

Equilibrium Studies by Electron Spin Resonance. 15. The Effect of Solvent Polarity Changes by the Addition of Secondary Solvents upon Ion Pair Dissociation

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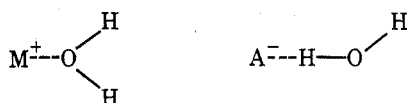
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The dissociation constant for the ninhydrin anion radical ion pair in hexamethylphosphoramide (HMPA) containing added water was found to increase linearly with increasing percentage of water in the solvent media, up to about 24% water. Extrapolation of this trend to 100% water predicts a dissociation constant of about 2 compared with the value of 0.014 found in pure HMPA. In contrast to these results, the addition of ammonia (a polar solvent) or hexane (a nonpolar solvent) to an equilibrium mixture of *p*-benzosemiquinone in HMPA results in an increase in the concentration of the ion pair with respect to that for the free ion. For the case of the ammonia addition this can be ascribed to the formation of the hydrogen bonded ion pair. The decrease in the ion pair dissociation constant with the addition of hexane was found to be due to an increase in the enthalpy of dissociation, while the entropy term varied only slightly. The unexpected increase in the enthalpy of dissociation is explained in terms of the special solvation properties of HMPA.

Recently the actual single ion enthalpies and free energies of solution have been determined by Parker et al.¹ for a number of cations in a series of solvents that are commonly used as solvents for anion radicals. For the alkali metal cations they found that the general order of solvation is hexamethylphosphoramide (HMPA) > dimethyl sulfoxide > dimethylformamide >> water > acetonitrile > methanol. In view of the fact that the bulk dielectric constant for water (78.3) is larger than that for HMPA (30.5)² it is surprising that the free energy of the alkali metal cations is more negative in HMPA than it is in water. However, it can be readily explained in terms of solvent-solvent interactions that exist in water and not in HMPA and other chemical properties of the two solvents.³

HMPA is one of the most powerful solvents for alkali metal cations known,⁴ and a wide variety of anion radicals can be generated in this solvent that are free of ion pairing. However, due to the fact that the anion radicals in HMPA remain practically unsolvated, the addition of alkali metal salts to anion radical solutions in HMPA often results in the formation of ion pairs.⁵ On the other hand, water is a strong solvator of both anions and cations.⁶ Its ability to solvate anions is explained by the fact that water can act as a proton donor to form hydrogen bonds.



Although water is a poorer solvator of cations than is HMPA, ion pairs are essentially unknown in this solvent. Since a variety of organic anions is formed in biological systems where the concentrations of alkali metal cations (K^+ and Na^+) are quite large, it is presumably true that ion pairing, if it exists, may play an important role in the thermodynamic stability of biologically important anions.

It is our intention here to report free energies of ion pairing in mixtures of HMPA and water with the hope of extrapolating these results to estimate the free energies of ion pair dissociation in pure water. HMPA is particularly well suited to the experimental determination of ion pair dissociation

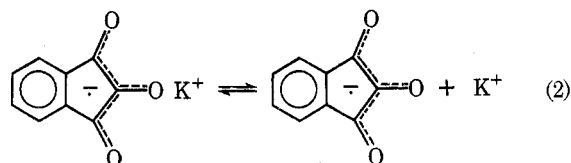
constants since the equilibrium between the ion pair (β) and the free ion (α) can be described by the two-site model expressed in⁷



The major obstacle to any ESR study of anion radicals in H_2O is the fact that the vast majority of anion radicals are not stable in this solvent. Russell and Young⁸ have reported one of the most stable anion radicals, that of ninhydrin. The ninhydrin radical anion is stable enough for continued observation in an aqueous media, and is particularly well suited to this study due to the fact that the charge localization in the oxygens should lead to facile ion pair formation.

Results and Discussion

Solutions (10^{-2} to 10^{-4} M) of ninhydrin in HMPA will dissolve small amounts of potassium metal to yield a solution of the very stable ninhydrin anion radical. Upon ESR analysis this solution yields a nine-line pattern consisting of two triplets, each due to two equivalent protons with coupling constants of 0.93 and 1.18 G. These values are completely consistent with those reported in dimethyl sulfoxide.⁸ Addition of KI or $KClO_4$ to the anion radical solution results in a change in both of the coupling constants. The total line width (distance between the first and last ESR line) changes even more dramatically with the addition of salt. These changes in total line width (ΔW_t) and in the coupling constants are due to the formation of ion pairs which exist in rapid equilibrium with the free ion



Since the observed value for ΔW_t decreases smoothly with increasing salt concentration, it must be a weighted average between the total line width for the free ion (ΔW_t^0) and that for the ion pair ($\Delta W_t'$).⁹

It has been demonstrated previously that weighted average total line widths can be used along with eq 3 for the determi-

$$1/(\Delta W_t - \Delta W_t^0) = K_{eq}/(K^+)(\Delta W_t' - \Delta W_t^0) + 1/(\Delta W_t' - \Delta W_t^0) \quad (3)$$

nation of ion pair dissociation constants.⁹ If the two-jump model expressed in eq 2 (ion pair to free ion) is correct, a plot of $1/(\Delta W_t - \Delta W_t^0)$ vs. $1/(K^+)$ should give a straight line and have an intercept of $1/(\Delta W_t' - \Delta W_t^0)$ and a slope of $K_{eq}/(\Delta W_t' - \Delta W_t^0)$. Treated in this manner our data did yield a straight line, Figure 2. From the slope and intercept of this line $\Delta W_t'$ and K_{eq} were found to be 4.07 G and 0.014, respectively.

Unlike most of the other anion radicals studied in HMPA, we were not able to assume that the anion radical generated in the absence of added salt was free of ion pairing. Upon close examination of the ESR spectrum obtained before the addition of salt, some asymmetry can be observed in the line amplitudes. That is, the high-field lines have larger amplitudes than do the low-field lines due to the fact that both the ion pair and free ion exist in solution, and they are rapidly interconverting. Since the two species have different coupling constants and g values,¹⁰ an asymmetry is expected.^{5a} Being unable to generate a solution containing only free ion, ΔW_t^0 had to be obtained indirectly by extrapolating a plot of the total measured line width vs. the ratio of line amplitudes for the first and last line for systems reduced with different amounts of potassium metal to one for this ratio. The value obtained for ΔW_t^0 (4.39 G) is only slightly different than that observed before the addition of salt.

Addition of water to the HMPA solutions without added salt results in the disappearance of the asymmetry, Figure 1, which is certainly due to the dissociation of the ion pair. Thus, for anion radical solutions containing more than 1% water, ΔW_t^0 can be taken from the ESR spectrum of the solution before any salt is added. In general it was found that the larger the concentration of water in the anion radical solution the larger the portions of added salt had to be in order to observe a change in the total line width. For all of the water concentrations studied a linear plot was obtained when the data were treated according to eq 2, Figure 2. The results from these experiments are given in Table I for water concentrations varying from 0 to 25 wt % H₂O. For concentrations of water larger than 25% copious quantities of KClO₄ had to be added to observe a change in the total line width making it impractical to study these solutions.

Even though the ion pair dissociation constant could not be measured in pure water, it can be estimated from an extrapolation of the results reported in Table I. A plot of the weight percent of water in the HMPA solution vs. K_{eq} is essentially linear (Figure 3). Extrapolation of this plot to 100% H₂O yields a K_{eq} of 2.1. It is certainly not certain that this plot will remain linear all the way to 100% water, but even with considerable curvature K_{eq} is not likely to be less than one. All of this indicates that ion pair dissociation constants are very large in pure water.

In order to compare these results to systems of biological interest, it is helpful to review some of the ion pair dissociation constants for other anion radicals in HMPA (Table II).

Several compounds found in biological systems have the potential of acting as radical scavengers and may pull an electron off of an undesired radical to form the anion radical of the scavenger molecule. If this is the case the thermodynamic stability of the resulting anion radical will be of immense importance to the biological system, and ion pairing

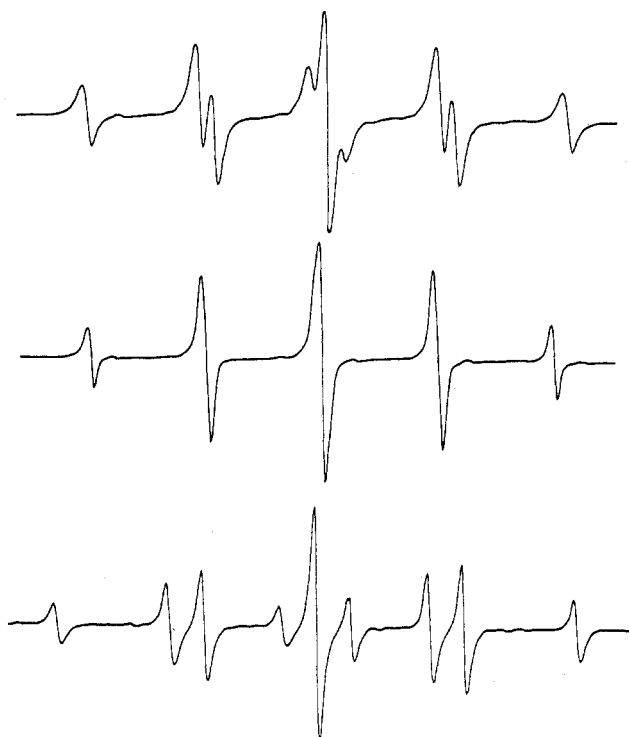


Figure 1. ESR spectra of the ninhydrin-HMPA-K system: (top) containing added potassium perchlorate (0.05 M); (middle) containing 15.2% H₂O; (bottom) no salt or water added. Note the asymmetry in the amplitudes of the first and last ESR lines.

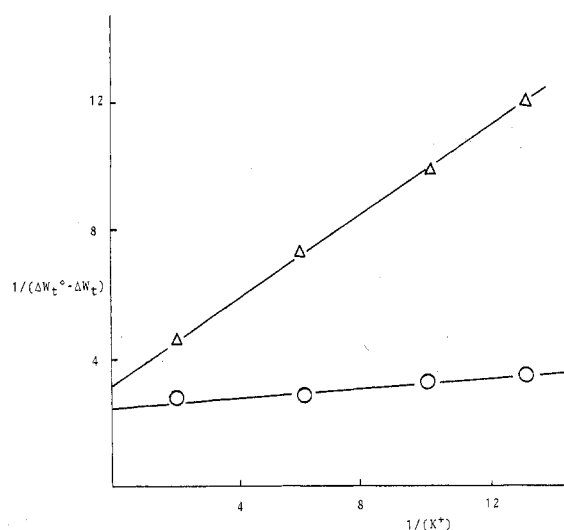


Figure 2. Plots of $1/(\Delta W_t - \Delta W_t^0)$ vs. $1/(K^+)$ for the ninhydrin anion radical in HMPA (O) and in HMPA containing 6.8% H₂O (Δ).

is an important factor influencing this thermodynamic stability. The list of possible radical scavengers includes coenzyme Q (I) and vitamin K (II) both of which have quinoidlike structures.¹⁰

In HMPA the ion pair dissociation constant for our model compound (ninhydrin) is several times smaller than those for compounds with structures similar to I and II. It follows then that since there is little ion pairing of the ninhydrin anion radical in water, ion pairing is probably of little importance in biological systems for the anion radicals of I and II in an aqueous environment.

TABLE I: Equilibrium Constant for Reaction 2 in HMPA with Added Water; $\Delta W_t'$, ΔW_t° , and the Slope of the Line Shown in Figure 2

% H ₂ O	Slope	ΔW_t° , G	$\Delta W_t'$, G	K_{eq}	X_{H_2O}
0.00	0.042	4.39 ^a	4.07 ± 0.04 ^b	0.014 ± 0.002 ^b	0
1.55	0.21	4.12	3.86 ± 0.04	0.054 ± 0.006	0.13
2.02	0.16	4.08	3.85 ± 0.06	0.037 ± 0.05	0.17
5.10	0.35	4.03	3.79 ± 0.06	0.084 ± 0.02	0.35
6.82	0.66	3.96	3.66 ± 0.06	0.15 ± 0.02	0.41
12.4	0.84	3.83	3.60 ± 0.04	0.19 ± 0.03	0.58
17.5	2.97	3.59	3.44 ± 0.06	0.45 ± 0.03	0.68
24.7	6.55	3.67	3.59 ± 0.06	0.52 ± 0.03	0.77

^a The error in ΔW_t° is 0.03 G. ^b These errors were propagated from a computer calculation of the standard deviation in the best slope and intercept. ^c These are the mole fractions of H₂O.

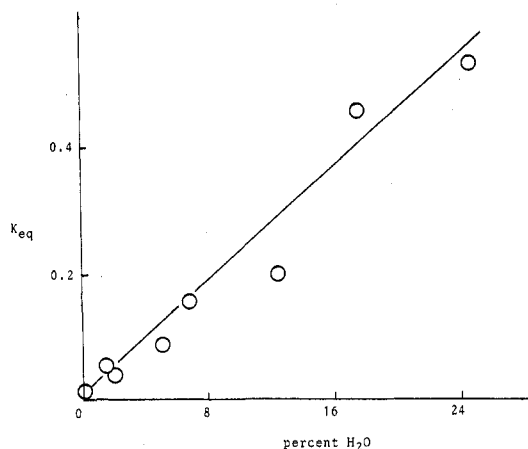
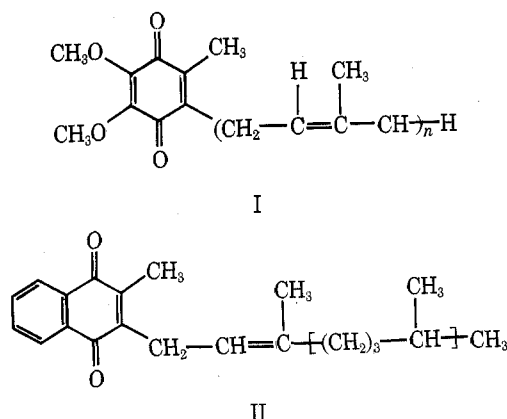


Figure 3. Plot of the ion pair dissociation constant for the ninhydrin anion radical ion pair in HMPA vs. the percent of added water.

TABLE II: Ion Pair Dissociation Constants at 25 °C in HMPA for Anion Radicals Ion Paired with Potassium

Anion radical	K_{eq}	Anion radical	K_{eq}
	0.036 ^a		0.25 ^b
	0.075 ^a		0.060 ^b
	0.29 ^a		0.014 ^c
	0.14 ^a		



It is clear that the addition of water shifts the ion pair dissociation to the right because of specific interactions between the water and the ions and not just due to an increase in the polarity of the solvent medium. However, it would be predicted that the addition of a nonpolar secondary solvent (hexane) would lead to a shift to the left.

The ion pair and free ion of the ninhydrin anion radical cannot be observed individually, as only the time-averaged species is seen. For the anion radical of benzoquinone in HMPA both the free ion and ion pair are observed simultaneously, and the ion pair dissociation constant can be obtained from their respective line intensities.^{5a} The observation of both the ion pair and free ion yields more information concerning the structure of the ion pair.

When small amounts of hexane (0.1 to 2 M) were added to solutions of benzoquinone in HMPA with added KI, the equilibrium constant for the ion pair dissociation was found to decrease. The effect of increasing the free energy of a reaction in which charge is created by decreasing the polarity of the solvent has been observed many times, and is normally due to the entropy term.¹¹ A nonpolar solvent undergoes much more ordering than does a polar solvent upon charge creation.

As can be seen in Figure 4, the shift to more positive free energies in the dissociation of the *p*-benzoquinone ion pair (eq 1) is due to an increase in the enthalpy term and not a decrease in the entropy. In fact, the entropy for eq 1 undergoes a slight increase upon addition of hexane to the solvent system (Table III). These results can be explained in terms of the special solvation properties of HMPA. HMPA is a polar solvent; but, due to the large steric interaction around the electropositive phosphorus center, there is little dipole-dipole ordering of this solvent. However, since HMPA is one of the most powerful cation solvators,⁴ it is strongly bound to the cation (free of ion pairing). Thus the enthalpy of ion pair dissociation is negative. The addition of hexane to the system decreases the polarity of the solvent medium, but does not change the ordering of the solvent in the absence of ions. However, when the ion pair dissociates HMPA must compete with hexane in the solvation of the newly formed cations. Since the interaction between the cation and hexane cannot be as strong as that between the cation and HMPA, both the entropy and the enthalpy increase with the addition of hexane. It should be noted here that the splitting due to the ³⁹K nucleus in the ion pair (0.30 G) does not vary with the

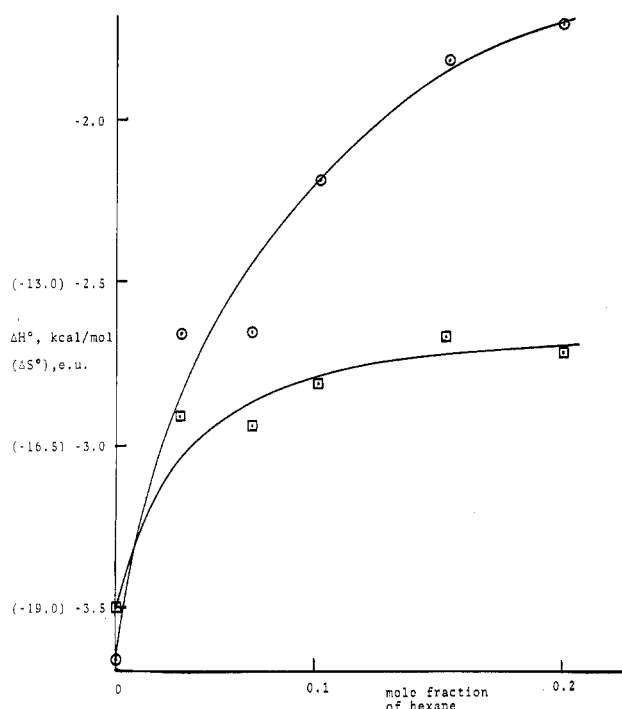


Figure 4. Plots of the enthalpy and entropy of ion pair dissociation vs. the mole fraction of added hexane. The entropy values are given in parentheses, and the plot is represented by \square . The enthalpy plot is represented by \circ . The data for this plot were taken at 25 °C for the *p*-benzoquinone-HMPA-K system.

TABLE III: Thermodynamic Parameters Controlling the Dissociation of the Potassium *p*-Benzosemiquinone Ion Pair in HMPA with Added Hexane

Mole fraction of hexane	K_{eq}	ΔH° , kcal/mol	ΔS° , eu
0	0.036 ^a	-3.68 ± 0.1 ^b	-19.0
0.033	0.028	-2.66 ± 0.06	-16.0
0.068	0.025	-2.65 ± 0.02	-16.2
0.102	0.016	-2.18 ± 0.1	-15.5
0.165	0.012	-1.80 ± 0.1	-14.8
0.225	0.0095	-1.71 ± 0.06	-15.0

^a The relative error in the equilibrium constants is 0.001. This small relative error is due to the fact that the sample without any added hexane, for which the K_{eq} is known,⁵ was used as a standard. Samples were taken from the same anion radical solution after various quantities of hexane were added and compared to the standard. ^b These errors represent standard deviations in the slope.

addition of hexane up to 0.2 M suggesting that the nature of the ion pair does not change with the addition of small amounts of hexane.

The addition of a polar or protic solvent to the system *p*-benzoquinone-HMPA-K with added KI would be expected to have the opposite effect upon the ion pair dissociation equilibrium from that due to the addition of hexane. That is, the free ion concentration should increase relative to that for the ion pair with the addition of ammonia.

Again, the opposite of the expected result is obtained experimentally. Small additions of NH_3 to the free ion-ion pair equilibrium mixture result in an increase in the concentration of ion pair relative to that for the free ion (Figure 5). The only way a negative slope for a plot of K_{eq} vs. the concentration of

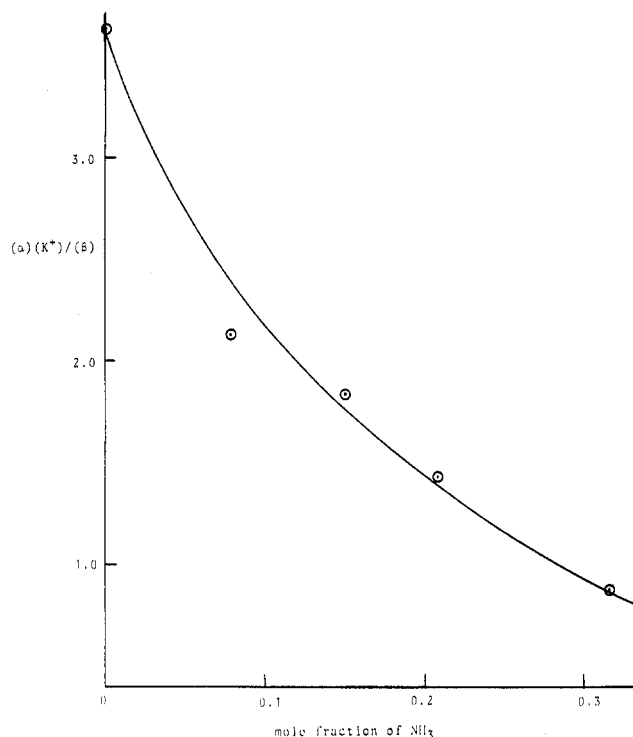


Figure 5. A plot of the free ion concentration (α) times the potassium ion concentration divided by the ion pair concentration (β) vs. the mole fraction of added ammonia.

added NH_3 can be interpreted is to assume an exothermic interaction between the ion pair and ammonia, which is most probably due to the formation of a hydrogen bonded ion pair. A similar effect upon the ion pair dissociation equilibrium for the nitrobenzene anion radical in HMPA was observed when NH_3 was added to the system,¹² and was shown to be due to the formation of a hydrogen bonded ion pair for which a structure was proposed.¹² Hydrogen bonded ion pairs have also been reported by Hirota et al.¹³

No change in the metal splitting was observed for additions of NH_3 to the benzoemiquinone ion pair. However, at higher concentrations of NH_3 (4 M) a decrease in A_K is observed due to the displacement of the cation by the hydrogen bonding ammonia molecules. These two similar (both can form hydrogen bonds to an anion and both can coordinate an alkali metal cation) solvents (water and ammonia) act in an opposite manner in their effect upon ion pairing. The hydrogen bonded ion pair formed upon ammonia addition is stabilized presumably by simultaneous hydrogen bonding to the anion and interaction of the lone electron pair on the nitrogen with the cation. The anion radical of benzoquinone is not sufficiently stable for study in solutions containing water.

Experimental Section

All of the organic compounds used were purchased from Aldrich Chemical Co. and recrystallized before use. Potassium iodide and potassium perchlorate were dried in a vacuum oven at 100 °C for 48 h prior to use.

The method of reduction of the neutral molecule to form anion radicals and the purification of HMPA has been previously described.^{7b} Quantitative addition of NH_3 to the anion radical solution was carried out by the use of a toepler pump connected to a gas buret as previously described.¹² Hexane and water were added to the anion radical solutions via break seals in the manner previously described.¹⁴

The ESR spectra were recorded on an x-band E-9 ESR spectrometer. The temperature was controlled with a Varian V-4557 variable-temperature controller calibrated with an iron constantan thermocouple. The method used to determine the thermodynamic parameters for the dissociation of the *p*-benzosemiquinone ion pair (eq 1) was exactly the same as previously described.^{7a}

Care must be taken in the handling of HMPA, since it has been found to be a possible carcinogen.¹⁵

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Proton Diffusion and Activity in the Presence of Electrolytes

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Proton diffusion in pure water and in the presence of electrolytes is of particular importance in biological systems. In pure water the rate-determining step is the rotational or librational freedom of the water molecule. The tunneling of the proton in the H bond is very rapid and has a low activation energy. In the presence of most electrolytes the rotational and librational freedom of the water molecules is only slightly affected. In the case of structure breakers the water molecules are freer than in pure water. However, the highly polarizable H bond in which the proton tunnels is strongly polarized by the presence of electrolytes and the potential well deformed with increasing electrolyte concentration. Consequently as the concentration of electrolyte increases the Grotthuss mechanism is suppressed and the hydrodynamic mechanism becomes more important. Another consequence of the polarization of the H bond and its final dehydration by ion-dipole interaction is the increase in activity of the hydrogen ion in the presence of electrolytes owing to its increased localization. Tetraalkylammonium salts, where alkyl is propyl and butyl, do not polarize the H bond as much as the surrounding water molecules, and the decrease in proton diffusion appears to be due to the reduced orientation time of the water molecule. The activity of the hydrogen ion is less in the presence of these electrolytes and reflects the decreased localization of the hydrogen ion.

Introduction

It is well established that proton and deuteron diffusion¹ in normal and heavy water solutions of electrolytes is very sensitive to the presence of electrolytes, Figure 1a and 1b.²⁻⁷ The aim of this paper is to consider critically the present theories of proton diffusion in water and to ascertain the mechanism in the presence of electrolytes. Our recent work on proton diffusion and activity in the presence of electrolytes is briefly summarized and the interpretation is considerably extended in the light of recent infrared investigations of acid solutions containing electrolytes. The results are of importance for aqueous biological systems where hydrogen ion mobility and activity are markedly affected by the type of electrolytes present.

Mechanism for Proton Diffusion

The currently accepted mechanism for proton mobility in aqueous solutions is that advanced by Conway, Bockris, and Linton in 1956,⁸ and most text books quote it as the only likely mechanism. However, Eigen⁹ in 1958 postulated a slightly different mechanism and pointed out some of the shortcomings in the treatment by Conway, Bockris, and Linton. Both groups of workers agreed that the proton tunneled through a hydrogen bond rapidly and that this process had almost no activation energy, however, they disagreed on the rate-determining step. Conway et al. considered that the rate-determining step in proton mobility was the rotation of hydrogen bonded water molecules in the field of H_3O^+ ion (preceded and succeeded by fast tunneling protons). Eigen⁹ maintained