Research Article

Molecular Self-Assembling of *N*-Methylacetamide in Solvents

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The self-association of *N*-methylacetamide (NMA), which is one of the most simple compound having a peptide bond, in various solvents such as carbon tetrachloride (CCl_4), chloroform, dichloromethane, and acetonitrile was studied through the near-infrared (NIR) spectroscopic observation at various temperatures and concentrations. An analysis assuming a successive association processes for the NMA molecules was applied to the sharp 1470-nm band (the first-overtone band of NH stretching vibration mode attributed to free NH group of NMA monomer and partly to the free, terminal NH group of NMA aggregate); the mean association number for NMA in CCl_4 increases with increasing concentration and decreases with increasing temperature. Comparisons of the association number of NMA in various solvents indicate that the degree of association is in the following order: $\text{CCl}_4 \gg \text{chloroform} \approx \text{dichloromethane} > \text{acetonitrile}$. Interestingly, the association number of NMA in CCl_4 is thought to be larger than that in its pure liquid.

1. Introduction

Near-infrared (NIR) spectroscopy is a useful analytical method for practical materials [1] and has been applied to various industrial and agricultural problems [2, 3]. The applications, however, have been mostly based on mathematical treatments of the NIR spectra but not on analytical knowledge which the NIR spectra should give. Its applicants to basic chemical problems are still very limited probably because detailed spectral analyses of standard compounds have not been well carried out. On the other hand, NIR spectroscopy has such important technical merits that a liquid quartz cell with the path length of 10 mm or more can be used, remote spectroscopy is applicable, and so on. The use of the long-path-length cell makes us able to obtain the more reliable results especially in concentration. To make full use of the advantages, it is absolutely important to utilize the analytical information which NIR absorptions possess.

By the way, hydrogen-bonding interactions are now known to be important in determining the structural properties of proteins. In particular, hydrogen bonding between the carboxyl oxygen and amide hydrogen atoms in the protein backbone help to stabilize the β -sheet and other motifs [4]. Among the forces that contribute to the stabilization of configuration of protein molecules in solution, intramolecular

hydrogen bonds have often been assigned a key role. Furthermore, hydrogen bonding between peptide groups has indeed been definitely demonstrated in proteins and polypeptides, as well as in model amino acids and small peptides, in the solid state. Hydrogen-bonding interactions play an essential role in protein-ligand interactions and in the mechanism of peptide- and protein-mediated reactions [5–7].

One of the simple protein model peptide system is *N*-methylacetamide (NMA). Therefore, NMA has been extensively studied by a variety of experimental and theoretical methods [8–19]. However, uncertainties still exist concerning the effect of hydrogen bonding on its structure and conformation. In the present study, we measured the NIR spectroscopy of NMA in various solvents such as CCl_4 , CHCl_3 , CH_2Cl_2 , and CH_3CN and calculated the aggregation number by assuming a successive association processes for NMA molecules.

2. Experimental

2.1. Materials. The sample of *N*-methylacetamide (NMA, its purity greater than 99.8%, Tokyo Kasei Kougyou Co. Ltd.) was used after distillation. Sample of NMA- d_1 was synthesized by using the deuterium-proton exchange reaction, by stirring the NMA sample in a large excess amount

FIGURE 1: NIR spectrum of NMA in CCl_4 (0.8 mol dm^{-3}) at 30°C .

of CH_3OD (ten times amount to the NMA sample) at 40°C , and then by the distillation of the alcohol. This deuterium-proton exchange process was repeated 7 times. Its deuterium content was determined to be 98% by NIR spectroscopic observation. Carbon-disulfide-free sample of carbon tetrachloride (CCl_4 , its purity greater than 99.5%, Nakaraitesk Co. Ltd.) was dried by 7 hrs refluxing over P_2O_5 and distilled under an atmosphere of dried nitrogen. The samples of dichloromethane and chloroform (CH_2Cl_2 and CHCl_3 , their purities greater than 99%, Wako Junyaku Kogyo Co. Ltd.) were used after distillation also under nitrogen gas atmosphere. The sample of acetonitrile (CH_3CN , its purity greater than 99.9%, Wako Junyaku Kogyo Co. Ltd.) was used without further purification.

2.2. Near-Infrared Spectropic Measurement. The NIR spectra were measured at a resolution of 1.0 nm on a Hitachi-3500 spectrophotometer. A quartz cell having 5.0 or 10 mm path length was used. A Hitachi temperature-regulated cell holder (No. 131-0040) was used to maintain the temperature of the sample within $\pm 0.05^\circ\text{C}$. Temperature control of the thermostat water was carried out with a temperature controller (Yamato-Komatsu colonics circulator model CTE 32).

2.3. Density Measurement. The densities for the samples of pure liquid and the CCl_4 solution of NMA were measured on a vibration-type densimeter (Anton Paar Model DMA 58) over temperature range of $10.0\text{--}65.0 \pm 0.05^\circ\text{C}$. Degassed pure water was used for calibrating the densimeter. The absorbances were corrected for variation in the number of molecules in the light path due to the density change with temperature.

3. Results and Discussion

NIR spectra of the NMA in its pure liquid and in its CCl_4 solutions were measured in the 800–1800 nm region over a temperature range of $10\text{--}60^\circ\text{C}$.

As an example, Figure 1 shows the NIR spectrum of NMA in CCl_4 (0.8 mol dm^{-3}) at 30°C . According to [20, 21],

FIGURE 2: NIR spectra of samples of pure NMA (solid line) and $\text{NMA-}d_1$ (dashed line) at 30°C . Comparison of the two spectra indicates that the bands of the pure sample of NMA in the 1460–1620-nm region are only due to the vibration of NH group of NMA molecule.

the 1180-nm band is assigned to the second overtone of symmetric C-H stretch vibration; the 1380-nm band, to the combination bands of CH vibration; the strong bands near 1680 and 1720 nm, to the first overtone of asymmetric and symmetric C-H stretch vibrations. On the other hand, the sharp 1470-nm band is thought to be attributable to the free NH vibration of monomer NMA; the large and broadband around 1520 nm, to the vibration of the free, terminal NH moiety of hydrogen-bonded NMA aggregate [21]; and the broad 1560 and 1600-nm bands, to the hydrogen-bonded NMA aggregates [21]. Liu et al. [22] studied precisely the dissociation of hydrogen-bonded NMA in the pure liquid state by two-dimensional Fourier-transform NIR correlation spectroscopy. They reported that the 1473-nm (6790 cm^{-1}) band is assigned to the free NH group of monomer NMA; the 1504-nm (6650 cm^{-1}) band, to the terminal-free (free-end) NH groups of the dimer; the 1536-nm (6510 cm^{-1}) band, to the free-end NH group of oligomer; the 1553-nm (6440 cm^{-1}), to the hydrogen-bonded NH groups of dimer or small oligomers; the 1600-nm (6250 cm^{-1}) band, to the hydrogen-bonded NH groups of oligomers. In order to confirm additionally the validity of this NH band assignments in the 1460–1620 nm region, we measured the NIR spectrum of $\text{NMA-}d_1$ sample at 30°C .

Figure 2 shows the NIR spectra of pure liquid NMA (solid line) and $\text{NMA-}d_1$ (dotted line) samples at 30°C . The bands existing around 1460–1620 nm in the spectrum of the pure liquid sample of NMA apparently disappear in the spectrum of $\text{NMA-}d_1$. The bands due to CH vibrations are not observed in this region of the spectrum of $\text{NMA-}d_1$. This means that the bands of NMA in its pure liquid in the 1460–1620 nm region are attributable almost to the several vibrations of NH groups. Furthermore, in the spectrum of the pure liquid sample of NMA, the 1470-nm band due to the free NH moiety of NMA monomer is almost negligible; the two large bands are attributable to the free-end NH moiety of the hydrogen-bonded NMA aggregates and to the hydrogen-bonded NH of aggregates, respectively.

FIGURE 3: Concentration dependence of the apparent molar absorptivity ϵ of NMA in CCl_4 (0.12, 0.25, 0.6, 1.0, 4.0, and 8.0 mol dm^{-3}) and in pure liquid (13.0 mol dm^{-3} ; dashed line) at 30°C. The ϵ value was obtained by dividing the observed absorbance by the light-path length of the cell and the NMA concentration. The 1470-nm band due to the free NH moiety of monomer steeply increases with decreasing concentration of NMA, while the 1520 and 1600-nm bands due to the hydrogen-bonded NMA aggregates slightly decrease. The dashed line denotes the pure liquid sample of NMA. The ϵ of pure liquid at 1470 nm is very small compared with those at low concentrations.

Figure 3 represents the concentration dependence of the spectra in the 1460–1620 nm region of NH vibration of NMA in CCl_4 solutions and in pure liquid state (dashed line) at 30°C. In this figure, the intensity of the absorption bands for NMA is presented in terms of the apparent molar absorptivity ϵ which was obtained by dividing the observed absorbance by the light path length of the cell and the NMA concentration. Concentrations, C , of NMA solutions were 0.12, 0.25, 0.6, 1.0, 4.0, 8.0, and 13.0 mol dm^{-3} (pure liquid sample), respectively.

The apparent ϵ of 1470-nm band due to the NH vibration of NMA monomer steeply increases with a decrease in the NMA concentration; the relatively broad 1520-nm band due to the free, terminal NH moiety of the hydrogen-bonded NMA aggregate slightly decreases; the broad 1550–1600 nm band due to the NH groups in the NMA aggregates also slightly decreases.

As denoted by the dashed line in Figure 3, the apparent molar absorptivity value, ϵ_p , for the terminal NH group of the hydrogen-bonded NMA for the pure liquid was $0.0206 \text{ cm}^{-1} \text{ mol}^{-1} \text{ dm}^3$ at 1470 nm.

Apparently, at low concentration, the contribution of the tail part of the terminal NH band of NMA aggregate to the free monomer NH band at 1470 nm is extremely small. Thus, the contribution of the tail part of the free, terminal NH moiety of the hydrogen-bonded NMA aggregates is almost negligible at low concentrations.

From the spectra of the pure liquid NMA and NMA- d_1 samples, we have estimated that the bands due to the CH vibrations would not exist in the 1460–1620-nm region. However, there remains a possibility that the deuterium-

hydrogen exchange of NMA is not complete. Consequently, the slight contribution of CH vibration may still remain in the 1460–1620 nm region.

Therefore, to eliminate completely the bands due to the CH vibrations from the 1470-nm band due to the NH vibration of NMA monomer, we adopted the spectrum of the pure-liquid NMR sample as a reference at 30°C. One reason is that, as the melting point of NMA crystal is 26–28°C, the pure liquid sample of NMA would not have its monomers at this temperature. In fact, as shown in Figures 2 and 3, pure-liquid NMA sample does not show the 1470-nm monomer band at 30°C. Namely, to obtain the spectra, the spectrum of NMA in pure liquid measured at 30°C was subtracted from all the raw spectra after concentration and density corrections.

In the previous paper [23], to calculate the aggregation numbers of butanol in CCl_4 , we utilized the intensity of the free OH band of monomer butanol.

In the case of NMA, we used also the intensity of the free NH band of NMA monomer at 1470 nm for the calculation of the aggregation number of the NMA in CCl_4 .

Figures 4(a) and 4(b), for examples, show the temperature dependence of the difference spectra of the 0.12 and 0.25 mol dm^{-3} samples of NMA in CCl_4 . At each constant concentration, the 1470-nm band due to the free NH monomer steeply increases with increasing temperature while the broad 1600-nm band due to the hydrogen-bonded NMA aggregate slightly decreases.

Judging from the profiles of Figures 4(a) and 4(b), in the low concentration regions, the subtraction using the spectrum of NMA in pure liquid state seems to be acceptable. However, in the high concentration regions (0.8, 2.5, and 8 mol dm^{-3}) as shown in Figures 4(c)–4(e), the contribution of the tail part of the band due to the free-end NH moiety of the hydrogen-bonded NMA aggregates to the 1470-nm monomer band becomes too large; we probably do the oversubtraction of the contribution of the tail part at high concentrations above 0.8 mol dm^{-3} . Thus, we evaluated the mean aggregation number of NMA in CCl_4 only below 0.25 mol dm^{-3} .

In the evaluation of the mean aggregation number of NMA, it is essential to know the monomer concentration of NMA; the monomer concentration was calculated by using the apparent molar absorptivity, ϵ , and the molar absorptivity, ϵ_m , for the 1470-nm band due to the free NH group of NMA monomer.

The ϵ_m was obtained from the concentration (C_t) dependence of the absorbance, A , at the peak position of the free NH band of monomer in a low-concentration region, where the NMA molecules exist predominantly as monomers.

NMA gave good straight line in the A - C_t relationships under the condition of $C_t < 0.008 \text{ mol dm}^{-3}$ at various temperatures. From the slopes of the lines, we evaluated $2.08 \pm 0.13 \text{ cm}^{-1} \text{ mol}^{-1} \text{ dm}^3$ as ϵ_m of free NH vibration of monomer NMA. The obtained ϵ_m value is almost independent of temperature. This value is good agreement with the reported data by Klotz and Franzen [24] ($2.0 \text{ mol}^{-1} \text{ cm}^{-1} \text{ dm}^3$) and by Liu et al. [21] ($1.97 \text{ mol}^{-1} \text{ cm}^{-1} \text{ dm}^3$) and is somewhat larger than that by Krikorian [25] ($1.63 \text{ mol}^{-1} \text{ cm}^{-1} \text{ dm}^3$).

FIGURE 4: Temperature dependence (10–60°C) of difference spectra of NMA in CCl_4 ((a) 0.12 mol dm^{-3} ; (b) 0.25 mol dm^{-3} ; (c) 0.80 mol dm^{-3} ; (d) 2.5 mol dm^{-3} ; (e) 8.0 mol dm^{-3}). The spectrum of pure liquid sample of NMA at 30°C was taken as a reference. The subtraction was carried out after the concentration and density corrections of the pure NMA and CCl_4 solution samples. The 1470-nm band due to the free NH of monomer increases with increasing temperature and the 1520-nm band due to the free, terminal NH moiety of hydrogen-bonded NMA aggregates decreases with increasing temperature. The free, terminal NH moiety of the hydrogen-bonded NMA aggregates seems to be oversubtracted below 30°C as shown in Figures 4(c), 4(d), and 4(e).

FIGURE 5: $C_t/[M_1]$ versus $[M_1]$ relationship for NMA at 20°C.

3.1. Evaluation of the Mean Association Number. Trabelsi et al. [26] reported that the NMA molecules exist somewhat as the ring cis trimer as well as the linear trans trimer at liquid state. However, in the relatively dilute CCl_4 solution, the NMA molecules would associate into large aggregates through the following successive process:

For i -mer, in general,

$$M_{i-1} + M_1 = M_i; \quad \beta'_i = \frac{[M_i]}{[M_{i-1}][M_1]}, \quad \therefore [M_i] = \beta_i [M_1]^i,
 \tag{2}$$

where $\beta_i = \beta_2\beta'_3, \dots, \beta'_{i-1}; \beta'_3, \beta'_4, \dots$, and β'_i are the association constants for each process, and $\beta_2, \beta_3, \dots$, and β_i , the overall association constants for the formation of dimer, trimer, and i -mer, respectively. $[M_1], [M_2], [M_3], \dots$ and $[M_i]$ denote the concentrations of monomer, dimer, trimer, and i -mer, respectively. In the equations, both types of aggregates, that is, linear and cyclic ones, are possible for the i -mers. In practice, however, cyclic aggregates would not be coexistent with open-linear species. This is because most NMA molecules exist in flat, transform structure; the formation of cyclic aggregates is thought to be very difficult. In addition, cyclic structures exhibit more order (less freedom), and, therefore, their formation involves greater entropy loss than for the formation of the equivalent open structures. Consequently, the main oligomer species would be linear types of species. Thus, as a first approximation we applied the simple successive aggregation process for the formation of the linear-type oligomer species.

The total concentration, C_t , can be expressed in terms of the monomer concentration, $[M_1]$.

$$\begin{aligned}
 C_t &= [M_1] + 2[M_2] + 3[M_3] + \dots + i[M_i] + \dots \\
 &= \sum i[M_i] = \sum i\beta_i [M_1]^i.
 \end{aligned}
 \tag{3}$$

On the other hand, if we regard the oligomers (dimer, trimer, tetramer, and so on) as a sort of particle, the total concentration of the particles, C_m , would be represented by (4)

$$\begin{aligned}
 C_m &= [M_1] + [M_2] + [M_3] + \dots + [M_i] + \dots \\
 &= \sum [M_i] = \sum \beta_i [M_1]^i.
 \end{aligned}
 \tag{4}$$

Differentiation of (4) with respect to $[M_1]$ and combination with (3) leads to (5)

$$\frac{dC_m}{d[M_1]} = \sum i\beta_i [M_1]^{i-1} = \frac{\sum i\beta_i [M_1]^i}{[M_1]} = \frac{C_t}{[M_1]}.
 \tag{5}$$

Thus, the C_m is represented by the integral of (5)

$$C_m = \int_{\sim 0}^{[M_1]} \frac{C_t}{[M_1]} d[M_1].
 \tag{6}$$

In practice, the C_m can be evaluated graphically through the successive area integral of the $C_t/[M_1]$ versus $[M_1]$ relationship, with the use of $[M_1]$ at an arbitrary C_t .

Then, the mean association number, $\bar{N}$, which includes monomer species, is expressed as follows:

$$\bar{N} = \frac{C_t}{C_m}.
 \tag{7}$$

The value of $[M_1]$ necessary for evaluating the C_m and finally $\bar{N}$ values can be estimated from the apparent molar absorptivity, ϵ , and the molar absorptivity ϵ_m for the free NH band (at 1470 nm) of monomer.

As a typical example, the $C_t/[M_1]$ versus $[M_1]$ relationship for NMA at 30°C is shown in Figure 5. $C_t/[M_1]$ increases gradually and steeply with an increase in $[M_1]$. The graphical successive area integral of the relationship gave the C_m at an arbitrary $[M_1]$ or C_t . Then, the $\bar{N}$ at the arbitrary C_t was evaluated with (7) by using the obtained C_m value.

The $\bar{N}$ versus C_t relationships at various constant temperatures for NMA in CCl_4 are shown in Figure 6. At a constant temperature, the $\bar{N}$ value increases with an increase in concentration. At constant concentration, the $\bar{N}$ value decreases with increasing temperature.

Similar observations were carried out for the NMA samples in CH_2Cl_2 , CHCl_3 , and CH_3CN solutions. In these cases, the absorptions due to the solvents themselves are included in the observed spectra. Therefore, the removal of the spectra due to the solvents from the observed spectra was carried out after the back ground and density corrections. After these calculating procedures, similar calculation as same as the case of CCl_4 solution was carried out.

As an example the obtained results for the mean aggregation number $\bar{N}$ of NMA in these solvents at 20°C are

FIGURE 6: Mean aggregation number, $\bar{N}$, versus total concentration, C_t , of NMA at various temperatures: • denotes 10°C; Δ , 20°C; ■, 30°C; $\diamond$, 40°C.

FIGURE 7: Mean aggregation number, $\bar{N}$, versus total concentration, C_t , of NMA in various solvents at 20°C. • denotes CCl₄; $\blacktriangle$, CH₂Cl₂; $\square$, CHCl₃; $\diamond$, CH₃CN.

plotted in Figure 7. In the case of the solvents such as CH₂Cl₂, CHCl₃, and CH₃CN, the contributions of the free, terminal NH groups of the NMA aggregates to the monomer band were very small, and then the concentration regions for the calculation of aggregation number are wide, compared with the case in CCl₄. The $\bar{N}$ value of NMA in CH₃CN is almost 1 and very slightly increases with increasing concentration of NMA. In addition, the $\bar{N}$ values of NMA in CH₂Cl₂ and CHCl₃ also slightly increase with increasing concentration of NMA but slightly larger than that in CH₃CN. Namely, the NMA molecules aggregate most greatly in CCl₄. The dielectric constants of CH₃CN, CH₂Cl₂, CHCl₃, and CCl₄ have been reported as 37.5, 9.1, 4.9, and 2.205 at 20°C [27], respectively. The dielectric constant of the solvents is thought to contribute the degree of association of NMA molecule.

In the low dielectric solvent such as CCl₄, the NMA aggregation progresses steeply with increasing the concentration of NMA molecule.

By the way, is there a difference in the profile of the aggregates of NMA in nonpolar solvent such as CCl₄ and in pure liquid? Then, we investigated effect of CCl₄ on the aggregation profile of NMA.

3.2. Effect of Nonpolar Solvent on the Aggregation Profile of NMA Molecules. Figures 4(c) and 4(e) exhibit the temperature dependence of the difference spectra for NMA in CCl₄ solution at high concentrations: 0.8, 2.5, and 8.0 mol dm⁻³. The difference spectra were obtained by subtracting the spectrum of pure NMA sample at 30°C as a reference from other spectra measured at various temperatures after density correction.

Interestingly, the difference spectra below 30°C has a large minimum at 1510 nm which is very close to the band of the free, terminal NH of aggregate of NMA, while the 1600 nm band due to the hydrogen-bonded aggregates of NMA does not so decrease. This suggests that the number of terminal NH group decreases in CCl₄ and that the aggregates become more large-sized clusters in CCl₄. Namely, non-polar solvent such as CCl₄ may promote the formation of larger aggregate of NMA molecules. The solvent having low dielectric constant dislike the NMA molecules and may promote the formation of large clusters. With increasing temperature, the large cluster would dissociate more easily and then monomer band increases in its intensity. In addition, the number of the free, terminal NH groups of the oligomers would increase with increasing temperature. The aggregate structures in CCl₄ and in liquid, however, should be clarified by more additional experiments.

4. Conclusions

Aggregation numbers of NMA in various solvents, such as CCl₄, CHCl₃, CH₂Cl₂, and CH₃CN, were obtained by using NIR spectroscopic observation. The order of the degree of association is CCl₄ $\gg$ CHCl₃ $\approx$ CH₂Cl₂ $>$ CH₃CN. The cluster size increases with increasing NMA concentration and decreases with increasing temperature. In the solvent having a high dielectric constant, the aggregation number of NMA is very small, while in the solvent having a low dielectric constant that of NMA is very large. In addition, the non-polar solvent such as CCl₄ promotes the cluster size of NMA.

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