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Communication

The Relative Hydrogen Bonding Strength of Oxygen and Nitrogen Atoms as a Proton Acceptor

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The thermodynamic parameters for the formation of the hydrogen bonding were widely used to understand the protein-ligand interaction.[1-3] We have been interested in the hydrogen bonding strength of various proton acceptors toward the amide in a nonpolar solvent.[1,2] This work is in the line of our interest.

In drug design, the functional group is often replaced in order to enhance or reduce the binding affinity, which is usually determined by hydrogen bonding strength.[4] Therefore, to understand this biochemical process the knowledge of relative hydrogen bonding strength is of importance.

The comparative study on the hydrogen bonding interactions of DMA (N,N-dimethylacetamide) and DMTA (N,N-dimethylthioacetamide) with TA (thioacetamide), *i.e.* C=O···H-N and C=S···H-N interactions, showed that the sulfur atom is a stronger proton acceptor for TA than more electronegative oxygen atom in CCl_4 solution.[2] Böhm *et al.* indicated that simple correlation with electronegativity or partial charges are not sufficient to explain the hydrogen bonding ability of proton acceptor.[5] Etter *et al.* also reported that the hydrogen bonding properties of functional groups clearly depend on the local intramolecular environment.[6]

In present work, we compared the hydrogen bonding strength of the nitrogen atom and the oxygen atom as a proton acceptor. Our previous studies indicated that the carbonyl-type oxygen atom in DMA forms a slightly stronger 1 : 1 hydrogen-bonded complex with TA than the imine-type nitrogen atom in pyridine.[1(b),(c)] Strictly speaking, however, it is difficult to compare the strength of hydrogen bonding directly under the condition that the chemical environments are different. Thus, the structural isomers, N-methylcaprolactam (NMC) and O-methylcaprolactim (OMC), were chosen to compare the relative hydrogen bonding ability of the oxygen atom and the nitrogen atom as a proton acceptor for TA; *i.e.* C=O···H-N and C=N···H-N.

TA (Aldrich, 99%) was dried under the reduced pressure (10^{-3} Torr) for 24 hours, and then stored in a glove box. NMC (99%) and OMC (99%) purchased from Aldrich were used without further purification. CCl_4 (HPLC grade, J. T. Baker inc.) was used after removing the last traces of water using 4 molecular sieve. The concentration of TA was 4.8 mM, and that of NMC and OMC was in the range of 9.4-25.4 mM and 96-296 mM, respectively. The NMC (OMC)/CCl_4 solution in a matched cell was placed in the path of a reference beam to compensate the absorption of proton acceptor and solvent.

The near IR spectrum of TA was obtained by a Cary 5G Spectrophotometer (Varian, Inc.), using 1-cm path length quartz cells. The sample and reference cells were placed in cell holders connected to a constant temperature controller (Varian, Inc.), the temperature was varied in the range of 5°C-55°C. The temperature fluctuation during the measurement was less than 0.1 °C. The spectrum was taken after the temperature of the sample solution was stabilized at a fixed temperature (about 30 minutes). During the measurement, the cells were purged by nitrogen gas passed over calcium chloride to remove the humidity. All spectra are fitted by a Gaussian-Lorentzian product function, as shown using the commercially available Peak Fit program (Jandel Scientific Software). A detailed experimental method was described in our previous works.[1,2]

The AM1 semiempirical quantum-mechanical calculations were performed to obtain the optimized structure of

OMC and NMC with a MOPAC V6.0 program implemented in SYBYL[7,8] on IDIGO 2 workstation.

Near-IR spectroscopy. The near-IR ν_{N-H}^{as} + Amide II combination band spectra of TA show the isosbestic point for the temperature range of 5°C-55°C and the concentration range such as TA 4.8 mM, NMC 9.4-25.4 mM, and OMC 96-296 mM, showing that TA forms an 1 : 1 complex with NMC (OMC) in CCl_4 solution.

The equilibrium constant (K) for the hydrogen bonding formation is represented by the following equations:

$$\text{TA} + \text{NMC (OMC)} \rightleftharpoons \text{TA:NMC (OMC)}$$
$$K = C_{1:1}/C_{mono}C_{free},\ C_{1:1}/C_{mono} = C_{free}\,K, \qquad (1)$$

where $C_{1:1}$ is the concentration of the hydrogen-bonded TA, C_{mono} is the concentration of monomeric TA, and C_{free} is the concentration of the free proton acceptor, NMC (OMC). The resolved ν_{N-H}^{as} + Amide II combination bands of NMC (16.5 mM)/TA (4.8 mM)/CCl_4 and OMC (216 mM)/TA (4.8 mM)/CCl_4 at 25°C are shown in (A) and (B) of Figure 1, respectively. The ratio of $C_{1:1}$ to C_{mono} is obtained directly from the area of the two resolved bands, and the linear fit of $C_{1:1}/C_{mono}$ *vs.* C_{free} plot yields the equilibrium constant. Although the equilibrium constant should be expressed by the activity rather than the concentration, the use of concentration can be justified in dilute solution.

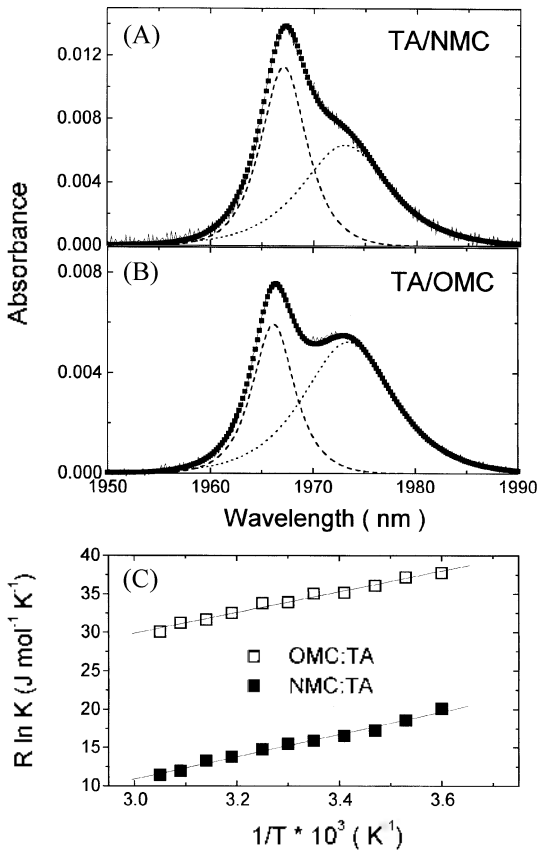

Figure 1. The ν_{N-H}^{as} + Amide II combination band of (A) NMC (16.5 mM)/TA (4.8 mM)/CCl_4 and (B) OMC (216 mM)/TA (4.8 mM)/CCl_4 at 25 °C. The full line, dashes line (---), and dots (···) represent the measured absorption spectrum, resolved band of monomeric TA, and resolved band of hydrogen bonded TA, respectively. The filled squares (■) are the sum of resolved monomeric and hydrogen bonded TA bands. (C) The van't Hoff plot for the 1 : 1 NMC:TA and OMC:TA complex formations in CCl_4 solution.

Table 1 lists the equilibrium constants for the formation of 1 : 1 NMC:TA and OMC:TA hydrogen bonded complex in the temperature range of 5°C-55°C. Thermodynamic parameters were evaluated from the van't Hoff equation, -d(lnK)/d(1/T) = $\Delta H^\circ/R$. The thermodynamic parameters are also summarized in the Table 1. The plot of R lnK *vs.* 1/T yields the values of $-\Delta H^\circ$, as shown in Figure 1(C), indicating the intrinsic strength of the hydrogen bonding, are -13.6 kJ/mol and -14.7 kJ/mol for 1 : 1 NMC:TA and 1 : 1 OMC:TA complex formations, respectively. The results show that OMC can form a slightly stronger 1 : 1 hydrogen bonded complex with TA than NMC in CCl_4 solution. The thermodynamic data for 1 : 1 pyridine:TA and DMA:TA complex formations are listed in Table 1. The ΔH° value of the 1 : 1 pyridine:TA complex is slightly less than that of DMA:TA complex. These results indicate that the imine-type nitrogen atom can form the hydrogen bonding as strongly as the carbonyl-type oxygen atom.

The equilibrium constant (K) for the formation of hydrogen-bonded 1 : 1 NMC:TA and OMC:TA complexes at 25°C are 67.92 and 6.77, respectively. The smaller equilibrium constant of 1 : 1 OMC:TA complex formation than that of NMC:TA is due to the entropy effect of complexation. OMC which has a flexible methyl group undergoes a large loss in entropy upon binding to TA. Whereas, NMC has no flexible methyl group should experience less of an entropic change and binds more effectively to TA than OMC. The equilibrium constant at 25 °C for 1 : 1 pyridine:TA complex formation is 5 times less than that of DMA:TA due to the entropy effect, as listed in Table 1, despite the fact that the ΔH° values is slightly less than that of DMA:TA.

Table 1. Thermodynamic parameters for the 1:1 hydrogen-bonded complex formation of TA with NMC, OMC, DMA, and pyridine in CCl_4 solution

Proton Acceptors	K (M^{-1}) 5°C	15°C	25°C	35°C	45°C	55°C	$-\Delta H^\circ$ (kJ/mol)	$-\Delta S^\circ$ (J $mol^{-1}K^{-1}$)
NMC	94.0	76.9	67.9	58.3	45.1	37.2	13.5	10.8
OMC	11.2	8.0	6.8	5.9	5.0	4.0	14.6	32.9
DMA[a]	75.6	65.4	51.3	42.1	35.3	30.1	14.4	15.5
Pyridine[b]	15.2	12.8	10.1	8.8	7.3	6.4	13.3	25.3

[a] Ref. 1(b). [b] Ref. 1(c).

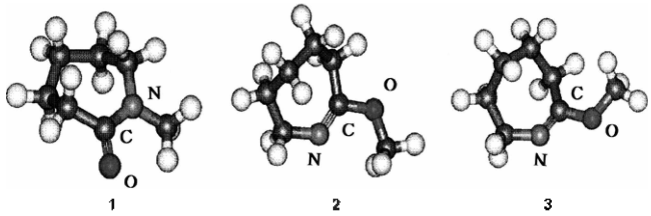

Figure 2. The optimized conformers of NMC (**1**) and OMC (**2** & **3**).

Semiempirical Calculation. We optimized the structure of NMC and OMC molecules using AM1 semiempirical quantum-mechanical calculations. For OMC, the most stable conformer is that the methoxy group is in *cis* to nitrogen atom, as shown as **2** in Figure 2. The conformer **3** of OMC, which the methoxy group is in *trans* to nitrogen atom and the oxygen and nitrogen atoms are in the same plane, is less stable than the conformer **2** by 36.6 kJ/mol. The lone-pair electrons repulsion between nitrogen and oxygen atoms becomes large in conformer **3**, which may result in the destabilization. We expect that the conformer **2** is also favored in the solution phase. The complexation of *cis* OMC with TA restricts the free rotation of methyl group, which would yield a large loss in the entropy.

From the near IR spectroscopic results and the theoretical calculations, we report a remarkable conclusion that the hydrogen bonding strength between carbonyl-type oxygen atom of NMC and imine-type nitrogen atom of OMC are not much different and but the entropy effect reduces the hydrogen-bonding formation of OMC.

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References

1. (a) Choi, Y. S.; Huh, Y. D.; Bonner, O. D. *Spectrochim. Acta* **1985**, *41A*, 1127. (b) Lee, K. -B.; Kim, B. C.; Bonner, O. D.; Choi, Y. S. *J. Korean Chem. Soc.* **1986**, *30*, 510. (c) Lee, S. -H.; Park, J.; Yoon, C. -J.; Choi, Y. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 831. (d) Choi, Y. S.; Kim, J. K.; Park, J.; Yu, J. A.; Yoon, C. J. *Spectrochim. Acta* **1996**, *52A*, 1779. (e) Lee, H. -J.; Park, J.; Yoon, C. -J.; Choi, Y. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 110.
2. Min, B. K.; Lee, H. -J.; Choi, Y. S.; Park, J.; Yu, J. A.; Yoon, C. -J. *J. Mol. Struct.* **1998**, *471*, 283.
3. Raevsky, O. A. *J. Phys. Org. Chem.* **1997**, *10*, 405.
4. (a) Kikumoto, R.; Tamao, Y.; Ohkubo, K.; Tezuka, S.; Tonomura, S.; Okamoto, S.; Funahara, Y.; Hijikata, A. *J. Med. Chem.* **1980**, *23*, 830. (b) Matthews, D. A.; Bolin, J. T.; Burridge, J. M.; Filman, D. J.; Volz, K. W.; Kaufmann, B. T.; Bedell, C. R.; Champness, J. N.; Stammers, D. K.; Kraut, J. *J. Biol. Chem.* **1985**, *260*, 381. (c) Badger, J.; Minor, I.; Kremer, M. J.; Oliveira, M. A.; Smith, T. J.; Griffith, J. P.; Guerin, D. M. A.; Krishnaswamy, S.; Luo, M.; Rossmann, M. G.; McKinlay, M. A.; Diana, G. D.; Dutko, F. J.; Fancher, M.; Ruecker, R. R.; Heinz, B. A. *Proc. Natl. Acad. Sci. USA*, **1988**, *85*, 3304.
5. Böhm, H. -J.; Brode, S.; Hesse, U.; Kelbe, G. *Chem. Eur. J.* **1996**, 1509.
6. Etter, M. C.; Reutzel, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 2586.
7. SYBYL 6.3; Tripos, Inc. **1996.**
8. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.