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Kinetic Isotope Effects of Proton Transfer Reaction for Amines by Ultrasonic Relaxation Methods: Unexpected Evidence from the Results in Ethylamine Solutions

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Ultrasonic absorption coefficients for ethylamine in heavy water (D_2O) and in light water (H_2O) have been measured in the frequency range from 0.8 to 220 MHz at 25 °C. A single relaxational process has been observed in these two kinds of solutions. From the concentration dependence of the ultrasonic relaxation parameters, and following the reaction mechanism proposed by Eigen et al. for ethylamine in H_2O, the causes of the relaxations have been attributed to a perturbation of an equilibrium associated with a deuteron or proton transfer reaction. The rate and equilibrium constants have been estimated from deuterioxide or hydroxide ion concentration dependence of the relaxation frequency, and the kinetic isotope effects have been determined. In addition, the standard volume changes of the reactions have been calculated from the concentration dependence of the maximum absorption per wavelength, and the adiabatic compressibility has also been determined from the density and sound velocity for ethylamine in D_2O and in H_2O, respectively. These results are compared with those for propylamine and butylamine and are discussed in relation to the different kinetic properties between D_2O and H_2O, the reaction radii derived by Debye theory, and the structural properties of the reaction intermediate.

Introduction

It is well-known that isotope effects for various chemical properties provide useful information concerning static and dynamic behaviors in liquids and solutions.[1−4] However, fast kinetic isotope effects have not been investigated much previously.

In our series of kinetic studies of the isotope effect on the proton transfer reaction by ultrasonic relaxation methods,[5,6] it has been clarified that the diffusion-controlled rate constant is facilitated in heavy water (D_2O) while the ion separation rate constant in D_2O is diminished when compared with those in H_2O from the experimental results in propylamine and butylamine solutions. These have been interpreted from the decrease in the activation energy for the diffusion-controlled process and the decrease in the energy level of the intermediate. This has been considered from the fact that all of the amino hydrogen atoms are exchanged to the heavier deuterium atom when D_2O is used as a solvent. Then, we expected that smaller amine molecules may cause a more pronounced isotope effect. With respect to this consideration, the ultrasonic absorption measurements for ethylamine in H_2O and D_2O have been performed. However, unexpected results have been observed in ethylamine which are represented and interpreted in this report.

Experimental Section

Ethylamine (70% with water) purchased from Wako Pure Chemical Ltd. was used without further purification. Heavy water was also from Wako Pure Chemical Ltd. and was guaranteed to be more than 99.75%. Light water was purified by a Milli-Q SP-TOC System from Japan Millipore Ltd. The prepared sample solutions were kept in a nitrogen gas atmosphere and were stored at low temperature (4 °C). The concentrations of amine solutions were determined by titration using oxalic acid dihydrate (Wako Pure Chemical Ltd.) and a phenol phthalein indicator (Katayama Chemical).

Ultrasonic absorption measurements were carried out by a pulse method in the frequency range from 15 to 220 MHz using 5 and 20 MHz fundamental x-cut quartz crystals. Two resonators constructed from 3 MHz quartz crystals with a diameter of 3 cm and 5 MHz crystals with a diameter of 2 cm were used to obtain the ultrasonic absorption coefficients, α's, in the frequency range from 0.8 to 7 MHz. The details of these apparatuses were described elsewhere.[7,8] Measurements of sound velocity and density of the solutions were carried out by a 3 MHz resonator and a vibrating density meter (DMA 60/602 Anton Paar), respectively. Solution pH was measured by inserting a glass electrode (HM-60s, Toa Denpa) into the pulse ultrasonic absorption cell while the measurements were proceeding. The measurement temperature for the pulse apparatus was maintained at 25 °C with a water bath (EYELA UNI ACE BATH NCB-2200) and that for the resonator was controlled by circulating water (LAUDA, RM20).

Results and Discussion

As the concentration of ethylamine is much smaller than that of solvent D_2O (less than 1%), the amino hydrogen atoms of

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TABLE 1: Ultrasonic Parameters for Ethylamine in D_2O and in H_2O at 25 °C

C_o mol dm^{-3}	C_{H2O} mol dm^{-3}	pH	f_r MHz	A 10^{-15} s^2 m^{-1}	B 10^{-15} s^2 m^{-1}	ν m s^{-1}	ρ kg dm^{-3}
			Ethylamine in D_2O				
0.5203	0.561	12.53	80 ± 2	113 ± 2	25.8 ± 0.6	1430.9	1.0941
0.4333	0.468	12.43	73 ± 2	115 ± 2	25.0 ± 0.6	1424.1	1.0964
0.3058	0.330	12.35	54 ± 2	98 ± 3	34.1 ± 0.4	1417.9	1.0986
0.0867	0.094	11.88	49 ± 5	61 ± 6	23.0 ± 0.8	1409.2	1.1021
0.0245	0.026	11.58	45 ± 11	26 ± 6	26.5 ± 0.7	1405.7	1.1032
			Ethylamine in H_2O				
0.3988		12.17	120 ± 7	57 ± 1	24.6 ± 1.4	1511.5	0.9930
0.2963		12.09	90 ± 7	59 ± 2	28.9 ± 1.3	1509.2	0.9939
0.0798		11.68	73 ± 3	50 ± 1	20.9 ± 0.4	1499.3	0.9965
0.0237		11.44	49 ± 6	38 ± 5	20.0 ± 0.6	1497.7	0.9969

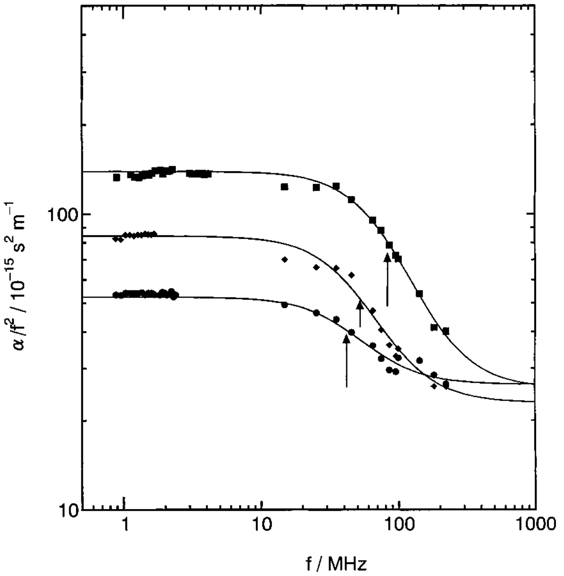

Figure 1. Representative ultrasonic absorption spectra for ethylamine in D_2O at 25 °C: (■) 0.5203 mol dm^{-3}; (◆) 0.0868 mol dm^{-3}; (●) 0.0245 mol dm^{-3}. The arrows indicate the positions of the relaxation frequencies.

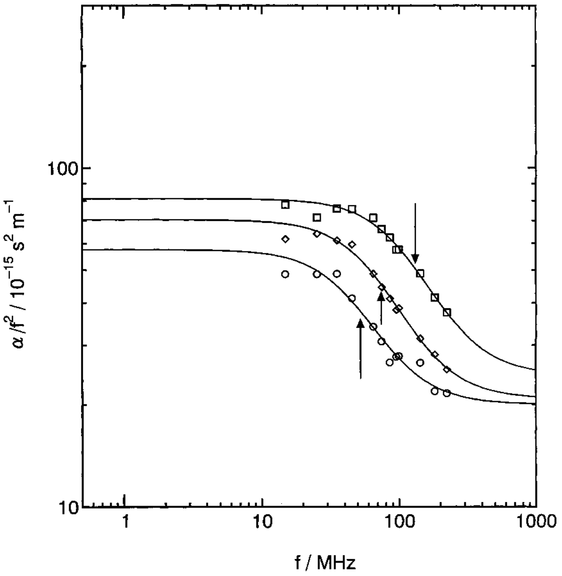

Figure 2. Representative ultrasonic absorption spectra for ethylamine in H_2O at 25 °C. (□) 0.3988 mol dm^{-3}; (◇) 0.0798 mol dm^{-3}; (○) 0.0237 mol dm^{-3}. The arrows indicate the positions of the relaxation frequencies.

ethylamine are considered to be spontaneously exchanged with deuterium,[9] even if 70 wt % ethylamine is used. Therefore, most of the amine molecules are deuterated as $R{-}ND_2$. The concentration of ethylamine was determined in H_2O by titration to yield the original concentration of ethylamine to be 69.90 ± 0.03 wt %. This result has enabled us to determine the H_2O concentration, C_{H2O}, in D_2O, which is indicated in Table 1.

Figures 1 and 2 show representative ultrasonic absorption spectra of ethylamine in D_2O and in H_2O, respectively. As shown in these figures, clear relaxational absorptions are observed in the concentration range from 0.0245 to 0.5203 mol dm^{-3} for ethylamine in D_2O and from 0.0237 to 0.3988 mol dm^{-3} for that in H_2O. That is, the absorption coefficients divided by the square of the frequency, α/f^2, are dependent on the frequency. The frequency dependence has been analyzed by a Debye-type relaxation equation as follows:

$$\alpha/f^2 = A/[1 + (f/f_r)^2] + B \qquad (1)$$

where f_r is the relaxation frequency, A is the amplitude of the ultrasonic absorption, and B is the background absorption. The ultrasonic parameters, f_r, A, and B, which are listed in Table 1, have been determined by a nonlinear least-mean-squares method. The solid curves shown in Figures 1 and 2 are generated from the parameters in Table 1 by means of eq 1. Good agreement between the experimental and calculated values confirms that the Debye-type single relaxation processes are surely observed in these solutions. The ethylamine concentration dependences of the relaxation frequency both in D_2O and in H_2O (Table 1) indicate the very similar trends of the monotonic increase, although the magnitudes are dependent on the solvents; that is, the relaxation frequency in D_2O shifts to a lower frequency range when compared with that in H_2O. In D_2O, the interrelation between the concentration and the obtained excess absorption amplitude, A, or the background absorption, B, also show the similar trends to those in H_2O (Table 1). The above phenomena have also been observed for propylamine and butylamine in D_2O and in H_2O solutions.[5,6] From these concentration dependences of the ultrasonic parameters, the source of the relaxation of ethylamine in D_2O is predicted to be associated with the hydrolysis of amine, which has been proposed for various amines in H_2O by Eigen et al.[10] Therefore, a deuteron transfer reaction is considered for the reaction of ethylamine in D_2O, as follows:

$$R{-}ND_3^{+} + OD^{-} \underset{\text{step I}}{\xrightleftharpoons[k_{21}]{k_{12}}} R{-}ND_3^{+}\cdots OD^{-} \underset{\text{step II}}{\xrightleftharpoons[k_{32}]{k_{23}}} R{-}ND_2 + D_2O \qquad (2)$$

where k_{ij} is the rate constant at each step. In general, the coupled mechanism (step I and step II) is considered when the relation between the relaxation frequency and the reactant concentrations

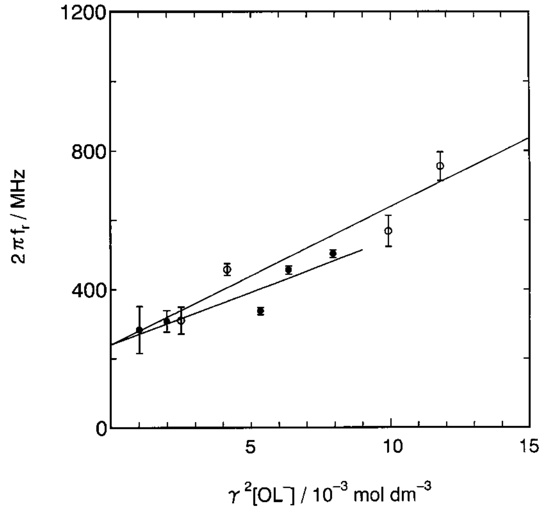

Figure 3. Plots of $2\pi f_r$ vs $\gamma^2[OL^-]$ for ethylamine in D_2O (●) and in H_2O (○).

is derived. However, for the observed relaxation process, the analysis through the coupling reaction mechanisms gave unreasonable rate and equilibrium constants.[11,12] Therefore, we assume that step II may proceed too fast to affect step I.[5,6] Then, the relationship between the relaxation frequency and the reactant concentrations is simply given as

$$\tau^{-1} = 2\pi f_r = k_{12}\gamma^2([R{-}ND_3^{\ +}]+[OD^-]) + k_{21} = 2k_{12}\gamma^2[OD^-] + k_{21} \quad (3)$$

where τ is the relaxation time and γ is the activity coefficient which is calculated by Davis equation.[13] Here, the concentration of deuterioxide ions, $[OD^-]$, is obtained according to the pH meter reading using the proposed formula[14−17] as $pD_{\text{in }D2O} = pH_{\text{meter reading in }D2O} + 0.41$, where the ionization constant, $pK_w = 14.955$ for D_2O at 25 °C,[18] is taken. Figure 3 shows plots of $2\pi f_r$ vs $\gamma^2[OL^-]$, in which L represents H or D. The good linear relations shown in this figure confirm that the source of the relaxational absorption is due to the deuteron or proton transfer reaction associated with the hydrolysis of ethylamine. The rate constants, k_{12} and k_{21}, have been determined from the slope and intercept of the plots using a linear least-mean-squares method and are listed in Table 2 along with those of propylamine and butylamine for comparison. The forward rate constants are reasonable for diffusion-controlled reactions, and the value in H_2O is very close to the reported one.[10]

Table 2 also shows the dissociation constant, K_b, which is estimated from the deuterioxide or hydroxide ion concentration and the analytical concentration of propylamine, C_o, using the relationship $K_b = \gamma^2[OL^-]^2/(C_o - [OL^-])$. Thus, the determined K_b for ethylamine in H_2O is consistent with the literature value.[19] The relationship between K_b in D_2O and that in H_2O is proposed[14] as $pK_{b,\text{in }D2O} \fallingdotseq 1.02pK_{b,\text{in }H2O} + 0.42$. This gives us $K_b = 1.3 \times 10^{-4}$ mol dm^{-3} for ethylamine in D_2O, which is considered to be in satisfactory agreement with that in Table 2.

With the help of the equilibrium constant defined as $K_{21} = k_{21}/k_{12}$ and the dissociation constant, K_b, the equilibrium constant K_{32} for step II can be calculated using the relationship $1/K_b = 1/K_{21} + 1/K_{21}K_{32}$. The obtained K_{32} values for ethylamine in D_2O and in H_2O are listed in Table 2 along with those for propylamine and butylamine for comparison.

The maximum absorption per wavelength, μ_{max}, is obtained with the use of the relaxation frequency, f_r, the amplitude of the relaxation, A, and the sound velocity, ν. μ_{max} is related to the standard volume change of the reaction, ΔV. For the reaction under consideration, μ_{max} is derived as

$$\mu_{max} = 0.5Af_r\nu = \pi\rho\nu^2\Gamma(\Delta V)^2/2RT \quad (4)$$

where ρ is the solution density, Γ is the concentration term given as $\Gamma = (1/[OL^-] + 1/[R{-}NL_3^{\ +}] + 1/[R{-}NL_3^{\ +}\cdots OL^-])^{-1}$. The contribution of the activity coefficient to Γ is considered to be negligible.[20] The calculated ΔV values are listed in Table 2. It should be noticed that ΔV values for amines in D_2O are greater than those in H_2O.

From the solution density and sound velocity, it is possible to estimate the adiabatic compressibility, β_s, using Laplace's equation as $\beta_s = -(1/V)(\partial V/\partial P)_s = 1/\rho\nu^2$. The dependence of β_s on the concentration for ethylamine along with those for propylamine and butylamine in D_2O and in H_2O is shown in Figure 4 in the concentrations less than 0.80 mol dm^{-3}. It is seen that the values in D_2O are greater than those in H_2O, and they decrease in the order ethylamine, propylamine, and butylamine in both solvents, D_2O and H_2O.

First, the result for the forward reaction process is considered. For hydrolysis of amine, the kinetic isotope effects for propylamine and butylamine have been investigated by the present authors,[5,6] the results of which indicate $k_{12}^{\ H}/k_{12}^{\ D} < 1$ for the forward rate constants (Table 2). The greater forward rate constants in D_2O for the above-mentioned two amines have been interpreted by the decrease in the activation energy for the forward process. If the isotope effect were associated only with the mass difference of the reactants, a similar and further pronounced effect should have been observed when the smaller amine molecules were used as the reactants. On the contrary, however, in the case of ethylamine, $k_{12}^{\ H}/k_{12}^{\ D}$ is estimated to be 1.3 (Table 2), which shows the opposite trend of those for propylamine and butylamine. This is an unexpected result, but the quantitative interpretation has not been performed at this stage. However, the qualitative analysis may be as follows. According to Debye, the diffusion-controlled reaction rate is well described by the next equation and it is satisfactorily applied to the reactions for various amines and amino acids.[21−23]

$$k_{12} = \sigma N z_A z_B e_0^{\ 2}(D_A + D_B)/\epsilon\epsilon_0\kappa T[\exp(z_A z_B e_0^{\ 2}/4\pi\epsilon\epsilon_0 r_d \kappa T) - 1] \quad (5)$$

where σ is a steric factor, N is Avogadro constant, z_i is the algebraic charge of ions, e_0 is the electronic charge, D_i is the diffusion coefficient of the reacting ions, ϵ_0 is the dielectric constant in a vacuum, ϵ is the dielectric constant of the solvent, κ is Boltzmann constant, and r_d is an effective radius for reaction. Following this theory, the model calculations have proved that the crucial parameter for proton or deuteron transfer is the reaction radius, r_d.[5] The calculations for ethylamine in D_2O and in H_2O give almost the same r_d to be 5×10^{-10} m (Table 2), which seems to correspond to the idea that there exists a similar number of water molecules in the intermediate as $E{-}ND_3^{\ +}(D_2O)OD^-$ or $E{-}NH_3^{\ +}(H_2O)OH^-$, in which E represents an ethyl group. In this case, the vibrational energy level for the activated complex for step I in eq 2 does not decrease too much to influence the forward rate constant so drastically as those for propylamine and butylamine. The greater viscosity and smaller ion mobility in D_2O than those in H_2O may lead to slightly smaller forward rate constant for ethylamine. Since the hydrophobicity of ethylamine is considered to be small, the hydrogen bond network of water is not promoted by the solute hydrophobicity so much. However, it is interesting to notice

TABLE 2: Rate and Thermodynamic Constants of Deuteron or Proton Transfer Reaction for Ethylamine, Propylamine, and Butylamine in D_2O and in H_2O at 25 °C

	k_{12}, 10^{10} mol^{-1} dm^3 s^{-1}	k_{21} 10^7 s^{-1}	k_{12}^H/k_{12}^D	k_{21}^H/k_{21}^D	K_{21}, 10^{-3} mol dm^{-3}	K_{32}	K_b, 10^{-4} mol dm^{-3}	r_d 10^{-10} m	ΔV, 10^{-6} m^3 mol^{-1}
ethylamine in D_2O	1.5 ± 0.2	24 ± 3	1.3	1.0	16	0.006	1.0 ± 0.3	5	47 ± 3
propylamine in D_2O[a]	2.7 ± 0.1	7.1 ± 1.3	0.8	1.8	2.6	0.04	1.0 ± 0.1	13	40 ± 3
butylamine in D_2O[a]	3.1 ± 0.3	5.4 ± 2.8	0.9	1.7	1.8	0.07	1.1 ± 0.2	16	34 ± 1
ethylamine in H_2O	2.0 ± 0.3	24 ± 5			12	0.03	4.1 ± 0.6	5	33 ± 6
propylamine in H_2O[a]	2.1 ± 0.2	13 ± 4			6.2	0.10	5.6 ± 1.5	5	33 ± 8
butylamine in H_2O[a]	2.8 ± 0.1	9.3 ± 2.1			3.3	0.11	3.4 ± 0.4	9	27 ± 4

[a] Quoted from refs 5, 6.

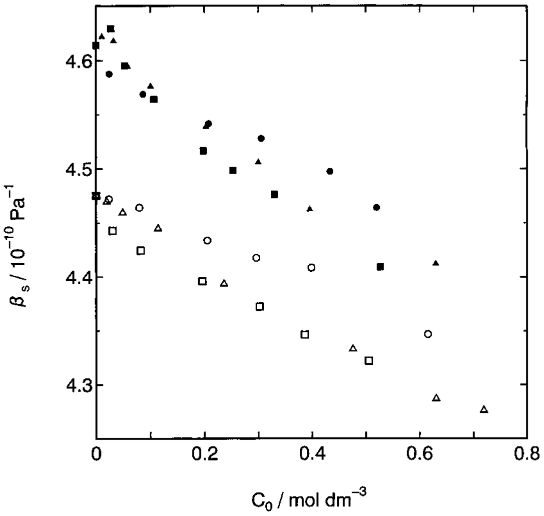

Figure 4. Concentration dependence of the adiabatic compressibility, β_s, for ethylamine (●), propylamine[5,6] (▲) and butylamine[5,6] (■) in D_2O, and ethylamine (○), propylamine[5,6] (△), and butylamine[5,6] (□) in H_2O.

that the diffusion-controlled rate constant decreases in the order butylamine, propylamine, and ethylamine, which is the same order of their hydrophobicity.

Second, the backward rate constant, k_{21}, is taken into account. As is seen in Table 2, the isotope effect is unity, which is contrary to those for propylamine and butylamine. This may also be related to the structures of the activated complex and the intermediate, which are not so stabilized when compared to those for other amines. The vibrational energy level for the intermediate in D_2O does not decrease as much as that in H_2O in the case of ethylamine.

If the reaction radius reflects the number of the solvent molecules in the intermediates, it is qualitatively interpreted that the forward and backward rate constants are dependent on the number of the solvent molecules in the intermediates because the structures of the activated complexes are considered to be close to the intermediates. However, the comparison of the reaction radius for the same solute in different solvents may be appropriate because they are calculated in the same condition as the steric factor. Then, it is also recognized that the isotope effect is less than unity for the forward rate constant and greater than unity for the backward rate constant when the number of the solvent molecules in the intermediate increases from H_2O to D_2O solvents (for the cases of propylamine and butylamine). When the number is similar, the opposite isotope is found (as observed for ethylamine). The number of solvent molecules in the intermediates may be dependent on the hydrophobicity of amine molecules because the reaction radius seems to decrease with the decreasing of the hydrocarbon.

Third, the results for the standard volume change of the reaction, ΔV, are discussed. The structural information is also available from the volume change of the reactions and many data have been accumulated.[24] However, little attention has been paid to the comparison of the ΔV values for hydrolysis in H_2O and those in D_2O. It is seen in Table 2 that the ΔV values tend to increase when the solvent is changed from H_2O to D_2O. It is interesting to notice that the isotope effect for ΔV, $\Delta V_H/\Delta V_D$, has a value similar to 0.77 ± 0.07 for these amines in this study. Considerably greater values for ΔV may indicate that the solvent molecules in the intermediate are still interacting with those in the bulk phase. Therefore, more hydrogen bonds in D_2O than in H_2O lead to greater ΔV values. The situation of the hydrogen bonds is also reflected in the results of the compressibility data. In all of the solutions, greater adiabatic compressibility values have been obtained in D_2O than in H_2O, as is seen in Figure 4.

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