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Ultrasonic Relaxation Measurements in Aqueous Solution and Molecular Orbital Calculation on Imipramine

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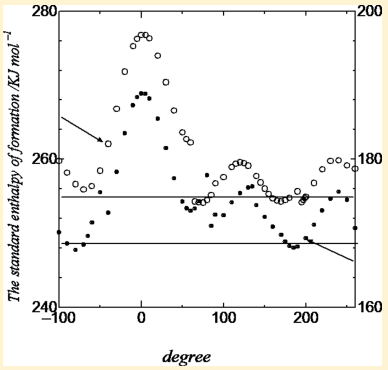
ABSTRACT: Ultrasonic absorption coefficients have been measured in aqueous solution of imipramine {3-(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)-*N*,*N*-dimethyl-propan-1-amine} in the frequency range of 0.8−220 MHz at 25 °C. The frequency dependences of the observed absorption was characterized by a Debye-type relaxational equation with two relaxation frequencies, although only one relaxation had been observed in aqueous solutions of the related molecule amitriptyline. Both of the relaxation frequencies in imipramine solutions were found to be independent of the solute concentration and the amplitudes of the relaxational absorptions increase linearly with increasing solute concentration. It was therefore concluded that these two relaxations are associated with unimolecular reactions, such as a structural change due to rotational motions of the bond in the specified group in the imipramine molecule. To analyze quantitatively the source of the relaxations, semiempirical molecular orbital methods have been applied to determine the standard enthalpy of formation of the imipramine molecule at various dihedral angles around the bonds in the alkylamine side chain. According to the results, only one rotational motion of carbon−carbon bond in the side chain was found to be appropriate and the three minima of the standard enthalpy of formation was obtained as a function of the rotational angle. At the three minimum positions, the values of the standard enthalpy of formation are almost the same. With the assumptions (a) that rotational motion is not accompanied by a volume change of the reaction and (b) that the standard free energy change is close to the difference in the values between the standard enthalpies of formation, the equilibrium constants for the rotational isomerization have been calculated to be near unity. Hence, the forward and backward rate constants of the isomerization reactions are nearly the same. If one assumes that there are two kinds of rotational motions in one bond of the molecule, one proceeds with a rate constant on the order of 10^8 s^{-1}, whereas the other with a rate constant on the order of 10^6 s^{-1}. The faster and slower processes are also distinguished by the height of the standard enthalpy of formation.



1. INTRODUCTION

In our previous study by experimental ultrasonic relaxation techniques and semiempirical molecular orbital calculation,[1] it was shown that the combination of these two methods gives very useful information for macroscopic and microscopic properties in solutions. We reported that the cause of an ultrasonic single relaxational absorption of amitriptyline aqueous solution in the megahertz frequency range is related to a rotational isomerization reaction of a specific bond in the molecule. The rate constants and the equilibrium constant for the isomerization process were determined from the ultrasonic relaxation parameters with the help of a standard enthalpies of formation. This enthalpy could be calculated independently by semiempirical molecular orbital methods. We considered that the above interpretation by the experimental ultrasonic relaxation method and the theoretical molecular orbital calculation should be also verified in additional system. The calculation by the semiempirical method may provide the absolute values of the standard enthalpy of formation of molecules, entropy, free energies, and so on. However, these thermodynamic parameters are only computationally accessible under the assumption that the target molecule locates in vacuum. Fortunately, the difference between the standard enthalpies of formation is sufficient for the estimation of the related parameters such as the equilibrium constant.

Imipramine is another tricyclic antidepressant belonging to the first generation of antidepressant drugs and its structure is quite similar to that of amitriptyline. Therefore, we have chosen this drug as a good test case for the applicability of the semiempirical molecular orbital calculations, to help clarify the ultrasonic relaxation results. This article is our second report using this dual approach. In this paper, we report experimental ultrasonic absorption data in the frequency range from 0.8 to 220 MHz and semiempirical molecular orbital calculations for the isomerization of the imipramine molecule. This isomerization has been considered to be caused by the rotational motion of a specific bond in the alkylamine side chain branch. The rate and thermodynamic constants have been estimated from the ultrasonic absorption data and the semiempirical molecular orbital calculations.

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2. EXPERIMENTAL SECTION

Chemicals. Imipramine was purchased from Wako Pure Chemical Co. Ltd. as the purest grade and was used without further purification. Sample solutions were prepared by weighing using distilled water filtered through a Milli-Q SP-TOC filter. Flasks with the sample solutions were filled with N_2 gas and they were kept in a refrigerator until use.

To define the positions of the chemical bonds in imipramine, the individual atoms are numbered as seen in Figure 1. This is useable when the calculation is performed by a personal computer.

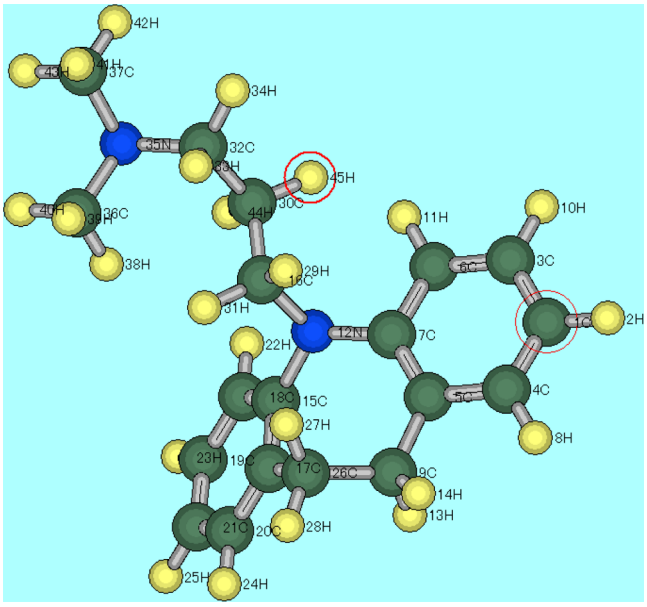

Figure 1. Structure of imipramine. The number for individual atoms is artificial. This is the result of the standard enthalpy of formation for the rotation of the 16C-30C bond.

Apparatus. The measurements of the ultrasonic absorption coefficients, α, were carried out by the resonance method in the frequency range from about 0.8 to 9 MHz. This method is very effective and convenient for the absorption measurement in the frequency range less than 10 MHz. This is because the quartz crystals with 3 and 5 MHz fundamental frequencies may provide a lot of the resonance signals. Also, the apparatus is appropriate for the sample solutions with relatively low absorption amplitude because the resonance signals are not significantly affected by the satellite signals near the resonance peaks. The pulse method in the range from 15 to 220 MHz was applied for the measurements and the apparatus using the pulse method can provide the absolute values of the absorption coefficient. Details about the absorption apparatus and the procedures for determining the absorption coefficient and sound velocity are described elsewhere.[2−4]

The solution densities were measured by a vibrating density meter (Anton Paar DMA 60/602). All of the measurements were performed at 25 °C.

Calculation. Semiempirical molecular orbital methods by AM1 (Austin Model 1) and PM3 (Modified Neglect of Diatomic Overlap Parametric Method 3) were applied to determine the standard enthalpy of formation of imipramine with the help of the free software package *Winmostar ver.4*. The calculation procedure was the same as that used for the study of amitriptyline. Gradual changes of the structure reflected by small dihedral angle change may provide smooth energy maps.

3. RESULTS AND DISCUSSION

Representative ultrasonic absorption spectra are shown in Figure 2. A single relaxational equation was applied and it was found to be inadequate for analyzing the observed spectra. The criteria used for fitting is discussed elsewhere,[5] resulting in the use of the double relaxational equation.

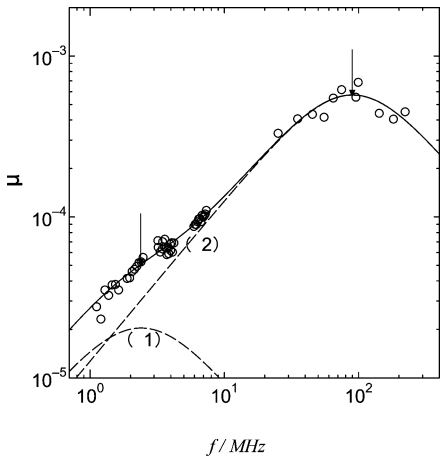

Figure 2. Representative ultrasonic absorption spectrum at 0.200 mol dm^{-3} imipramine at 25 °C. The solid curve represents the calculated values for double relaxational eq 1′, the dashed curves, (1) and (2) are the components of the individual single relaxation. The arrows indicate the position of the relaxation frequency.

$$\alpha/f^2 = A_1/[1 + (f/f_{r1})^2] + A_2/[1 + (f/f_{r2})^2] + B \quad (1)$$

or

$$\begin{aligned} \mu &= \alpha\lambda \\ &= (\alpha/f^2 - B)fc \\ &= A_1 fc/[1 + (f/f_{r1})^2] + A_2 fc/[1 + (f/f_{r2})^2] \end{aligned} \quad (1')$$

where f_{ri} is the relaxation frequency, A_i is the amplitude of the relaxational absorption, B is the background absorption, and μ or $\alpha\lambda$ is the absorption per wavelength. A nonlinear least-mean square computer program was used to calculate the most probable values and the probable errors for A_1, A_2, f_{r1}, f_{r2}, and B. The resulting ultrasonic relaxation parameters and the sound velocity, c, are listed in Table 1, along with the solution density, ρ. The probable errors are quite large because of the small amplitudes of the relaxational absorptions. As seen in Figure 2, the double relaxational equation fits well to the experimental data.

It has been reported that imipramine aggregates to form micelles.[6] The CMC's (critical micelle concentration) for imipramine at various temperatures is also determined[7] and the CMC at 25 °C is 0.0044 mol kg^{-1}. The CMC of 0.0057 mol dm^{-3} is also found at 25 °C by Junquera et al.[8] Further, Alam et al. have examined the effect of salt on micelle formation and the results are similar to those found for surfactants.[9] Ultrasonic relaxation methods have been widely used for dynamic studies of many surfactants.[10−12] The relaxational absorption due to aggregate (micelle) formation appears just above CMC or at concentrations slightly lower than CMC. The relaxation

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Table 1. Ultrasonic Parameters and Density in Aqueous Solution of Imipramine at 25 °C

C_0	f_{r1}	f_{r2}	A_1	A_2	B	c	ρ
mol dm^{-3}	MHz			10^{-15} s^{2}m^{-1}		m s^{-1}	kg m^{-3}
0.075	0.8 ± 1.7	70 ± 5	28 ± 104	5.8 ± 0.3	20.0 ± 0.1	1504.0 ± 0.9	1000.4
0.100	1.6 ± 1.6	99 ± 13	15 ± 20	5.0 ± 0.3	20.7 ± 0.2	1507.0 ± 0.8	1000.9
0.200	2.4 ± 1.0	90 ± 5	11 ± 6	8.4 ± 0.3	23.3 ± 0.1	1515.4 ± 0.8	1004.9
0.250	4.0 ± 2.0	147 ± 10	8.7 ± 4.8	13.8 ± 0.4	22.6 ± 0.6	1522.4 ± 1.0	1008.2
0.266	1.2 ± 0.5	98 ± 5	48 ± 28	12.8 ± 0.3	26.2 ± 0.2	1524.5 ± 1.1	1008.9
0.300	1.5 ± 0.6	98 ± 5	36 ± 20	12.8 ± 0.3	26.2 ± 0.2		

frequency increases with surfactant concentration. Even if the number of aggregate is small, the trend of appearance of the relaxational absorption is similar.[13] The relaxational absorption in aqueous solution of imipramine is observed above 0.075 mol dm^{-3}. The concentration dependences of the relaxation frequencies are shown in Figure 3 and it reveals that both of

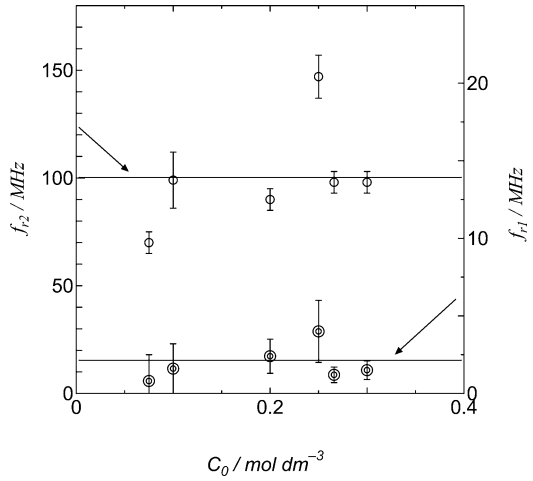

Figure 3. Concentration dependences of the relaxation frequency at 25 °C. ◎, the lower relaxation frequency, f_{r1}; and ○, the higher relaxation frequency, f_{r2}.

the relaxation frequencies are independent of the analytical concentration, C_0. The amplitudes of the relaxational absorption, A_i, display linear increase with increasing concentration as is seen in Figure 4. From these results, it is concluded that the observed ultrasonic relaxation is not associated with the aggregate.

The concentration dependences of the observed ultrasonic relaxation frequency and the amplitude of the relaxational absorption allowed us to predict that the observed relaxations are due to perturbations of the chemical equilibria associated with unimolecular reactions according to the following two step unimolecular reaction:

$$\mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{B} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{C} \tag{2}$$

where k_i's are the rate constants. The analytical interpretation of the ultrasonic relaxations is clearly defined by Eigen and De Maeyer.[14] The same analysis has been applied to the perturbation of the above chemical equilibria. As can be seen in Table 1, the lower relaxation frequencies are located at around 1 MHz, whereas the higher ones are at around 100 MHz. Hence, the equations for the two relaxation processes are derived as their approximate forms and they are expressed as:

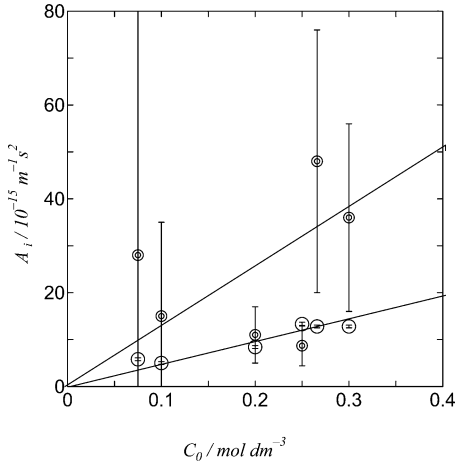

Figure 4. Concentration dependences of the amplitude of the relaxational absorption at 25 °C. ◎, the amplitude for the lower relaxation, A_1; and ○, the amplitude for the higher relaxation, A_2.

$$2\pi f_{r1} = \tau_1^{-1} \cong k_1 + k_{-1} \tag{3}$$

$$2\pi f_{r2} = \tau_2^{-1} \cong k_2 + k_{-2} - (k_2 k_{-2})/(k_1 + k_2) \tag{4}$$

where f_{r1} is the higher relaxation frequency and f_{r2} is the lower one and τ_1 and τ_2 are the corresponding relaxation times. Although the experimental concentration independent results for f_{ri} may match with eqs 3 and 4, the rate constants can not be determined at this stage.

Another parameter obtained by the ultrasonic absorption measurement is a maximum absorption per wavelength, μ_{mi}, which is generally given by the equation.

$$\mu_{mi} = A_i f_{ri} c/2 = [\pi\rho c^2 \Gamma_i/(RT)] \, [\Delta V_i - \alpha_p^{\infty} \Delta H_i/(\rho C_p^{\infty})]^2 \tag{5}$$

where R is the gas constant, T is the absolute temperature, ΔV_i is the volume change related to the reaction under consideration, α_p^{∞} is the thermal expansion coefficient at infinite frequency, ΔH_i is the related enthalpy change, and C_p^{∞} is the specific heat at constant pressure at infinite frequency. Γ_i is the concentration term which depends upon the reaction type. Eqs 6 and 7 are derived for the perturbation of the chemical equilibria, eq 2, as:

$$\Gamma_1 = C_0 K_{12} K^{-1} (1 - K_{12} K_{23} K^{-1}) K_{23} / [2 - K_{12}(K_{23} - 1) K^{-1}] \tag{6}$$

$$\Gamma_2 = C_0 \{K_{12} K_{23} K^{-1} (1 - K_{12} K_{23} K^{-1})\} \{1 + K_{12}^{-1}\} / [(2 - K_{12} K_{23} K^{-1})(1 + K_{23})] \tag{7}$$

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where K_{12}, K_{23} and K are defined as $K_{12} = k_{-1}/k_1$, $K_{23} = k_{-2}/k_2$ and K = $K_{12}K_{23} + K_{23} + 1$. ΔV_i, and ΔH_i in eq 5 are approximated to be constant and the contributions of ρ, c, α_p^∞, and C_p^∞ to eq 5 are considered to be negligible because their concentration dependences are not so significant. From these results, the amplitude of the ultrasonic relaxation, A_i, may increase linearly with respect to the analytical concentration because the relaxation frequencies are independent of the analytical concentration. The plots in Figure 4 support the above approach.

One of the reactions for unimolecular processes is the conformational change of the tricyclic hydrophobic moiety of imipramine (three ring core). This may be excluded because the structure is rigid and it has not special substituent,[15] which could undergo a conformational change except the branch bonded to 12N in Figure 1.

To a good approximation, the volume change of the reaction is negligibly small when the reaction is associated with rotational isomerization of the imipramine molecule. However, the determination of enthalpy change of the reaction from the absorption data is not appropriate because the equilibrium constants, K_{12} and K_{23}, in eqs 6 and 7 are not known.

Instead, an estimation of the equilibrium constants is carried out by means of a computer calculation. In our previous report,[1] we successfully applied semiempirical molecular orbital methods to calculate the standard enthalpy change of the isomerization reaction using a personal computer. The molecular orbital package (Winmostar) has been used to calculate the standard enthalpy of formation of the imipramine molecule. The package has the AM1 (Austin Model 1) and PM3 (Modified Neglect of Diatomic Overlap Parametric Method 3) methods. The calculation is carried out as follows: (1) The most stable molecular structure is searched to provide a convergent value of the standard enthalpy of formation. (2) Possible conformations or rotations in the molecule were examined using conventional ball-and-stick molecular models. (3) The dihedral angle, which is focused on the alkylamine side chain was fixed and the convergent standard enthalpy of formation is calculated. Next, the dihedral angle is slightly changed and is fixed in the computer. This procedure is repeated for 360 degree of the rotation. (3-1) Rotations of the 35N-32C and 30C-32C bonds (Figure 1), were tested. However, the smooth energy map was not obtained or impossible double bond was created in the calculated molecular structure. (3-2) Also, rotation around the 12N-16C bond was not suitable because the hydrogen atoms at 30C get close to the ring core. (3-3) These considerations only left 360 degree rotation around the 30C-16C bond. The calculated standard enthalpy of formation is shown in Figure 5. The trends of the given by AM1 and PM3 are similar although the absolute values of the standard enthalpy of formation are different. Three minima are found in both calculations and the minimum positions and the amplitudes of the energy are similar to each other. However, the values of the enthalpy at the minimum positions seem to indicate little difference in both AM1 and PM3 plots. It is difficult to calculate the difference of the standard enthalpies of formation, which correspond to the enthalpy change of the isomerization due to the rotational motion of imipramine. The equilibrium constant is related to the standard free energy change of the reaction, ΔG, as $K = \exp(-\Delta G/RT)$. ΔG is related to the standard enthalpy change, ΔH, and the standard entropy change, ΔS, as $\Delta G = \Delta H - T\Delta S$. The entropy change for the rotational motion of isomers

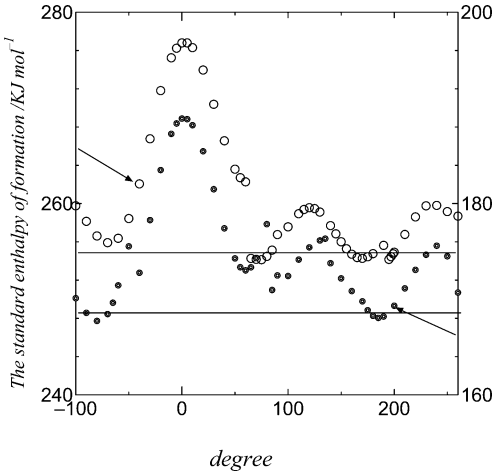

Figure 5. Standard enthalpy of formation of imipramine at various angles for the rotation of 16C-30C in Figure 1. ◎, the results by PM3 with scale on left; and ○, those by AM1 with scale on right.

is well approximated to be constant or very small[15] meaning that the contribution of the entropy change to the free energy change is not dominant. Therefore, it can be assumed that the free energy change is approximated by the change of enthalpy, ΔH. The small enthalpy change calculated by the semiempirical molecular orbital methods falls into the very small standard free energy change, meaning that the equilibrium constants, K_{12} and K_{23}, can be considered to be near unity. Therefore, the faster rate constants, k_1 and k_{-1} are almost the same, and also $k_2 \cong k_{-2}$. These conditions are applied to eqs 3 and 4 and the estimated rate constants are $k_1 \cong k_{-1} \cong 6 \times 10^8$ s^{-1} and $k_2 \cong k_{-2} \cong 6 \times 10^6$ s^{-1}.

It is interesting to compare the present results with those in aqueous solution of amitriptyline. In two molecules, the rotating bond is quite similar (30C-16C for imipramine in Figure 1 and 30C-33C for amitriptyline in reference.[1] Slight differences of the structures cause the different rotating styles. Imipramine has to go over the two potentials for one rotation, whereas the bond in amitriptyline rotates smoothly. The faster rotational rate in imipramine is close to the rate of amitriptyline and it is of the order of 10^8 s^{-1}. The slower rate in imipramine may be due to the higher potential energy (higher standard enthalpy of formation).

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Notes

The authors declare no competing financial interest.

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