopically, and hence one may expect their activity coefficients to vary similarly with changing medium.

One can ask whether the neglect of the medium effects is expected to cause detectable differences between measured values and those predicted by the equations.

As pointed out by Halevi, Long, and Paul,[11] the various limiting formulations ("Gross," "linear," and "simple medium effect") cannot be experimentally distinguished from each other for acids of relatively high K_H/K_D, viz. about 2.5 or greater. So at least in these cases the equations can be considered as good approximations. It is doubtful, unfortunately, that monobasic acids of essentially lower K_H/K_D values (or low k_D/k_H values for acid-catalyzed reactions involving monobasic transition states) will be found. Relatively low values of K_H/K_D always seem to be associated with more than one exchangeable hydrogen.

For polybasic acids the equations can be shown to be even less sensitive to the neglect of medium effects than those for monobasic acids. For instance, in the case of a tribasic acid with K_H/K_D equal to 1.5, the maximum differences between the values calculated from eq. 6 and those calculated by assuming that exchange and transfer have equal contributions to the variation of K_n with solvent are less than 2%.

It is thus evident that the equations that neglect the medium effects are at least satisfactory approximations, by virtue of their insensitivity, and will usually hold within the limits of experimental error. Therefore, the apparent failure of the simple Gross theory in many previous applications is to be attributed mainly to the use of equations that are appropriate only for monobasic acids. It should be emphasized, however, that there is no justification in concluding that the free energies of transfer, i.e., medium effects, play an unimportant role in the equilibria under study. Any such effects, the magnitudes of which are not presently estimable, will be incorporated into the values of the calculated fractionation factors.

D. **The Ionic Product of Water.**[21]—We have not thus far considered the problem of the functional form of the term containing l in the denominator of the equations, which in the case of unspecified solvation assumes a linear form, and in the case of a model of monohydrated lyons takes a cubic form. One of the few examples which permits an experimental distinction among the various formulations to be made is the autoprotolysis of water, a case in which the equations take a special form. Although water contains two exchangeable hydrogens, the equations do not contain adjustable parameters in addition to l because the fractionation factor for water is unity by definition. Equation 9 thus reduces to

$$K_H/K_n = (1 - n + nl)^{-3}(1 - n + n(K_D/K_H)l^{-3})^{-1} \quad (10)$$

The corresponding "linear" equation for unspecified solvation is

$$K_H/K_n = (1 - n + nl')^{-1}(1 - n + n(K_D/K_H)l'^{-1})^{-1} \quad (11)$$

The experimental values determined in the present study for the relative ionic product of water in H_2O–D_2O mixtures at 25° obey the empirical equation, $pK_n - pK_H = 0.663n + 0.146n^2$ (for which pK_H was determined to be 14.00, in agreement with its known value) derived by the method of least squares. In Fig. 2 are plotted the curves predicted by eq. 10 and 11 together with the experimental points.[22] It is seen that the "cubic"

(19) An alternative assumption leading to the same conclusion is that the carboxylic acid strengths of the acids $DOCH_2COOH$ and $HOCH_2COOH$ are the same (as are those of the carboxylic acids $DOCH_2COOD$ and $HOCH_2COOD$) in the same solvent. This assumption is well supported by experimental data on secondary isotope effects on acid strengths. Thus, for example, Bell and Jensen[20] showed that the acid strengths of HCOOH and DCOOH were virtually the same, and, in the present example, even smaller secondary effects are to be expected owing to the larger distance of the site of isotopic substitution from the acidic hydrogen or deuterium.

(20) R. P. Bell and M. B. Jensen. Proc. Chem. Soc., 307 (1960).

(21) (a) After this work was completed, we learned that a similar study on the ionization of water in H_2O–D_2O mixtures had been made by Gold and Lowe.[21b] Although the K_H/K_n values obtained by these workers are systematically higher than ours, their conclusions are essentially identical with those arrived at here. We are grateful to Dr. Gold for forwarding us a preliminary manuscript of his work. (b) V. Gold and B. M. Lowe, to be published.

(22) The present data show excellent agreement with the earlier results obtained by Abel, Bratu, and Redlich.[23] As pointed out by Kingerley and La Mer,[24] Wynne-Jones[25] has erroneously corrected the values of the former authors. Without such an erroneous correction their value[22] for the ionic product of D_2O, 1.60×10^{-15}, is substantially the same as that given by Kingerley and La Mer, 1.54×10^{-15}, and that obtained in the present work,

equation gives a good fit to the data, whereas the "linear" does not. In the latter equation we have used the previously[11] adopted value of 0.45 for l'. It can be shown that the fit cannot be significantly improved by adjusting this parameter.[21,26]

The failure of the linear equation does not imply, however, that the equation in which the solvated lyon is taken to be L_3O^+ offers a uniquely good fit to the data.[21] An equation based on $L_9O_4^+$,[27] with the proper choice of the parameter $L^{-1/18}$, can be made to fit the data equally well. Unlike the cubic, however, this ninth power equation is quite sensitive to the choice of L, and no single value of this constant suffices to permit the relevant form of the equation to be fitted to both the water and the acetic acid data. It is tempting to speculate that the solvated hydrogen ion in dilute aqueous solutions actually exists as an equilibrium mixture of H_3O^+, $H_5O_2^+$, $H_7O_3^+$, and $H_9O_4^+$.[28]

Application to Kinetics

E. General Considerations.—It is clear from the preceding that no single equation can be expected to accommodate the kinetic behavior of acid-catalyzed reactions in H_2O–D_2O mixtures. The form of the relevant equation will depend on the number and character of exchangeable protons in both transition state and reactant molecules.[8,12,13] This latter point has been considered in detail by Swain and Thornton[12,13] who have derived equations relating k_n/k_H to n for a number of types of transition states. For those cases in which more than two fractionation factors are involved, however, Swain and Thornton impose the additional restrictions that the fractionation factor of all ROL lyons is unity while that for all $R\overset{+}{O}L_2$ lyons is equal to l. A brief examination of the validity of these assumptions seems in order.

Regarding the first of the Swain and Thornton assumptions, it may generally be stated that the fractionation factor of an ROL lyon will be *different* from unity for the same reasons that K_H/K_D for monobasic oxygen acids is not always equal to l^{-3}.[29] Swain and Thornton cite as evidence for the first of their assumptions the report of Brodskii that the average fractionation factor for 22 substrates investigated by seven authors was found to be 1.04 ± 0.05.[35] This generalization is, however, rendered doubtful for the following reasons: (1) The experiments in question usually entailed isotopic analysis of the water distilled from an equilibrated solution made up by dissolving light substrate in deuterium-enriched water. The question can be raised

whether precautions were taken to assure that the original equilibrium was maintained throughout the distillation. (2) All calculations were based on an incorrect value, 3.27, for the equilibrium constant of reaction 1. However, this introduces no appreciable error for experiments in which the deuterium content is less than about 10%. (3) The water available to Brodskii contained initially a maximum deuterium content of only 4.6%.[35] (4) Brodksii[35] obtained exchange constants of 1.01 for sulfuric acid and 0.98 for sodium hydroxide, values which are obviously erroneous.[24] (5) The results of at least one worker[36] could not be verified.[37]

With respect to the second assumption, reliable information concerning the exchange constants of $R_2\overset{+}{O}L$ lyons is equally scarce. The pK_a's of the conjugate acids of neutral oxygen bases, e.g., ethers and ketones, are generally lower than -1.74[38]; thus one might reasonably expect their exchange constants to be correspondingly less than l. The theoretical ground for this supposition is not firm, however.[34] Nor is the available experimental evidence decisive. The K_H/K_D value of benzalacetophenone, $pK_a = -5.73$, is 1.4,[34] corresponding to an exchange constant of 0.42. For mesitaldehyde, with $pK_a = -5.3$ and $K_H/K_D = 2.3$,[39] the exchange constant is calculated to be 0.69. Clearly a larger body of reliable numbers is necessary before any firm conclusions can be drawn. Therefore, while the assumptions of Swain and Thornton lead to satisfactory qualitative assessments of the mechanistic implications of k_D/k_H ratios in a number of cases, the extension of these assumptions to *quantitative* estimates of charge distribution in transition states must be regarded as premature.

F. Specific Hydronium Ion Catalysis.—For a substrate having no exchangeable protons, reacting with water *via* a simple A-2 mechanism, the deuterium and mixed solvent isotope effects are given by the general eq. 12–13 where φ_1 and φ_2 are fractionation factors for L_2O- and $-SL$ transition state lyons, respectively.

$$S + L_3O^+ = SL^+ + L_2O$$

$$SL^+ + L_2O \xrightarrow{slow} (L_2O-SL)^+ \longrightarrow products \quad (12)$$
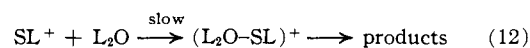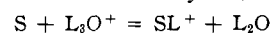
$$k_n/k_H = (1 - n + n\varphi_1)^2(1 - n + n\varphi_2)(1 - n + nl)^{-3} \quad (13)$$

For a transition state closely resembling product, most of the positive charge will reside on the incoming water molecule. If the fractionation factor of the L_2O-S lyons is taken as l (per lyon)[12] then $\varphi_1 = l$ and

$$k_n/k_H = (1 - n + nlk_D/k_H)(1 - n + nl)^{-1} \quad (14)[40]$$

Alternatively, one might take φ_2 as unity to obtain

$$k_n/k_H = (1 - n + nl^{3/2}(k_D/k_H)^{1/2})^2(1 - n + nl)^{-3} \quad (15)$$

In another mechanistic extreme, the transition state can be considered as closely resembling protonated substrate; this corresponds to the A-1 mechanism. Nucleophilic participation of water is minimal and the positive charge is largely shared between a protonated oxygen and an adjacent carbon atom. The exchange constant φ_1 becomes unity by definition and k_n/k_H is therefore given by the simple Gross equation.

It is instructive to compare the predictions of eq. 14, 15, and 4 with the results for the hydrolysis of ethylene oxide and epichlorohydrin, reactions which are now

1.56 × 10⁻¹⁵, but differs by 20% from the value of 1.95 × 10⁻¹⁵ of Wynne-Jones. The latter number, however, has been adopted by several investigators, e.g., by Swain and Bader[10] for calculating the equilibrium constant for the reaction, 2OD⁻ + H₂O = 2OH⁻ + D₂O.

(23) E. Abel, E. Bratu, and O. Redlich, *Z. physik. Chem.*, **A173**, 353 (1935).

(24) R. W. Kingerley and V. K. La Mer, *J. Am. Chem. Soc.*, **63**, 3256 (1941).

(25) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **32**, 1397 (1936).

(26) It is easily seen from eq. 11 that the values of K_H/K_n reach their maxima when $l' = \sqrt{K_D/K_H}$. The curve based on this value of l' does not, however, differ significantly from that drawn in Fig. 2.

(27) R. P. Bell, ref. 20, pp. 81–84.

(28) H. D. Beckey, *Z. Naturforsch.*, **15a**, 822 (1960); P. F. Knewstubb and A. W. Tickner, *J. Chem. Phys.*, **37**, 2941 (1962); E. Glueckauf and G. P. Kitt, *Proc. Roy. Soc.* (London), **A228**, 322 (1955).

(29) For example, the experimentally obtained values of K_H/K_D for the ionization of chloroacetic acid (2.7) and 2-chloroethanol (4.5³⁰) imply fractionation factors of 0.93 and 1.5, respectively, in accord with the prevailing view that K_H/K_D increases with increasing pK.³¹⁻³⁴

(30) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).

(31) A. O. McDougall and F. A. Long, *J. Phys. Chem.*, **66**, 429 (1962).

(32) C. K. Rule and V. K. LaMer, *J. Am. Chem. Soc.*, **60**, 1974 (1938).

(33) R. P. Bell, ref. 20, p. 188.

(34) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

(35) A. E. Brodskii, *Trans. Faraday Soc.*, **33**, 1180 (1937).

(36) W. J. C. Orr, *ibid.*, **32**, 1033 (1936).

(37) H. Kwart, L. P. Kuhn, and E. L. Bannister, *J. Am. Chem. Soc.*, **76**, 5998 (1954).

(38) R. Stewart and K. Yates, *ibid.*, **82**, 4059 (1960), and references cited therein; M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **84**, 1680, 1684 (1962).

(39) W. M. Schubert and H. Burkett, *ibid.*, **78**, 66 (1956), as recalculated by J. G. Pritchard and F. A. Long, *ibid.*, **80**, 4162 (1958).

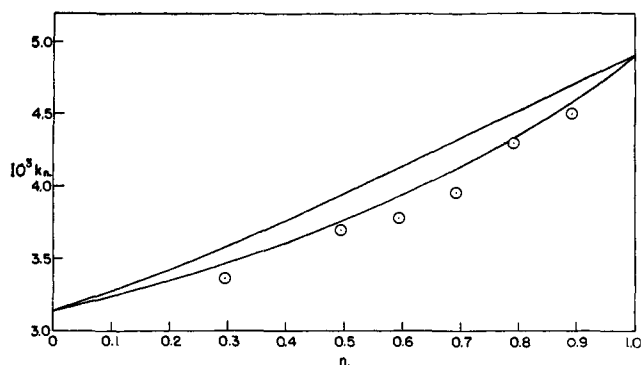(40) This equation is equivalent to eq. 2 of ref. 12.

Fig. 3.—Acid-catalyzed hydrolysis of ethyl formate at 25° in $H_2O–D_2O$ mixtures: upper curve, Gross equation; lower curve, eq. 18.

believed to utilize the A-2 path.[41a] Inspection of Table IV reveals that within experimental error all three formulations fit the epichlorohydrin data, while for ethylene oxide only eq. 14 falls outside the limits of error. Thus the only conclusion that might be drawn from the ethylene oxide data is that, *if* the mechanism is A-2, $C–\overset{+}{O}H_2$ bond formation probably lags behind ring opening. An identical conclusion has been drawn from a consideration of k_D/k_H alone.[13]

TABLE IV

H⁺-CATALYZED EPOXIDE HYDROLYSIS IN H_2O-D_2O
MIXTURES[41b]

n	k_n/k_H (obsd.)	Eq. 14(A-2)	Eq. 15(A-2)	Eq. 4(A-1)
	Ethylene oxide ($k_D/k_H = 2.20$)			
0.25	1.17	1.219	1.177	1.185
.50	1.39	1.481	1.413	1.428
.75	1.75	1.801	1.737	1.752
	Epichlorohydrin ($k_D/k_H = 1.89$)			
0.25	1.16	1.163	1.140	1.155
.50	1.34	1.357	1.322	1.347
.75	1.55	1.594	1.562	1.588

G. Acid-Induced Deoxymercuration.—The solvent deuterium isotope effects on the acid-catalyzed deoxy-mercuration of 1-iodomercuri-2-propanol (I) and 1-iodomercuri-2-methoxypropane (II) are 2.16 and 2.80, respectively.[42] For the present purposes the corresponding transition states[42,43] may be represented as Ia and IIa. In terms of exchange constants, $k_D{}^I/k_H{}^I = \omega_1{}^2\varphi_3{}^{-1}l^{-3}$ and $k_D{}^{II}/k_H{}^{II} = \varphi_2 l^{-3}$, where φ_3 refers to
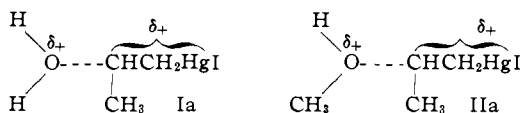
the exchangeable lyon of I. Since polar substituents influence the rates of hydroxy- and methoxymercu-rials to the same degree,[43] it is reasonable to suppose that $\varphi_1 = \varphi_2$. Then from the observed isotope effects, $\varphi_1 = 0.84$ and $\varphi_3 = 1.09$, from which k_n/k_H values for both cases may be calculated. Rate coefficients for the reaction of II are expected to follow the Gross equation[44] and this has indeed been observed for the case of 1-iodomercuri-2-methoxyethane.[44]

Another mechanistic possibility for deoxymercuration involves collapse of a π-complex or carbonium ion inter-

mediate in the rate-controlling step.[45] It is readily shown that the reaction of II would follow the simple Gross equation for this mechanism also. In the case of I, this mechanism requires $k_D/k_H = \varphi_3{}^{-1}l^{-3}$ and $k_n/k_H = (1 - n + n\varphi_3)^{-1}(1 - n + nl)^{-3}$. At $n = 0.5$, k_n/k_H so calculated is only 2% less than the value predicted on the basis of the transition state IIa and does not therefore allow any mechanistic distinctions to be made.

H. The Acid-Catalyzed Hydrolysis of Esters.—It has long been known that k_D/k_H ratios for the acid-catalyzed hydrolysis of carboxylic esters are comparatively small, and, for ethyl formate and methyl acetate, the kinetics are known not to obey the simple Gross equation.[6,11] A consideration of the data in terms of the number of exchangeable protons in the transition state suggests a plausible explanation of both of these observations. The detailed mechanism of acid-catalyzed ester hydrolysis is quite complex[46] and need not be specifically considered here. However, it is convenient to think of the mechanism in terms of a tetrahedral transition state

$$\left[\begin{array}{c} OH \quad\quad H \\ \overset{\displaystyle ||}{R-C---O} \\ \overset{\displaystyle ||}{OH} \quad\quad R \end{array} \right]^+$$
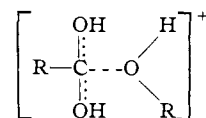
On the assumption that the fractionation factors, φ, of the three exchangeable lyons in the above representation are equal,[47] the equation for the kinetics of H_2O–D_2O mixtures becomes

$$k_n/k_H = \frac{(1 - n + n\varphi)^3}{(1 - n + nl)^3} \tag{16}$$

where $k_D/k_H = \varphi^3 l^{-3}$.

We have re-examined the acid-catalyzed hydrolysis of ethyl formate and methyl acetate in H_2O–D_2O solvent mixtures and the results are summarized in Table V. The isotope effects on the hydrolysis of ethyl formate and methyl acetate are seen to be 1.57 and 1.68,

TABLE V

HYDROLYSIS OF ETHYL FORMATE AND METHYL ACETATE IN
H_2O-D_2O MIXTURES AT 25°

n	No. of experiments	10^3k, M^{-1} sec.$^{-1}$	Error[a]	k_n/k_H
	Ethyl formate in 0.01–0.02 M hydrochloric acid			
0	6	3.13[b]	±0.02	..
0.296	1	3.37		1.08
.494	2	3.70, 3.70		1.18
.593	1	3.78		1.21
.692	1	3.96		1.27
.792	1	4.30		1.37
.891	1	4.51		1.44
.990	5	4.89	±0.11	1.56
1.000	..	4.92	(extrap.)	1.57
	Methyl acetate in 0.190 M hydrochloric acid			
0	5	0.103[c]	±0.001	..
0.50	2	.125, 0.128		1.23
0.99	5	.172	±0.002	1.67
1.00	..	.173	(extrap.)	1.68

[a] Average deviation from the mean. [b] A value of 3.12×10^{-3} was obtained by M. H. Palomaa, *Ber.*, **67B**, 949 (1934). [c] A value of 1.01×10^{-4} was obtained by H. S. Harned and A. M. Ross, *J. Am. Chem. Soc.*, **63**, 1993 (1941).

(41) (a) See L. L. Schaleger and F. A. Long, in V. Gold, Ed., "Recent Advances in Physical Organic Chemistry," Academic Press, Inc., New York, N. Y., 1963, p. 26, for a summary; (b) J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 6008 (1956).

(42) M. M. Kreevoy, *ibid.*, **81**, 1099 (1959).

(43) L. L. Schaleger, M. A. Turner, T. C. Chamberlin, and M. M. Kreevoy, *J. Org. Chem.*, **27**, 3421 (1962).

(44) M. M. Kreevoy and L. T. Ditsch, *J. Org. Chem.*, **25**, 134 (1960).

(45) M. M. Kreevoy and G. Bodem, *ibid.*, **27**, 452 (1962), and references to earlier work.

(46) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(47) The assumption of equivalent lyons leads to minimum values of k_n for a given value of k_D/k_H.

respectively, the former number being considerably larger than the 1.37 obtained previously at 15°.[48,49]

It is clear from Fig. 3 that, compared to the simple Gross equation, the curve calculated from eq. 16 corresponds much more closely to the experimental data. While the fit is not as good as one would hope, it is difficult to say whether the difference is real or experimental. It is worth noting that the fit can be improved somewhat through the use of equations based on five or more equivalent exchangeable protons in the transition state. To illustrate, the rate ratio at $n = 0.5$ calculated from the equation derived for a transition state having five equivalent exchangeable protons is

(48) J. C. Hornel and J. A. V. Butler, *J. Chem. Soc.*, 1361 (1936).

(49) The difference between the values 1.37 and 1.57 cannot be ascribed to the different temperatures of the experiments. On the contrary, it is expected from theory[50] that the reaction in light water should have a higher activation energy and that consequently the k_D/k_H ratios for acid-catalyzed reactions should decrease with temperature, as it is actually found.[50,51]

(50) M. Kilpatrick, *J. Am. Chem. Soc.*, **85**, 1036 (1963).

(51) P. Gross, H. Steiner, and F. Kraus, *Trans. Faraday Soc.*, **34**, 351 (1938).

1.196, compared with 1.18 (experimental) and 1.207 (eq. 16). For methyl acetate, the rate ratios calculated for $n = 0.5$ are 1.293 (simple Gross equation), 1.245 (eq. 16), and 1.236 ("fifth power equation") and are to be compared with the experimental ratio of 1.23. These results affirm the current view[52] that acid-catalyzed ester hydrolysis is not to be considered representative of the simple A-2 category of mechanism.

In conclusion we wish to emphasize that the utility of rate measurements in $H_2O–D_2O$ solvent mixtures appears to be somewhat limited by the relative insensitivity of k_n/k_H to mechanism, at least for acid-catalyzed reactions not involving slow proton transfer to carbon. However such data will continue to prove informative in certain cases, and this eventuality may now be decided beforehand for a particular reaction on the basis of the magnitude of k_D/k_H, the accuracy of the kinetics, the mechanistic possibilities to be considered, and the available independent information.

(52) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4978 (1961).

Ion Association in Polyvalent Symmetrical Electrolytes. VI. The Conductance of Manganese(II) Sulfate and Manganese(II) m-Benzenedisulfonate in Acetone–Water Mixtures at 25°

BY GORDON ATKINSON AND SERGIO PETRUCCI

The conductance of $MnSO_4$ has been measured in acetone–water mixtures up to 40% acetone and the conductance of $Mn(m)BDS$ up to 70% acetone. All data were analyzed using the linearized Fuoss–Onsager equation to give Λ^0, K_A, and a_J values. The behavior of these two salts shows marked specific solvent effects and is very similar to that in the previously measured methanol–water systems.

Recently the conductances of $MnSO_4$ and Mn *m*-benzenedisulfonate have been measured in both dioxane–water[1] and methanol–water mixtures.[2] The analysis of the data by the Fuoss–Onsager theory[3] gave strong indications of specific solvent effects. The association constants, mean distance of closest approach parameters, and limiting conductances at infinite dilution all showed marked effects. Qualitative analysis of the data showed that both salts seemed to be closer to the idealized Bjerrum–Fuoss association behavior in the dioxane–water mixtures. In the methanol–water mixtures, all parameters showed drastic changes when the mole fraction methanol exceeded 0.25. This is the same point where the properties of the methanol–water solvent mixture show maximum deviations from ideal behavior. It looked as if the Mn salts considered the water-rich mixtures as being distinctly different solvents from the methanol-rich mixtures. This does not mean that such specific solvent interaction is only observed with high charge salts such as $MnSO_4$. However, the small deviations noted for 1–1 salts[4,5] are greatly magnified by the enhanced ion–ion and ion–solvent forces in the 2–2 salt solutions. This is particularly true for transition metal ion salts. The recent advances in coordination chemistry[6] have emphasized the greatly different metal–ligand forces possible among ions of only slightly different ion radii. This difference in bond strength and character manifests itself both in the thermodynamics of metal–ligand interactions and in their kinetics.

It was decided to extend the previous work by examining the behavior of $MnSO_4$ and $Mn(m)BDS$ in acetone–water mixtures. This solvent system was chosen because it was thought to exhibit a nonideal behavior similar to the methanol–water system. The acetone molecule possesses a dipole and so might be presumed capable of coordination with the ions. The $Mn(m)BDS$ is essentially unassociated in water at 25° while the K_A for $MnSO_4$ is 133.

Experimental

The experimental technique is described in a previous publication by the authors.[7] The $Mn(m)BDS$ was a laboratory stock used in the previous work.[2,3] It was dried over $CaCl_2$ at room temperature to the definite weighing form $Mn(m)BDS \cdot 3.5H_2O$. The $MnSO_4$ was C.P. material recrystallized twice from conductance water. Dried at 105°, it was used in the form $MnSO_4 \cdot H_2O$. This is a definite weighing form that is not particularly hygroscopic but is best maintained in a desiccator over anhydrous $MnSO_4$.

The acetone was dried over anhydrous $CuSO_4$ for 2 hr.[8] and distilled through a 5-ft. fractionating column. The purity of the acetone was checked using its boiling point, refractive index, and dielectric constant. For each solvent mixture–salt combination, a batch of mixed solvent was prepared by weight. This same mixture was used for preparation of the concentrated stock solution and for the dilution run. The salt analyses were done as previously described.[1,2]

(1) G. Atkinson and C. J. Hallada, *J. Am. Chem. Soc.*, **84**, 721 (1962).

(2) C. J. Hallada and G. Atkinson, *ibid.*, **83**, 3759 (1961).

(3) R. M. Fuoss and F. Accascina, "Electrolytic Conductance," Interscience Publishers, Inc., New York, N. Y., 1959.

(4) (a) R. M. Fuoss and H. Sadek, *J. Am. Chem. Soc.*, **72**, 301, 5803 (1950); (b) R. M. Fuoss and E. Hirsch, *ibid.*, **82**, 1021 (1960); (c) S. Petrucci, *Acta Chem. Scand.*, **16**, 760 (1962).

(5) H. K. Bodenseh and J. B. Ramsey, *J. Phys. Chem.*, **67**, 140 (1963).

(6) *E.g.*, "Modern Coordination Chemistry," J. Lewis and R. G. Wilkins, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, Chapter 1.

(7) G. Atkinson and S. Petrucci, *J. Phys. Chem.*, **67**, 337 (1963).

(8) "Organic Solvents," Vol. VII of "Techniques of Organic Chemistry," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1955, p. 381.