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Solvent Effects on the Spin-Lattice Relaxation Times and Chemical Shifts of *N*-Methylacetamide and *N*,*N*-Dimethylacetamide in Hydrogen Bonding Solvents

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The proton spin-lattice relaxation and the chemical shift were studied in *N*-methylacetamide (NMA) and *N*,*N*-dimethylacetamide (DMA) in *p*-dioxane and chloroform. In the *p*-dioxane solution, it has been found that the self-association of NMA does affect its spin-lattice relaxation, whereas the amide-solvent association does not affect it entirely. This was interpreted in terms of the lifetime of the inter-amide ($\simeq 10^{-11}$—10^{-12} sec) and the amide-solvent association (much shorter than 10^{-11}—10^{-12} sec). On the other hand, the effect of the amide-solvent association on the spin-lattice relaxation is pronounced in chloroform, as is the effect of the self-association of NMA. The inter-amide interaction which leads the double-bond character of DMA to be more stable was not reflected distinctly in the concentration dependence of the spin-lattice relaxation times of DMA.

The inter-molecular interactions and self-association phenomena of amides in solutions have been the subjects of a considerable number of experimental and theoretical discussions, and have been studied quantitatively by using IR, the NMR-chemical shift, the thermodynamic technique, *etc.*[1]

In our previous paper,[2] we studied the proton spin-lattice relaxation and chemical shift of *N*-methylacetamide (NMA) and *N*,*N*-dimethylacetamide (DMA) in aqueous (D_2O) and non-polar (CCl_4) environments, and pointed out that, in addition to the chemical shift, the spin-lattice relaxation time (T_1) measurements are useful in providing basic information for understanding the molecular motion, the non-equilibrium properties, and the inter-amide interactions.

In this paper, we will report on T_1 and chemical-shift measurements of NMA and DMA as well as of solvent molecules, *p*-dioxane, and chloroform, which have been well known to act as hydrogen-bonding proton acceptors and donors respectively. We will discuss the molecular motion and the inter-amide and amide-solvent interactions in these solutions on the basis of our experimental results on the T_1's and chemical shifts of the protons of solute and solvent molecules. Moreover by comparing the results of the NMA solutions with those of the DMA solutions, further information on the peptide-bond character will be obtained.

It is useful to compare the results of the T_1's with those of the chemical shifts on amide solutions in order to understand the hydrogen-bonding phenomena in detail, for the former depends on non-equilibrium properties, whereas the latter depends on equilibrium properties.

Experimental

Materials. The NMA, DMA, *p*-dioxane, and chloroform were reagent-grade samples purchased from the Tokyo Kasei Co., Ltd. The chloroform-*d* and *p*-dioxane-d_8 were provided by E. Merck A G., Darmstadt. The atmospheric oxygen dissolved in the samples was carefully removed by several freeze-pump-thaw cycles in a NMR tube; then, under a vacuum, the sample tube was sealed off.

NMR Measurements. The NMR instrument used was a JNM-C-60H spectrometer operated at 60MHz; the measurements of T_1 were performed at 25 ± 1°C by adiavatic-rapid-passage or saturation-recovery methods. The experimental errors were smaller than $\pm5\%$ in every case. Two T_1's of the non-equivalent *N*-methyl protons of DMA were in agreement with each other within the range of experimental errors, so we adopted the T_1 of *N*-methyl as the average value. The chemical shifts were measured at 25 ± 1°C by the usual side-band-technique, using tetramethylsilane as the internal reference. Other experimental details appeared in the previous paper.

Results and Discussion

Before discussing the results of the spin-lattice relaxation and chamical-shift measurements, we should like to mention the method of analyzing the data. The obserbed spin-lattice relaxation time, $(T_1)_{\text{obs}}$, is expressed as follows for solute and solvent molecules respectively, taking all the possible contributions into account:

$$(T_1^{-1})^{\text{solute}}_{\text{obs}} = (T_1^{-1})_{\text{intra}} + (T_1^{-1})^{\text{solute-solute}}_{\text{inter}} + (T_1^{-1})^{\text{solute-solvent}}_{\text{inter}} \qquad (1)$$

$$(T_1^{-1})^{\text{solvent}}_{\text{obs}} = (T_1^{-1})_{\text{intra}} + (T_1^{-1})^{\text{solvent-solvent}}_{\text{inter}} + (T_1^{-1})^{\text{solvent-solute}}_{\text{inter}} \qquad (2)$$

where $(T_1^{-1})_{\text{intra}}$ and $(T_1^{-1})^{\text{solute-solute}}_{\text{inter}}$ represent the intramolecular and the solute-solute intermolecular magnetic dipolar contributions respectively, and where $(T_1^{-1})^{\text{solute-solvent}}_{\text{inter}}$ refers to the solute-solvent intermolecular contribution, which indicates the magnetic effects of the solvent protons on the spin-lattice relaxation of solute protons. Deuteron and chlorine are considered to contribute negligibly to the relaxation of the protons because of their small magnetogyric ratios. Each term in Eq. (2) represents a similar contribution.

$(T_1^{-1})_{\text{intra}}$ and $(T_1^{-1})_{\text{inter}}$ depend on the rotational and the relative translational motions of the molecules. $(T_1^{-1})_{\text{intra}}$ can be expressed as Eq. (3) in terms of

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[1] For example, S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York (1954), Chap. 6; G. C. Pimentel and A. L. McClellan "The Hydrogen Bond," W. H. Freeman and Company, San Francisco, California (1960), Chap. 3.

[2] K. Sato and A. Nishioka, This Bulletin, **44**, 52, (1971).

the interprotonic distance, r_{ij}, and the rotational correlation time, τ_c: [3,4]

$$(T_1^{-1})_{\text{intra}} = \frac{3}{2}\hbar^2\gamma^4\sum_j\langle r_{ij}^{-6}\rangle\cdot\tau_c \qquad (3)$$

where $\hbar$ is Plank's constant divided by 2π, and where γ is the magnetogyric ratio of the proton. We estimated the $(T_1^{-1})_{\text{intra}}$ of NMA and DMA by the extrapolation procedure to infinite dilution, and calculated τ_c by Eq. (3), taking into account the molecular geometries of NMA and DMA.[5]

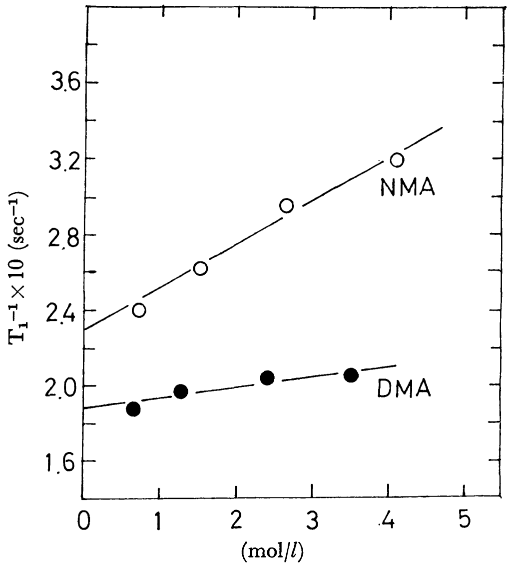

Fig. 1. Relaxation rate of methyl protons of amides *vs.* concentration of NMA (○) and DMA (●); *p*-dioxane solutions.

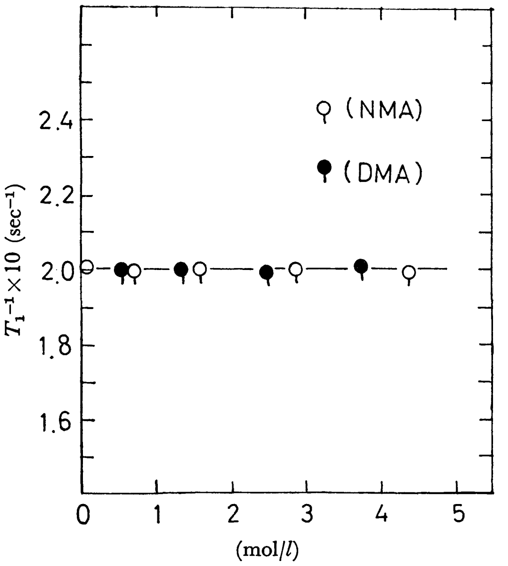

Fig. 2. Relaxation rate of solvent protons *vs.* solute concentration; *p*-dioxane solutions.
solute; NMA- ○, DMA- ●

p-*Dioxane Solution.* The concentration dependences of the spin-lattice relaxation rates, T_1^{-1}, of NMA, DMA, and the solvent are shown in Figs. 1 and 2 respectively. The T_1 values of the *C*-methyl protons are almost equal to those of *N*-methyl in both amides within the limits of experimental error. From the observed linear plot of T_1^{-1} *vs.* the concentration of the amide, we can extrapolate the results to infinite dilution. The T_1's of the solvent are almost independent of the concentration of the amide. This means that $(T_1^{-1})^{\text{solvent-solute}}_{\text{inter}}\simeq 0$ and $(T_1^{-1})_{\text{intra}}$, $(T_1^{-1})^{\text{solvent-solvent}}_{\text{inter}}$ are not affected by the amide-solvent interactions. It is interesting to note that the hydrogen bonding with NMA does not affect the spin-lattice relaxation of *p*-dioxane.

The spin-lattice relaxation is governed by the microscopic molecular motions and the ratio of the correlation times of the motion to the lifetime of molecular association. Recently, Anderson and Fryer[6,7] and Marshall[8] have discussed theoretically and experimentally the effect of molecular association on the spin-lattice relaxation, and concluded that, if the lifetime of the associated molecules moving as a unit is longer than the correlation times of motion (for most liquids, the correlation times are of the order of 10^{-11}—10^{-12} sec), the effect of association is pronounced, whereas the effect is small if the lifetime is shorter. In view of this, the lifetime of the hydrogen bonding between NMA and *p*-dioxane is probably much shorter than 10^{-11}—10^{-12} sec. We have previously studied the effects of the molecular association on the spin-lattice relaxation in mixtures of chloroform and proton-acceptor solvents, such as dimethyl sulfoxide, pyridine, acetone, and benzene, and shown that the association with a larger association constant does more remarkably affect the spin-lattice relaxation of chloroform, while the weak association has no effect at all.[9] Thus, it is considered that the association between NMA and *p*-dioxane through the hydrogen bonding is very weak and that the association constant may be small.

LaPlanche, Thompson, and Rogers[10] have studied theoretically the chain-association equilibria based on the model that the solute molecules form chain-like polymers through self-association, and that either the solvent molecules associate with the solute or do not. They have also applied the theory to the chemical-shift measurements of *N*-monosubstituted amides in solutions. From the equilibrium constants found for *N*-isopropylacetamide in *p*-dioxane and chloroform, they have concluded that chloroform and *p*-dioxane

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3) N. Bloembergen, E. M. Purcell, and R. V. Pound, *Phys. Rev.*, **73**, 679 (1948).

4) A. Abragam, "The Principle of Nuclear Magnetism," Clarendon Press, Oxford (1961), Chap. 8.

5) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca (1960), Chap. 8, p. 281. As in previous paper, we assumed that the geometry of DMA is the same as that of NMA except for the substituted *N*-methyl group, and internal rotation of methyl is almost free.

6) J. E. Anderson and P. A. Fryer, *J. Chem. Phys.*, **50**, 3784, (1969).

7) J. E. Anderson, *ibid.*, **51**, 3578 (1969).

8) A. G. Marshall, *ibid.*, **52**, 2527 (1970).

9) K. Sato and A. Nishioka, This Bulletin, **44**, 1506, (1971).

10) L. A. LaPlanche, H. B. Thompson, and M. T. Rogers, *J. Phys. Chem.*, **69**, 1482 (1965).

Table 1. Intramolecular relaxation times and the rotational correlation times of NMA and DMA estimated from extrapolating to infinite dilution

solvent	NMA observed protons	NMA $(T_1)_{intra}$	NMA $\tau_c \times 10^{12}$	DMA observed protons	DMA $(T_1)_{intra}$	DMA $\tau_c \times 10^{12}$
$CDCl_3$	$\overset{O}{\overset{\|}{-C}}-CH_3$	6.3_0 sec	2.8_5 sec	$\overset{O}{\overset{\|}{-C}}-CH_3$	7.1_1 sec	2.4_5 sec
	$\overset{\|}{-N}-CH_3$	6.3_0	2.7_6	$-N\langle(CH_3)_2$	7.1_1	2.4_0
$C_4H_8O_2$	$\overset{O}{\overset{\|}{-C}}-CH_3$	4.2_7	4.1_4	$\overset{O}{\overset{\|}{-C}}-CH_3$	5.4_2	$3{\cdot}2_9$
	$\overset{\|}{-N}-CH_3$	4.2_7	4.0_5	$-N\langle(CH_3)_2$	5.4_2	3.2_3

compete with approximately the same efficiency for the hydrogen bonding of *N*-isopropylacetamide. They have also studied NMA in chloroform, and found that chloroform associates with NMA; however, they have not examined it in *p*-dioxane. There is no guarantee that their conclusion about *N*-isopropylacetamide mentioned above holds also in the case of NMA in *p*-dioxane. Moreover, we must give attention to the fact that they measured the chemical shift on the basis of an internal reference. It has been established that the resonance frequncies of internal-reference compounds are often considerably influenced by solvent effects.[11] In order to discuss the results in detail and quantitatively, it will be necessary to measure the chemical shifts on the basis of an external reference and to correct for differences in the bulk diamagnetic susceptibility between the sample and the reference compound. It seems necessary to reexamine this problem over a wide range of experimental conditions for both the T_1 and the chemical shift.

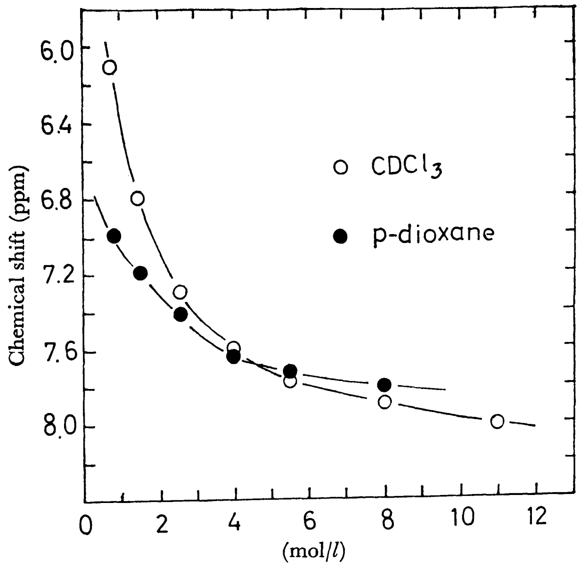

Fig. 3. Concentration dependence of N–H proton chemical shift of NMA in deuteriochloroform (○) and *p*-dioxane (●). Chemical shift were measured downfield from internal TMS.

From the experimental facts mentioned above, that $(T_1^{-1})^{\text{solvent-solute}}_{\text{inter}} \simeq 0$, and that the amide-solvent association does not affect the spin-lattice relaxation of *p*-dioxane, it can reasonably be assumed that the T_1's of amide protons are also not affected by *p*-dioxane. We measured the T_1 of NMA in *p*-dioxane-d_8(2.7 mol/*l* of NMA) and found that $T_1^{-1}=2.8\times10^{-1}(\text{sec}^{-1})$. This value is almost equal to that in *p*-dioxane, and the assumption that $(T_1^{-1})^{\text{solute-solvent}}_{\text{inter}} \simeq 0$ holds. Therefore, the values extrapolated to infinite dilution are identical to the $(T_1^{-1})_{intra}$ of amides. The values of $(T_1)_{intra}$ and τ_c of NMA and DMA are shown in Table 1. The τ_c's of *C*-methyl and *N*-methyl protons in the same molecule are almost equal for both NMA and DMA, but the values of NMA are longer than those of DMA by a factor of about 1.2—1.3. We consider that this is the effect of the self-association of NMA in solutions. Klotz and Fransen[12] also con-

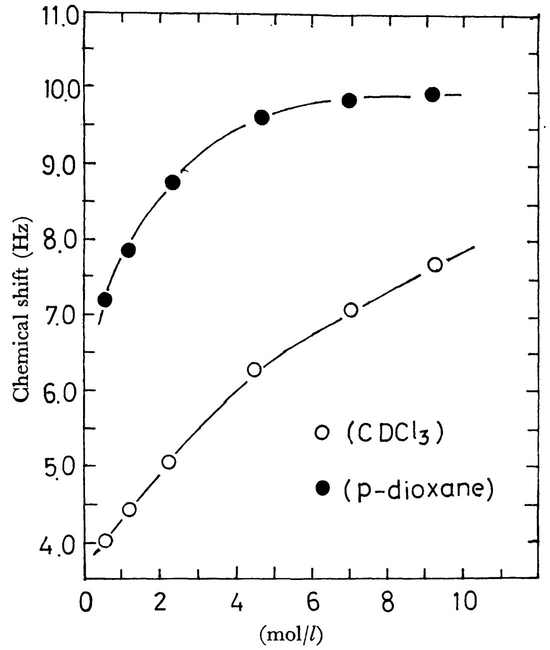

Fig. 4. Concentration dependence of the chemical shift between the two N–CH_3 signals of DMA in deuteriochloroform (○) and *p*-dioxane (●).

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[11] J. W. Emsley, J. Feeny, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford (1965), Chap. 7.

[12] I. M. Klotz and J. S. Fransen, *J. Amer. Chem. Soc.*, **84**, 3461 (1962).

cluded, on the basis of IR measurements, that, in *p*-dioxane, the self-association of NMA is appreciable at moderate concentrations. The low-field shift of the N–H proton with an increase in the concentration of NMA is considered to support the self-association of NMA in *p*-dioxane (Fig. 3).

The τ_c's of NMA estimated in the present study are considered to characterize the rotational motions of NMA restricted slightly in a weakly-associated chain. Moreover, it is concluded that the lifetime of the inter-amide hydrogen bonding may be of the order of 10^{-11}—10^{-12} sec. The larger concentration dependence of the T_1^{-1} of NMA than that of DMA also means that the rotational and translational mobilities of NMA are reduced through the hydrogen bonding.

In Fig. 4, the concentration dependence of the chemical shift between the two *N*-methyl protons of DMA is shown in *p*-dioxane as well as in chloroform. The origin of the nonequivalence of the two *N*-methyl groups has been understood to be due to the double-bond character of the central C–N linkage.[13] The increase in the chemical shift with an increase in the concentration of amide has been considered to be due to the inter-amide interaction, which leads the double-bond character to be more stable.[14–16] This inter-amide interaction has no appreciable effect on the concentration dependence of T_1, which is almost linear over the experimental range of the concentrations of amide. In carbon tetrachloride, remarkable effects of the inter-amide interaction on T_1 of DMA have been observed, and the concentration dependence of T_1 at moderate concentrations differs from that at dilute concentrations.[2] The absence of the effects of the inter-amide interaction on T_1 is considered to be due to the fact that, in *p*-dioxane, the lifetime of the inter-amide interaction is shorter than that in carbon tetrachloride. The chemical shift between two *N*-methyl protons in *p*-dioxane is smaller than in carbon tetrachloride; we consider this also to be due to the weak inter-amide interaction in *p*-dioxane. The slight increase in the relaxation rate with an increase in the concentration of amide may be the result of the increase in the spin-densities of the solutions.

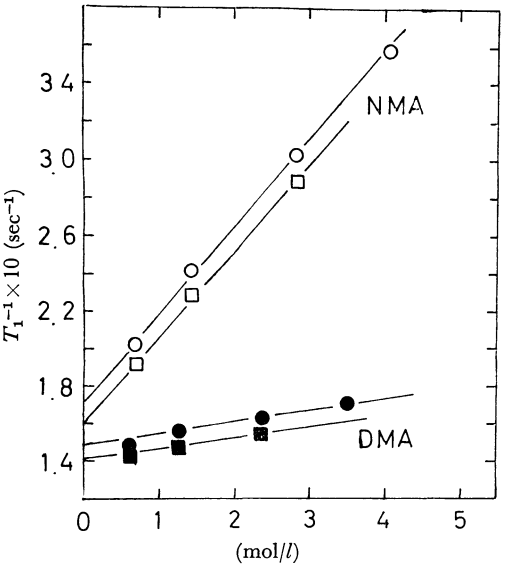

Fig. 5. Relaxation rate of methyl protons of amides *vs.* concentration of NMA (○-chloroform solutions, □-deuteriochroform solutions) and DMA (●-chloroform solutions, ■-deuteriochloroform solutions).

Chloroform Solution. The concentration dependences of the T_1^{-1}'s of NMA and DMA are shown in Fig. 5. As in the case of *p*-dioxane solutions, the T_1's of *C*-methyl and *N*-methyl protons in the same molecule are identical with each other, and the plot of T_1^{-1} *vs.* the concentration of the amide is also linear. By extrapolation in chloroform-*d* solutions, we obtained $(T_1)_{\text{intra}}$ and calculated the values τ_c of both amides (Table 1). The fact that the τ_c's of NMA are longer than those of DMA by a factor of about 1.2, and the large concentration dependence of T_1^{-1} of NMA are attributable to the self-association. Moreover, the lifetime of the association is considered to be almost identical to that in the *p*-dioxane solution. The effect of the association on the N–H proton chemical shift can easily be seen; it moves to a low field with an increase in the concentration of amide (Fig. 3).

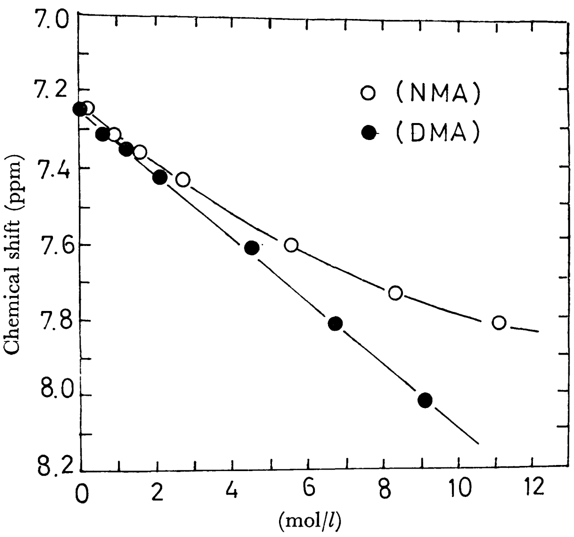

Fig. 6. Chemical shift of chloroform proton *vs.* solute concentration. solute; NMA-○, DMA-●. Chemical shift were measured downfield from internal TMS.

The chemical shifts of the chloroform proton depend upon the concentrations of the amides, as is shown in Fig. 6. A linear relation is observed in the DMA solution, but not in the NMA solution. The low-field shift of the chloroform proton is caused by the formation of hydrogen bonding with amides and the magnetic anisotropy effect due to the carbonyl group. The linear low-field shift in the DMA solution may be the result of the approximate 1 : 1 amide-solvent association. On the other hand, the smaller and non-linear change in the NMA solution suggests that the inter-amide hydrogen bonding becomes predominant over the amide-solvent hydrogen bonding with an increase

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[13] Ref. 11, Chap. 9.

[14] M. Rabinovitz and A. Pines, *J. Chem. Soc. B*, **1968**, 1110.

[15] M. Rabinovitz and A. Pines, *J. Amer. Chem. Soc.*, **91**, 1585 (1969).

[16] R. C. Neuman, Jr., W. R. Woolfenden, and V. Jonas, *J. Phys. Chem.*, **73**, 3177 (1969).

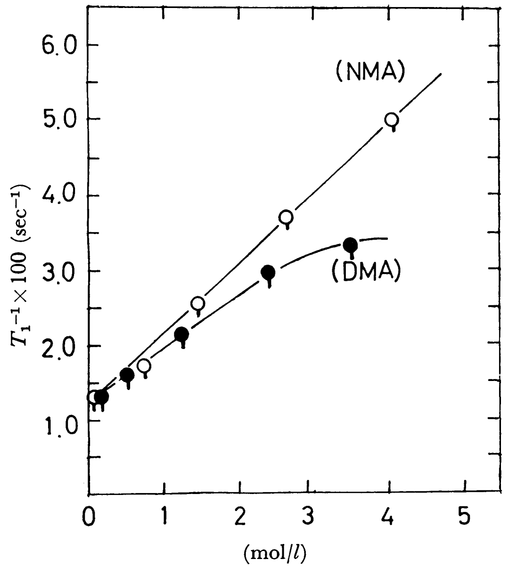

Fig. 7. Relaxation rate of solvent proton *vs.* solute concentration; chloroform solutions. solute; NMA-○, DMA-●

in the concentration and, consequently, decreases the fraction of the solvent molecules participating in the hydrogen bonding with amide.

In Fig. 7 the dependence of T_1^{-1} of the chloroform proton on the concentrations of the amides is shown. The spin-lattice relaxation of the solvent is considerably affected by the presence of amides; this is strikingly different from the case with *p*-dioxane solutions. This pronounced effect of amides can be interpreted in terms of the amide-solvent association, whose lifetime is almost equal to or longer than 10^{-11}—10^{-12} sec. As has been mentioned above, in the NMA solution the fraction of solvents participating in the hydrogen bonding with amides is considered to be smaller than in the DMA solution. Nevertheless, the effect of the NMA on the T_1's of the chloroform proton is more remarkable. In the NMA solution, chloroform associates with amide and breaks up the self-associated chain to some degree, and it must interact with the terminal carbonyl group of the broken chain. The molecular motion of chloroform associating with the chain-terminal is restricted to a greater degree than that in the DMA solution. Thus, the effect of the hydrogen bonding with NMA on the spin-lattice relaxation of the chloroform proton is considered to be more pronounced in spite of the samller fraction of associated chloroform molecules. As in the case of the *p*-dioxane solution of DMA, the effect of the inter-amide interaction of DMA which leads the double-bond character to be more stable is not observable distinctly over the range of experimental concentrations.

In our previous paper, we have estimated the τ_c's of NMA and DMA in D_2O solutions: $\tau_c=2.5\times10^{-12}$ sec. These values are almost equal to those in chloroform solutions. The BPP theory predicts $\tau_c=4\pi\eta a^3/3\boldsymbol{kT}$ for the rigid molecules, where η and a represent solution viscosity and the radius of a spherical molecule respectively.[3)] The solution viscosities of D_2O solutions are larger by a factor of about 2 than those of chloroform solutions;[17)] therefore, according to this theory, the τ_c's in chloroform must be shorter than those in D_2O. This can be explained by considering that, in chloroform, the molecular motion of amides is reduced through the amide-solvent association and the self-association of amide (NMA), which may in turn lead the micro-viscosities of the solutions to be higher.

[17)] unpublished data.