

activation enthalpy, ΔH^\ddagger , predicts correct order of k_2 except for the case of 2-butyl. This anomalous behavior of 2-butyl compound could be due to the solvent effect which was neglected in the gas-phase results in Table 7.

In summary, the TS for the S_N2 reaction at an acyclic secondary carbon is slightly tighter than that at an alicyclic secondary carbon. Despite the small variations, however, the overall TS tightness remains remarkably constant for all the secondary alkyl carbon compounds. The degree of bond-making in the TS increases successively with a more sterically crowded secondary carbon center, which is in accord with the BEP principle.

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The Near Infrared Spectroscopic Studies of the Hydrogen Bonding Between Thioacetamide and Azines in Nonaqueous Solutions

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The nature of hydrogen bonding between thioacetamide and azines has been thoroughly investigated using near IR absorption spectroscopy. The ν_{N-H} +amide II combination band in thioacetamide (TA) has been analyzed to determine the thermodynamic constants for the formation of hydrogen bonded 1:1 TA:azine complexes in CCl_4 and $CHCl_3$ solutions. The relative stabilities of TA-azine complexes (pyridine->1,2-diazine->1,3-diazine->1,4-diazine-TA) are in good agreement with the relative proton affinities of azines in the gas phase. The results serve as a basis for analyzing the factors which influence the hydrogen bonding formation of TA in nonaqueous solutions.

Introduction

Hydrogen bonding consists of two electronegative atoms bound to the same hydrogen. One good hydrogen bond donor

is the NH and one excellent acceptor is the C=O group in the polypeptide backbone. Hydrogen bonds between these donors and acceptors are the basis of the major units of protein secondary structure, namely the α -helix and the β -

pleated sheet. It is therefore of fundamental importance to understand the strength of the amide-amide hydrogen bond and the entropy and enthalpy of its formation. In an attempt to provide a better understanding of amide-amide system, many studies about small and isolated amides have been reported. Indeed, a variety of techniques such as IR, NMR, Raman, ultrasonic absorption, and UV/VIS spectroscopy have been employed to characterize both intramolecular and intermolecular bondings in amide system. The near IR spectroscopic method has been demonstrated to be one of the most suitable methods for hydrogen bonding studies, since the combination absorption bands in near IR region are well separated to assign and therefore provide the quantitative analysis.

In this work described here we investigated the hydrogen bonding between thioacetamide (TA) and azines in non-aqueous solutions using near infrared spectroscopic method. Thioacetamide is of considerable interest as a simple peptide analogue having no self-association behavior; however, there are relatively few studies of both theoretical and experimental natures. The azines form basic structures of some of the important compounds in nature. As such, they deserve especially careful examination. One of the most characteristics of these compounds is the π -electron delocalization characteristic,^{1,2} which leads to reduced reactivity,³ marked changes in keto/enol equilibria,⁴ and substitution rather than addition.⁵ We chose to study its hydrogen bonding with TA as models for more complicated complexes involving nucleic acid bases. The azines such as pyridine, pyridazine (1,2-diazine), pyrimidine (1,3-diazine), and pyrazine (1,4-diazine) are used as the proton acceptors for TA. Our approach is to examine the effects of electron density or geometry of azines on the strength of hydrogen bond by comparing the thermodynamic data such as equilibrium constant, ΔH , and ΔS .

Experimental Section

TA (Aldrich, 99%), pyridine (Aldrich, 99%+), and pyrazine (Aldrich, 99%) were dried at room temperature under reduced pressure for 24 hours. Pyridazine and pyrimidine (Aldrich, 99%) were purchased and used without further purification. Carbon tetrachloride (J. T. Barker, HPLC grade) was dried over 4 Å molecular sieves. The mole ratios of TA (1-9 mM) to pyridine, pyridazine, pyrimidine, and pyrazine in CCl_4 are 40, 7, 40, and 40, respectively. The mole ratios of TA (1-9 mM) to pyridine, pyridazine, pyrimidine, and pyrazine in CHCl_3 are 25, 20, 50, and 50, respectively. Densities of CCl_4 and CHCl_3 solutions were measured by pycnometer at various temperatures to calculate the concentration of solution. The samples were prepared in N_2 filled glove box.

The near-infrared absorption spectra of TA in the region of 1920-2160 nm were obtained with Cary 17DX spectrophotometer, using 10 cm path-length cylindrical quartz cell. The bands due to azine and solvent were eliminated by placing a matching cell containing equal amounts of azine and solvent in the path of reference beam. The sample and reference cells were placed in the jacketed cell holder connected to a constant temperature bath. The temperature fluctuation during the measurement was less than 0.2 °C.

Results and Discussion

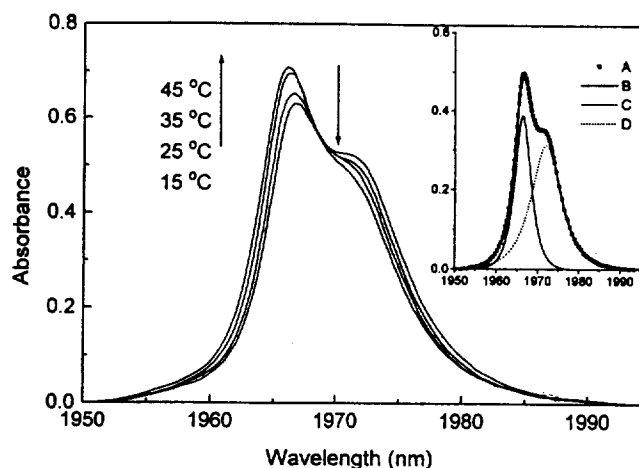


Figure 1. The $\nu_{\text{N-H}} + \text{Amide II}$ combination band of TA(6 mM)/1,3-diazine(0.24 M)/ CCl_4 as a function of temperature. The resolved monomeric and hydrogen bonded TA bands of TA(5 mM)/1,3-diazine(0.20 M)/ CCl_4 at 25 °C are shown in the inset. Measured absorption spectrum, fitted band of monomeric TA, and fitted band of hydrogen bonded TA are represented by squares (A), thin line (C), and dots (D), respectively. The thick line (B) is the sum of C and D.

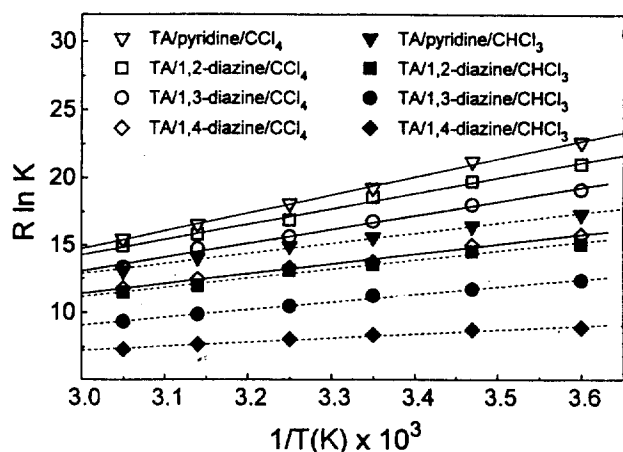
The near-infrared spectrum of TA in CCl_4 in the range of 1920-2160 nm was reported in previous studies.⁶ Among the several bands, the combination band of antisymmetric stretching and Amide II ($\nu_{\text{N-H}} + \text{Amide II}$) has been chosen for the study, because this band has a larger molar absorption coefficient compared to other bands, and is not interfered with other overtone or combination bands of azine compounds. The $\nu_{\text{N-H}} + \text{Amide II}$ combination band of TA (6 mM)/1,3-diazine (0.24 M)/ CCl_4 as a function of temperature is shown in Figure 1. The appearance of an isobestic point indicates an equilibrium of only two species, monomeric and hydrogen bonded TA. The hydrogen bonded complex should be 1:1 TA:1,3-diazine complex. Under the temperature range between 5 °C and 50 °C, the formation of 1:2 hydrogen bonded complex was not observed. An intensive peak at 1965 nm (5089 cm^{-1}) and a shoulder at 1971 nm (5076 cm^{-1}) were assigned to monomeric TA and the hydrogen bonded TA, respectively. The spectrum was resolved into its two Gaussian-Lorentzian product components, each of which was defined by the following equation;⁶

$$A(\nu)_{L-G} = X_1 [1 + X_3^2(\nu - X_2)^2]^{-1} \cdot \exp[-X_4^2(\nu - X_2)^2] \quad (1)$$

where, $A(\nu)$ is the absorbance at frequency ν , X_1 is the peak height at ν_{max} , X_2 is the frequency at band center (ν_{max}), X_3 is $1/b_L$ (b_L is the Lorentzian full width at half maximum), and X_4 is $\sqrt{\ln 2/b_g}$ (b_g is the Gaussian full width at half maximum). A modified simplex search algorithm was used for curve fitting. The program terminates its iteration when chi square is less than 1×10^{-9} . The fitted spectrum of TA (5 mM)/1,3-diazine (0.20 M)/ CCl_4 is shown in the inset of Figure 1. According to the previous study,⁶ the spectrum of only TA solution shows a shoulder at the same position of the hydrogen bonded TA band, which has been identified as an "unknown band". Therefore, we corrected the area of hydrogen bonded TA band by subtracting the area of the

Table 1. Thermodynamic parameters for the formation of TA-azine hydrogen bonded complexes

Proton Acceptor	Solvent	K (M ⁻¹)						ΔH° (kJ/mol)	ΔS° (J/mol K)
		5 °C	15 °C	25 °C	35 °C	45 °C	55 °C		
pyridine	CCl ₄	15.2	12.8	10.1	8.8	7.3	6.4	-13.3	-25.3
	CHCl ₃	8.0	7.2	6.5	6.0	5.4	4.8	-7.6	-9.9
1,2-diazine	CCl ₄	12.5	10.7	9.3	7.6	6.7	6.0	-11.4	-20.0
	CHCl ₃	6.1	5.7	5.1	4.8	4.2	4.0	-6.8	-9.2
1,3-diazine	CCl ₄	10.0	8.7	7.5	6.6	5.9	5.0	-10.3	-17.4
	CHCl ₃	4.4	4.1	3.9	3.5	3.3	3.1	-5.6	-7.4
1,4-diazine	CCl ₄	6.7	6.1	5.2	5.0	4.5	4.0	-7.3	-10.6
	CHCl ₃	2.9	2.9	2.7	2.6	2.5	2.4	-3.0	-1.6

**Figure 2.** The plot of $R \ln K$ vs. $1/T$ for the formation of TA-azine complexes.

unknown band.

It is observed that as the concentration of TA increases from 1 mM to 9 mM, the formation of hydrogen bonded 1:1 complex increases. In this low concentration range, 1:2 complex formation is not observed. As the temperature increases, the band intensity of monomeric TA increases, but that of 1:1 complex decreases. It implies that the equilibrium constant for hydrogen bond formation becomes smaller and the reaction is exothermic. The equilibrium for the hydrogen bond formation and the equilibrium constant K are following;



$$K = \frac{C_{1:1}}{C_{\text{mono}} C_{\text{free}}}, \quad \frac{C_{1:1}}{C_{\text{mono}}} = K \cdot C_{\text{free}} \quad (3)$$

where, $C_{1:1}$ is the concentration of the hydrogen bonded TA, C_{mono} is the concentration of monomeric TA, C_{free} is the concentration of the free azine. The ratio of $C_{1:1}$ to C_{mono} is directly obtained from the area of resolved two bands, and the linear fit for the $C_{1:1}/C_{\text{mono}}$ vs. C_{free} plot yields the equilibrium constant. The thermodynamic parameters for the hydrogen bonding can be evaluated from van't Hoff equation, $-d(\ln K)/d(1/T) = \Delta H^\circ/R$. The $R \ln K$ vs. $1/T$ plots for the formation of TA-azine complexes are shown in Figure 2. The

Table 2. The relative enthalpies for the formation of TA-azine hydrogen bonded complexes and the relative protonation energies of azine in the gas phase

Proton Acceptor	$-\delta\Delta H^\circ$ (kJ/mol)		$-\delta\Delta H^\circ$ (exp.)	$-\delta\Delta E^c$ 4-31G	$-\delta\Delta E^d$ 6-31G*/ 6-31G
	in CCl ₄	in CHCl ₃			
pyridine	0.0 (-13.3)	0.0 (-7.6)	0.0	0.0	0.0
1,2-diazine	-1.9	-0.8	-4.3	-7.1	-4.5
1,3-diazine	-3.0	-2.0	-9.5	-9.6	-10.7
1,4-diazine	-6.0	-4.6	-11.3	-17.9	-15.5

^aThe enthalpies relative to pyridine. ^bthe experimental relative proton affinities referred to pyridine in the gas phase (ref. 9), in kcal/mol. ^cthe relative gas phase proton affinities referred to pyridine (ref. 10), in kcal/mol. ^dthe relative gas phase proton affinities referred to pyridine (ref. 11), in kcal/mol.

thermodynamic parameters are listed in Table 1. The results show that the pyridine forms the most stable complex with TA and the 1,4-diazine forms the weakest complex. The stability of hydrogen bonded complex in CHCl₃ solution is lower than that in CCl₄ solution.

The electron densities of nitrogen atom in pyridine, 1,2-diazine, 1,3-diazine, and 1,4-diazine have been reported to be 1.425, 1.078, 1.155, and 1.068, respectively.^{7,8} It is evident that the electrostatic interaction between the proton donor and the acceptor may be an important factor which determines the stability of pyridine, 1,3-diazine, and 1,4-diazine hydrogen bonded complexes. In 1,2-diazine, however, lack of correlation between the stability and electron density indicates that the electrostatic interaction may not be the only factor to stabilize the TA-diazine complex. It is also apparent that a particular acid-base interaction is not determined only by the nature of the proton acceptor and donor individuals.

The proton affinities of azines in the gas phase have been measured by Taft.⁹ The proton affinities of diazines relative to a proton affinity of pyridine are listed in Table 2, showing the following order; pyridine > 1,2-diazine > 1,3-diazine > 1,4-diazine. In order to compare our results with the relative proton affinities of diazines, the enthalpies of hydrogen bonded TA-diazine complexes relative to that of TA-pyridine complex, which are referred to $-\delta\Delta H^\circ$, is listed in Table 2. The relative order of the enthalpies in nonaqueous solutions

is very consistent with the experimental order of proton affinities in the gas phase.

Del Bene performed *ab initio* SCF calculations with minimal STO-3G and 4-31G basis sets to determine the relative proton affinities of pyridine and diazines in the gas phase.¹⁰ The calculations predict that pyridine is the strongest and 1,4-diazine is the weakest base toward a proton. At the 4-31G level calculations, the proton affinity of 1,2-diazine is larger than that of 1,3-diazine. According to the calculations, the relative proton affinities do correlate with the nonbonding orbital energies (the ionization potentials of vertical nonbonding orbital as approximated by Koopman's theorem) of base. For diazines the interaction between two nonbonding orbital electron pairs on two nitrogen atoms results in a destabilization of the nonbonding orbital, which is delocalized over both nitrogen atoms. The nonbonding orbital energies of 1,2-diazine, 1,3-diazine, and 1,4-diazine are -10.75 eV, -10.84 eV, and -11.13 eV, respectively. In 1,2-diazine, the most unstable nonbonding orbital is attributed to the strong interaction of adjacent p orbitals. The calculated proton affinities of diazines relative to pyridine, $-\delta\Delta E$, are listed in Table 2. However, it should be noticed that the relative basicity of 1,2-diazine referred to pyridine is less than the experimental value measured by Taft.

Mo *et al.* have investigated the protonation energies of a set of azines by *ab initio* calculations using different basis sets ranging from minimal to split valence plus polarization.¹¹ The relative order of proton affinities (pyridine > 1,2-diazine > 1,3-diazine > 1,4-diazine) is reproduced at all levels of accuracy. This result does not agree with Del Bene's studies which concluded that the STO-3G basis set fails to discriminate the proton affinities of 1,2- and 1,3-diazines. The finding that 1,2-diazine is the most basic diazine followed by 1,3- and 1,4-diazines is a consequence of the extra stabilization of the protonated form via the intramolecular hydrogen bond between the acidic hydrogen and the second basic nitrogen. Obviously, such a case is not possible either in 1,3-diazine or in 1,4-diazine. This extra stabilization of the protonated form of 1,2-diazine is estimated at 6-31G*/6-31G level, which predicts this compound to be 4.5 kcal/mol less basic than pyridine. The relative proton affinities of other diazines are listed in Table 2, showing a good agreement with the experimental gas phase data.

The *ab initio* proton affinity calculations serve as a basis for analyzing the factors which influence the hydrogen bonding formation of azine compounds. In a particular series of nitrogen bases, the stability correlates with increasing the proton affinity of azine. The destabilized nonbonding orbital energy due to interaction between adjacent p orbitals¹⁰ and the formation of the intramolecular hydrogen bond¹¹ can explain the increased stability of hydrogen bonded TA-1,2-diazine complex in nonaqueous solutions. Unfortunately, however, there is no direct evidence for the formation of intramolecular hydrogen bonded complex in nonaqueous solutions. Therefore, in this respect, theoretical calculations at

ab initio molecular orbital level for the TA-azine hydrogen bonded complexes are necessary to understand the nature of hydrogen bond interactions more precisely.

The stability of hydrogen bonded complex is reduced in CHCl₃ solution, due to the hydrogen bonding between solvent and solutes. The extents of destabilization of TA-diazine complexes relative to TA-pyridine complex in the presence of hydrogen bonding with solvent are expected to parallel with hydrogen bonding abilities of diazines. The relative destabilizations represented by $\delta\Delta H^{\circ}(\text{CHCl}_3)/\delta\Delta H^{\circ}(\text{CCl}_4)$ which are 0.45, 0.67, and 0.76 for 1,2-diazine, 1,3-diazine, and 1,4-diazine, respectively, are in good agreement with the expectations.

In summary, the hydrogen bonding between thioacetamide and azine compounds has been studied using near IR absorption spectroscopy. The ν_3 +amide II combination band in thioacetamide has been analyzed to determine equilibrium constant, ΔH , and ΔS for the formation of hydrogen bonded 1:1 TA:azine complexes in CCl₄ and CHCl₃ solutions. The stabilities of complex are in following order; pyridine->1,2-diazine->1,3-diazine->1,4-diazine-TA complexes. This experimental results are consistent with the experimental proton affinities and with *ab initio* calculations for the protonation of azines in the gas phase.

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