June 1992 Notes Chem. Pharm. Bull. 40(6) 1601—1603 (1992) 1601

Heats of Dissolution of Fatty Acids–Nicotinamide Equimolar Complexes in Ethanol

Shoko YOKOYAMA,*[a] Misae SAKAMAKI,[a] Fumio UEDA,[b] Akiko KANEKO,[a] and Tadao FUJIE[a]

Kyoritsu College of Pharmacy,[a] 1-5-30, Shibakoen, Minato-ku, Tokyo 105, Japan and Research Laboratory, Kawai Seiyaku Co., Ltd.,[b] 6-3-5, Nakano, Nakano-ku, Tokyo 164, Japan. *Received January 6, 1992*

The heats of dissolution (ΔH_d) of fatty acids (FA)–nicotinamide (NAA) complexes, $(FA)_6(NAA)_6$, were measured at 310.15 K in ethanol using a calorimetric technique, where the FA were tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17) and octadecanoic acid (C18). The values of ΔH_d were 527.9, 574.6, 592.7, 640.1 and 656.6 kJ mol^{-1} for $(C14)_6(NAA)_6$, $(C15)_6(NAA)_6$, $(C16)_6(NAA)_6$, $(C17)_6(NAA)_6$ and $(C18)_6(NAA)_6$, respectively. The values of ΔH_d of $(FA)_6(NAA)_6$ increased by increasing the carbon numbers (*n*) of the constituent FA. However, the plots of ΔH_d of $(FA)_6(NAA)_6$ against *n* showed a zig-zag pattern with an upward convex at an odd-numbered position. This is the same tendency as observed for FA–thiamine disulfide (TDS) complexes, $(FA)_6(TDS)$.

The differences between ΔH_d of $(FA)_6(NAA)_6$ and ΔH_d of (6FA + 6NAA) were 30—48 kJ mol^{-1} for even-numbered FA and 45—53 kJ mol^{-1} for odd-numbered FA, indicating a stronger binding force for $(FA)_6(NAA)_6$ formed with odd-numbered FA than that formed with even-numbered FA. Furthermore, the estimated values of the binding force between FA and NAA are very small, leading to the conclusion that $(FA)_6(NAA)_6$ is an inclusion compound or a clathrate formed by van der Waals forces and hydrophobic interactions between FA and NAA.

Keywords dissolution heat; nicotinamide; fatty acid; complex; ethanol; calorimetry; binding force; van der Waals force; hydrophobic interaction

We previously reported[1] that fatty acids (FA) formed crystalline complexes with nicotinamide (NAA), [3-pyridine carboxamide], at a molar ratio of 1 : 1. In addition, it was suggested from studies on the release of NAA from the equimolar complexes that the binding force between FA and NAA was not very strong.[2] Recently, it has been verified[3] that the formula of the equimolar complex is $(FA)_6(NAA)_6$. However, further details regarding the interaction between FA and NAA have not yet been obtained.

Heats of dissolution (ΔH_d) is the difference in thermal quantities between the solid and solution states. A little information on the molecular interaction may be obtained by the measurement of ΔH_d. ΔH_d of FA in ethanol has been measured, and it has been shown that the plots of ΔH_d of FA against the carbon numbers (*n*) in the FA indicate a linear pattern.[4] On the other hand, the plots of the release rate constant of NAA from $(FA)_6(NAA)_6$ against *n* showed a zig-zag pattern with a downward convex at the odd-numbered positions, though the release rate constant decreased rather regularly with an increase of the alkyl chain length for either even-numbered or odd-numbered FA.[2] So it is interesting to know the ΔH_d of $(FA)_6(NAA)_6$.

From these points of view, ΔH_d of $(FA)_6(NAA)_6$ in ethanol were measured. ΔH_d of NAA in ethanol was also measured. The interaction force concerned in the formation of $(FA)_6(NAA)_6$ was estimated by using the values of ΔH_d of FA and NAA. Furthermore, the results obtained for $(FA)_6(NAA)_6$ were compared with those[5] obtained for FA–thiamine disulfide (TDS) complexes, $(FA)_6(TDS)$.

Experimental

Materials Tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17), octadecanoic acid (C18) and NAA were the same as those used previously.[1—3] $(FA)_6(NAA)_6$ was prepared as previously described.[1] Ethanol was the same as that used previously.[4,5]

Measurement of ΔH_d The apparatus for the measurement of ΔH_d was a twin differential conduction-type microcalorimeter (model TIC-22 of Tokyo Riko Co., Ltd.) as described in the previous paper.[4] About 0.24 g of $(FA)_6(NAA)_6$ sealed into glass ampules was immersed into 100 ml of ethanol (final solution concentration is 1.0×10^{-3} mol dm^{-3} for each $(FA)_6(NAA)_6$). For NAA, ΔH_d was measured at various concentrations. About 0.001—0.06 g of NAA sealed into glass ampules were immersed into 100 ml of ethanol (final solution concentration is 1.0×10^{-4}—5.0×10^{-3} mol dm^{-3}). The sealed ampules were kept in a calorimeter until thermal equilibrium was established. All measurements were carried out at 310.15 K. The reproducibility was estimated by measuring ΔH_d for each sample at least five times. The uncertainty was determined by twice the standard deviation of the mean of five experiments.

Results

Values of ΔH_d of NAA The final solution concentrations of NAA were 1.0×10^{-4}, 1.0×10^{-3}, 5.0×10^{-3} mol dm^{-3}. NAA dissolved endothermally in ethanol. The values of ΔH_d of NAA at three concentrations are shown in Table I. ΔH_d was nearly constant within this concentration range.

TABLE I. Heats of Dissolution, ΔH_d, of NAA in Ethanol at 310.15 K with Varying Final Concentrations

C (mol dm^{-3})	ΔH_d (kJ mol^{-1})
1.0×10^{-4}	22.8 ± 0.7
1.0×10^{-3}	22.3 ± 0.1
5.0×10^{-3}	22.4 ± 0.3

TABLE II. Heats of Dissolution, ΔH_d, of $(FA)_6(NAA)_6$ in Ethanol at 310.15 K, the Values of ΔH_d of (6FA + 6NAA), and the Differences, $\Delta\Delta H_d$, between $(FA)_6(NAA)_6$ and (6FA + 6NAA)

FA	ΔH_d		$\Delta\Delta H_d$ (kJ mol^{-1})
	$(FA)_6(NAA)_6$[a] (kJ mol^{-1})	6FA[4] + 6NAA (kJ mix.$^{-1}$)	
C14	527.9 ± 1.5	497.6	30.3
C15	574.6 ± 2.6	529.6	45.0
C16	592.7 ± 2.1	550.0	42.7
C17	640.1 ± 1.1	587.6	52.5
C18	656.6 ± 1.4	608.4	48.2

a) Final concentration is 1.0×10^{-3} mol dm^{-3}.

This is a phenomenon similar to that observed for the ΔH_d of TDS[5] and FA[4] in ethanol.

Values of ΔH_d of $(FA)_6(NAA)_6$ No concentration dependence of ΔH_d of FA [4] and NAA was found within the concentration range of 1×10^{-3}—2×10^{-2} and 1×10^{-4}—5×10^{-3} mol dm^{-3}, respectively. ΔH_d of $(FA)_6(NAA)_6$ was, therefore, measured at a constant concentration (final solution concentration of $(FA)_6(NAA)_6$ was 1.0×10^{-3} mol dm^{-3}), and the results are summarized in Table II. The large value of ΔH_d is due to that 1 mol of the complex $(FA)_6(NAA)_6$ is composed of 6 mol of FA and 6 mol of NAA. ΔH_d increased with an increase in carbon numbers (*n*) of the constituent FA.

Discussion

Effect of Alkyl Chain Length of FA on ΔH_d of $(FA)_6(NAA)_6$ The values of ΔH_d of $(FA)_6(NAA)_6$ were plotted against *n*, and shown in Fig. 1. In the results, the plots of ΔH_d *vs.* *n* displayed a significant zig-zag pattern with an upward convex at odd-numbered positions even though the standard deviation was taken into consideration. This phenomenon suggests a stronger binding force for $(FA)_6(NAA)_6$ formed with odd-numbered FA, $(C_{2a-1})_6(NAA)_6$, than that formed with even-numbered FA, $(C_{2a})_6(NAA)_6$. Because the ΔH_d of FA[4] increases linearly by increasing *n* taking the standard deviation into account. In addition, the zig-zag pattern observed for $(FA)_6(NAA)_6$ is similar to that observed [5] for $(FA)_6(TDS)$, suggesting that $(FA)_6(NAA)_6$ has a similar structure to $(FA)_6(TDS)$.

The significant zig-zag line may be able to be separated by two individual lines among $(FA)_6(NAA)_6$, with the even-numbered FA and the odd-numbered FA drawn by two dotted lines as in Fig. 1, though only a few runs. The upper line represents $(C_{2a-1})_6(NAA)_6$ and the lower one $(C_{2a})_6(NAA)_6$, where the dotted line for $(C_{2a-1})_6(NAA)_6$ was drawn according to the slope for $(C_{2a})_6(NAA)_6$ because only two runs are insufficient to draw a line. The difference between the two dotted lines is obtained as approximately 15 kJ mol^{-1}. The $\{(CH_2)_2\}_6$-increment of ΔH_d is obtained as 64.40±0.31 kJ (mol $-\{(CH_2)_2\}_6-)^{-1}$ from the slope of the dotted line for $(C_{2a})_6(NAA)_6$. This value, 64.40±0.31 kJ, is slightly larger than that obtained[5] for $(FA)_6(TDS)$, 61.50±0.25 kJ. One mole of $(FA)_6(NAA)_6$ is composed of 6 mol of FA. Therefore, the (CH_2)-increment of FA was obtained as 5.37±0.03 kJ (mol $-CH_2-)^{-1}$. The increment in ΔH_d of FA as a function of the number of methylene groups ($-CH_2-$) in the alkyl chain has been obtained as 4.40±0.10 kJ (mol $-CH_2-)^{-1}$.[4] The (CH_2)-increment of ΔH_d obtained from the values of ΔH_d of $(FA)_6(NAA)_6$ is slightly larger in comparison with that obtained from the value of FA.[4]

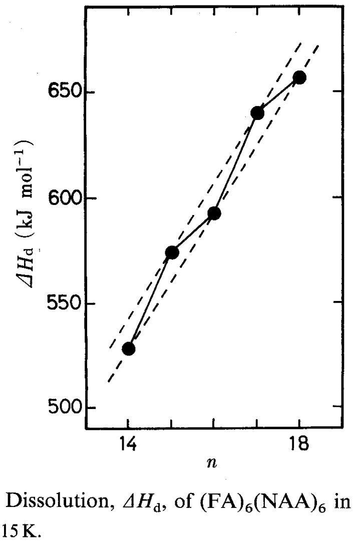

Fig. 1. Heats of Dissolution, ΔH_d, of $(FA)_6(NAA)_6$ in Ethanol
Temperature: 310.15 K.

Binding Force between FA and NAA It has been found that $(FA)_6(NAA)_6$ is not formed from the dissolved FA and NAA in an ethanol solution.[1] The binding force between FA and NAA will be estimated on the basis of the fact. The values of summation of ΔH_d of 6 mol of FA[4] and 6 mol of NAA were calculated, and summarized in Table II, where 22.3 kJ mol^{-1} at 1.0×10^{-3} mol dm^{-3} was used as the value of ΔH_d of NAA. The values of ΔH_d of $(FA)_6(NAA)_6$ are larger than those of (6FA + 6NAA). The differences ($\Delta\Delta H_d$) were shown in the righthand column of Table II. The value of $\Delta\Delta H_d$ for $(C_{2a-1})_6(NAA)_6$ was slightly larger than that for $(C_{2a})_6(NAA)_6$ whose alkyl chain of FA is one carbon number longer, though the values of $\Delta\Delta H_d$ increased rather ragularly with an increase of the alkyl chain length for only even-numbered or odd-numbered FA. It is suggested that the binding force between FA and NAA for $(C_{2a-1})_6(NAA)_6$ is stronger than that for $(C_{2a})_6(NAA)_6$.

Unfortunately, the values of $\Delta\Delta H_d$ are not exactly equal to the binding forces between FA and NAA because the enthalpies of the lattice fusion of FA and NAA in the $(FA)_6(NAA)_6$ may not be equal to those of FA alone and NAA alone. However, it may be possible to discuss approximately the magnitude of the binding force between FA and NAA. NAA has a functional group of $-CONH_2$, and FA has a functional group of $-COOH$. Regarding the hydrogen bond between $O-H\cdots O$, the enthalpy of hydrogen bond formation has been reported as -28 kJ mol^{-1} per hydrogen bond for the dimer of C18.[6] Regarding the hydrogen bond between $O-H\cdots N$, the enthalpies of the dimerization of formamide ($HCONH_2$)[7] and schiff bases[8] have been reported as -29 kJ mol^{-1} and -35—-40 kJ mol^{-1}, respectively. A comparison between these hydrogen bond values and the values of $\Delta\Delta H_d$ indicates that $(FA)_6(NAA)_6$ is formed by a weak binding force between FA and NAA roughly similar to single or double hydrogen bonding. However, it is unnatural that $(FA)_6(NAA)_6$ is formed by only one or two hydrogen bonds between 6 molecules of FA and 6 molecules of NAA. It is, therefore, suggested that $(FA)_6(NAA)_6$ is formed by van der Waals forces and hydrophobic interactions between FA and NAA. In addition, the value of $\Delta\Delta H_d$ for $(FA)_6(NAA)_6$ is larger than that[5] for $(FA)_6(TDS)$, though TDS[2a)] has functional groups of $-NH_2$, $-CHO$ and $-OH$. This result is reasonable, because it is considered that van der Waals forces and hydrophobic interactions are dominant rather than hydrogen bonds between $(FA)_6$ host and guest molecules for the formation of $(FA)_6(NAA)_6$ or $(FA)_6(TDS)$ and that the interactions of $(FA)_6$ with 6 molecules of NAA are larger than those with 1 molecule of TDS.

Conclusion

The plots of ΔH_d of $(FA)_6(NAA)_6$ against *n* showed a zig-zag pattern with an upward convex at odd-numbered positions, though ΔH_d increased by increasing *n*. The difference, $\Delta\Delta H_d$, between ΔH_d of $(FA)_6(NAA)_6$ and ΔH_d of $(6FA+6NAA)$ for $(C_{2a-1})_6(NAA)_6$ was slightly larger than that for $(C_{2a})_6(NAA)_6$, indicating that $(C_{2a-1})_6$-$(NAA)_6$ is formed by stronger binding forces than $(C_{2a})_6$-$(NAA)_6$. The value of $\Delta\Delta H_d$ was small as 30—53 kJ mol^{-1}. It is suggested that $(FA)_6(NAA)_6$ may be an inclusion compound or a clathrate formed by weak binding forces, van der Waals forces and hydrophobic interactions, between FA and NAA.

References

1) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, A. Kaneko, and S. Yokoyama, *Bitamin*, **62**, 669 (1988).
2) *a*) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 2696 (1991); *b*) *Idem*, *ibid.*, **39**, 3075 (1991); *c*) *Idem*, *ibid.*, **39**, 3114 (1991).
3) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 1634 (1991); *idem*, *Bull. Chem. Soc. Jpn.*, **64**, 3168 (1991).
4) S. Yokoyama and T. Fujie, *Chem. Pharm. Bull.*, **38**, 2347 (1990).
5) S. Yokoyama, F. Ueda, A. Kaneko, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 1573 (1991).
6) D. S. Sarkadi and J. H. De Boer, *Recl. Trav. Chim. Pays-Bas*, **76**, 628 (1957).
7) D. Poland and H. A. Scheraga, *Biochemistry*, **6**, 3791 (1967).
8) V. Buss and L. Simon, *J. Chem. Soc., Chem. Commun.*, **1986**, 1032.