Release Kinetics of Nicotinamide from Fatty Acid–Nicotinamide Equimolar Complexes. II.[1] Activation Thermodynamic Quantities

Shoko YOKOYAMA,*[,a] Fumio UEDA,[b] 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 July 15, 1991*

The rates of release of nicotinamide (NAA) from fatty acid (FA)–NAA complexes, FA–NAA, were determined at various temperatures, and the thermodynamic quantities for the release of NAA were estimated. The results were compared with the previous results obtained for FA–thiamine disulfide (TDS) complexes, $(FA)_6$(TDS).

The values of activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) for the release of NAA from FA–NAA were positive and negative, respectively, indicating that the release of NAA is disadvantageous from not only enthalpic but also entropic viewpoints. The plots of $\Delta H^{\ddagger}$ against the carbon number (n) in the constituent FA showed a zig-zag line with an upward convex at an odd-numbered position and the polts of the absolute values of $|-\Delta S^{\ddagger}|$ showed a zig-zag line with a downward convex at an odd-numbered position, though the positive value of $\Delta H^{\ddagger}$ increases and the negative value of $\Delta S^{\ddagger}$ decreases with an increasing n for either even-numbered or odd-numbered FA. It was found that the release of NAA from FA–NAA formed with odd-numbered FA is more disadvantageous enthalpically but more advantageous entropically as compared with that from FA–NAA formed with even-numbered FA. This phenomenon was similar to that observed for $(FA)_6$(TDS). Furthermore, it is suggested that FA–NAA is formed at least by van der Waals forces and hydrophobic interactions and that van der Waals forces are dominant for the formation of FA–NAA formed with odd-numbered FA and that hydrophobic interactions are dominant for the formation of FA–NAA formed with even-numbered FA.

Keywords nicotinamide; complex; fatty acid; release; release rate; kinetics; activation energy; activation enthalpy; activation entropy; odd–even effect

It has been found[2] that nicotinamide (NAA) forms the crystalline complex with higher saturated fatty acid (FA) whose molar ratio of FA to NAA is 1 : 1, FA–NAA. The release behavior of NAA from FA–NAA at 37 °C has already been determined.[1,3] In the study,[3] it was suggested that FA–NAA might be applicable to the preparation of sustained-release drug formulation and that FA–NAA is clinically useful from the viewpoint of little side effects. Furthermore, interesting phenomenon were found[1] from the physicochemical viewpoint: namely (1) the release rate of NAA from FA–NAA formed with odd-numbered FA is slower than that formed with even-numbered FA whose alkyl chain length is one more carbon number longer; (2) the relationship between the release rate constant (k) and the carbon number (n) of the constituent FA is a zig-zag one with a downward convex at an odd-numbered position.

On the other hand, FA–drug complexes have been found for thiamine disulfide (TDS), $(FA)_6$(TDS), and the release kinetics of TDS from $(FA)_6$(TDS) has already been carried out and the activation thermodynamic quantities for the release of TDS from $(FA)_6$(TDS) have been obtained.[4]

In the previous paper,[1] it was found that the plots of k *vs.* n at 37 °C indicate similar patterns for both FA–NAA and $(FA)_6$(TDS). In this paper, the values of activation energy, activation enthalpy and activation entropy will be estimated by the measurements of the release rates of NAA from FA–NAA at various temperatures, and the results will be compared with the results[4] obtained for $(FA)_6$(TDS).

Experimental

Materials NAA, tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17) and octadecanoic acid (C18) were the same as those used for the previous studies.[1-3] FA–NAA were prepared as follows: FA and NAA were dissolved in warm 1,2-dichloroethane, and the solution was set aside to crystallize.[1-3] The purity of each FA–NAA was examined by measuring the melting point of FA–NAA.[3] After it had been confirmed that no extra free FA and/or NAA was present, crystals of FA–NAA were passed through 48 and 60 mesh sieves, and the particles of 48—60 mesh[3] were taken for the release test.

Measurement of the Release of NAA from FA–NAA The release of NAA from FA–NAA was determined in a JP XI dissolution test apparatus (paddle method) in 500 ml of JP XI disintegration test medium No. 1 (pH 1.2) as described in the previous papers.[1,3] About 29—33 mg of each FA–NAA was used in the test. Experiments were carried out not only at 37 °C[1] but also at 32, 42 and 47 ± 0.2 °C. All experiments were carried out in triplicate and the results were highly reproducible.

Quantitative Analysis of NAA The concentration of released NAA was determined spectrophotometrically as previously described.[1,3]

Results

Release Behavior of NAA from FA–NAA The release behaviors of NAA from C14–NAA, C15–NAA, C16–NAA, C17–NAA and C18–NAA at four temperatures are shown as a relationship between the percentage of released NAA and time in Figs. 1—5, respectively. The percentages of released NAA were calculated with respect to the theoretical total concentration of NAA which is contained

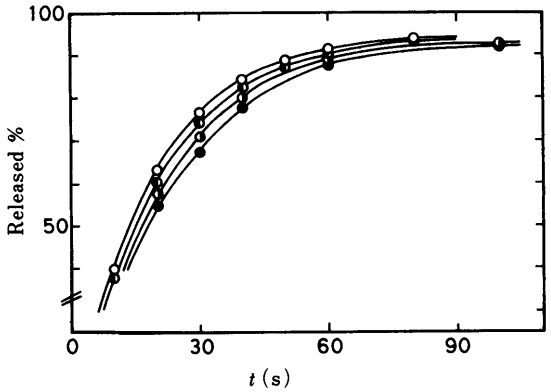

Fig. 1. Effect of Temperature on the Release Behavior of NAA from C14–NAA

Temperature: ●, 32 °C; ◑, 37 °C; ◐, 42 °C; ○, 47 °C. Particle size: 48—60 mesh.

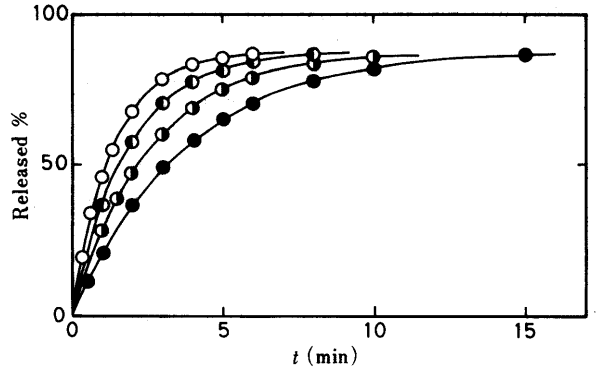

Fig. 2. Effect of Temperature on the Release Behavior of NAA from C15–NAA

Symbols are the same as in Fig. 1.

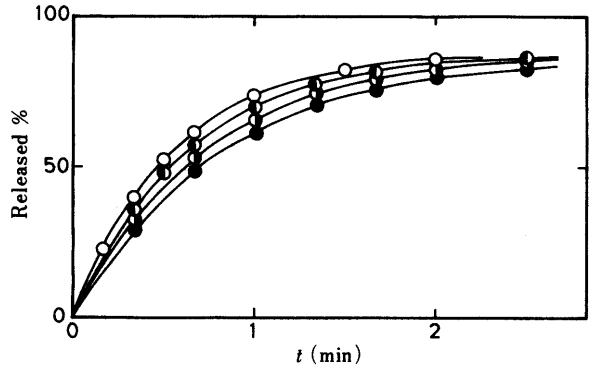

Fig. 3. Effect of Temperature on the Release Behavior of NAA from C16–NAA.

Symbols are the same as in Fig. 1.

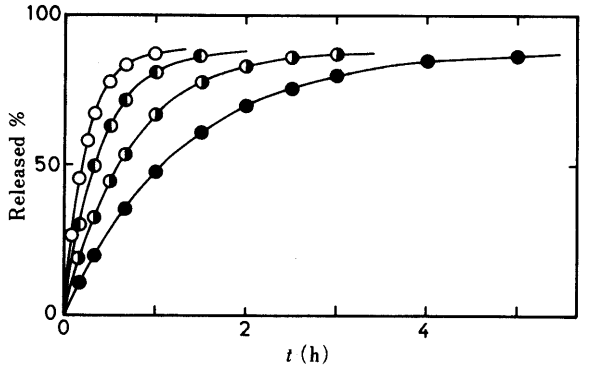

Fig. 4. Effect of Temperature on the Release Behavior of NAA from C17–NAA

Symbols are the same as in Fig. 1.

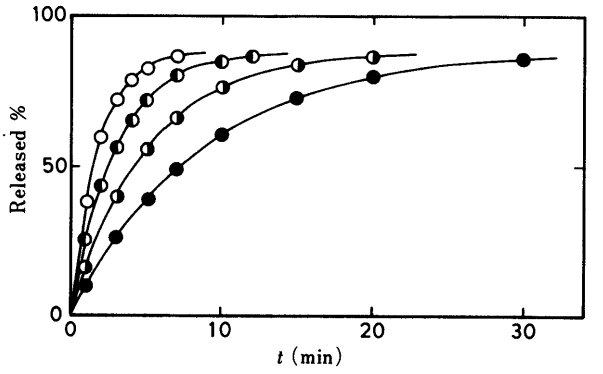

Fig. 5. Effect of Temperature on the Release Behavior of NAA from C18–NAA

Symbols are the same as in Fig. 1.

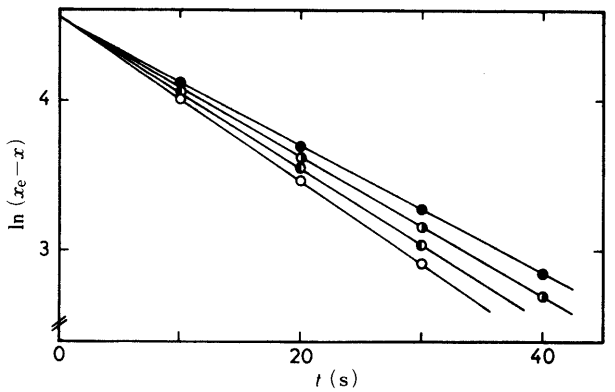

Fig. 6. Effect of Temperature on the Release of NAA from C14–NAA, $\ln(x_e-x)$ *vs.* Time

Symbols are the same as in Fig. 1.

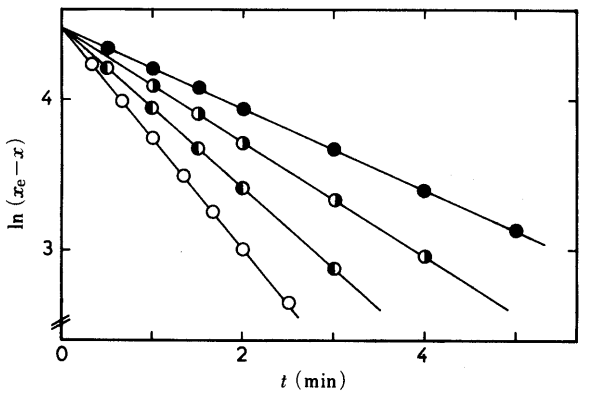

Fig. 7. Effect of Temperature on the Release of NAA from C15–NAA, $\ln(x_e-x)$ *vs.* Time

Symbols are the same as in Fig. 1.

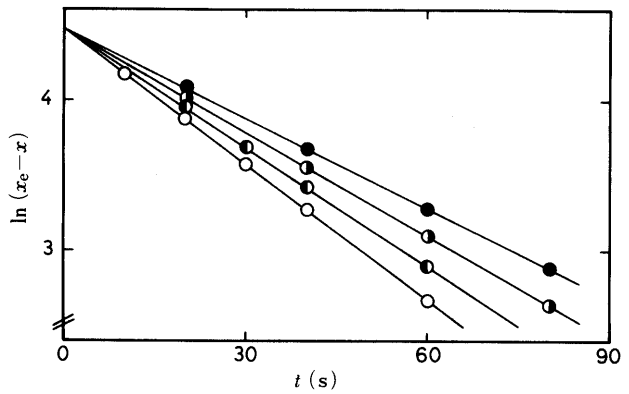

Fig. 8. Effect of Temperature on the Release of NAA from C16–NAA, $\ln(x_e-x)$ *vs.* Time

Symbols are the same as in Fig. 1.

in the 1 : 1 complex, FA–NAA. The equilibrium percent of released NAA was 90—95 under various conditions. The release rate of NAA is faster under the condition of higher temperature.

Rate Constants for the Release of NAA from FA–NAA It was confirmed[1] that the release of NAA from FA–NAA under the experimental conditions can be treated as a pseudo first-order reaction. The rate constant for the release of NAA is, therefore, defined as follows:

$$\ln(x_e-x)=\ln x_e-kt \quad (1)$$

where k is the rate constant of release, x is the percentage of NAA released from FA–NAA during time t, and x_e is the equilibrium percent of released NAA. Plots of $\ln(x_e-x)$ *vs.* t, calculated from the values shown in Figs. 1—5, are presented in Figs. 6—10. As can be seen in Figs. 6—10, good linear relationships were obtained in all cases. The values of k were obtained from the slopes shown in Figs. 6—10. The values of log k obtained for C14–NAA, C15–NAA, C16–NAA, C17–NAA and C18–NAA at three temperatures are plotted against n of the constituent FA in Fig. 11. As can be seen in Fig. 11, the plots of log k against n showed zig-zag lines with a downward convex at odd-numbered positions.

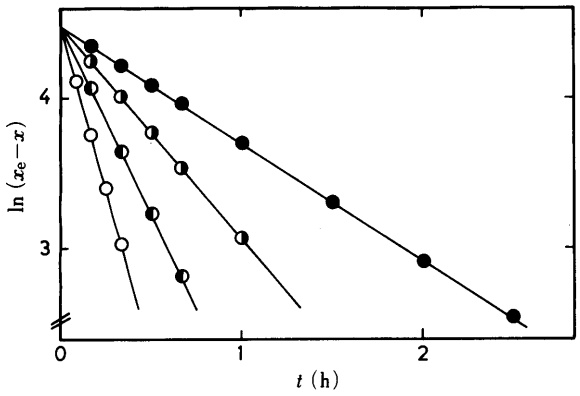

Fig. 9. Effect of Temperature on the Release of NAA from C17–NAA, $\ln(x_e-x)$ *vs.* Time

Symbols are the same as in Fig. 1.

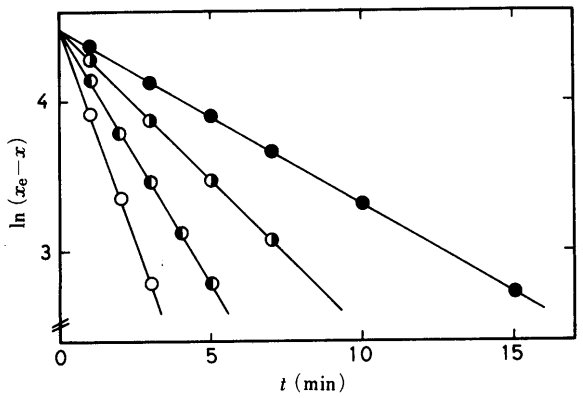

Fig. 10. Effect of Temperature on the Release of NAA from C18–NAA, $\ln(x_e-x)$ *vs.* Time

Symbols are the same as in Fig. 1.

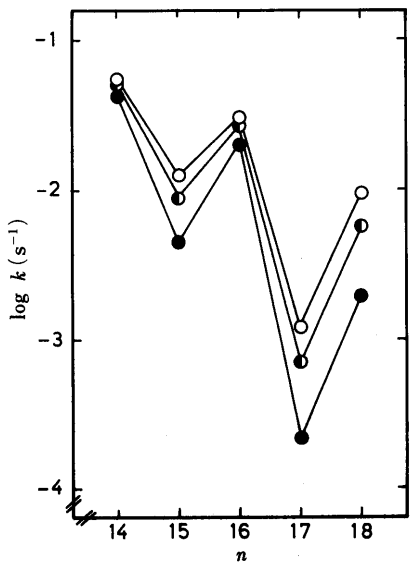

Fig. 11. Effect of FA on the Release Rate Constants (k) of NAA from FA–NAA

Symbols are the same as in Fig. 1.

Discussion

Activation Energy for the Release of NAA from FA–NAA The values of k were found to depend on the temperature. The activation energy (E^*) for the release can, therefore, be calculated from the values of k. According to the theory of Arrhenius, the relationship between k and the absolute temperature (T) is represented as follows:

$$\ln k = -\frac{E^*}{R}\cdot\frac{1}{T}+\ln A \qquad (2)$$

where R is the gas constant and A is a constant which is called frequency factor. Plots of $\ln k$ *vs.* $1/T$ based on Eq. 2 are shown in Fig. 12. As is clear in Fig. 12, the relationship between $\ln k$ and $1/T$ can be represented by a single line which depends on the alkyl chain length of FA. The values of E^* were, therefore, obtained from the values of the slopes, and the results were summarized in Table I. The positive value of E^* for FA–NAA formed with odd-numbered FA was larger than that for FA–NAA formed with even-numbered FA whose alkyl chain length is one more carbon number longer, though E^* increased rather regularly witn an increase of n for either even-numbered or odd-numbered FA. The slower release rate of NAA from FA–NAA formed with odd-numbered FA, which is shown in Fig. 11, could be explained by the relationship between E^* and n.

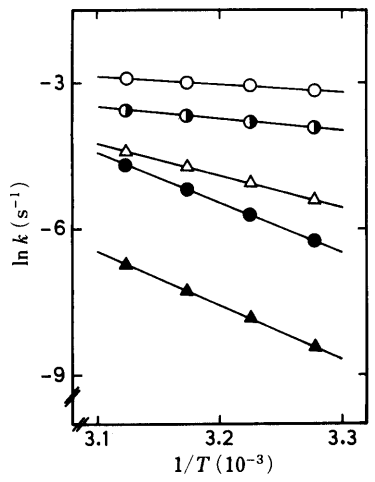

Fig. 12. Arrhenius Plots

Carbon numbers in FA: ○, 14; △, 15; ◑, 16; ▲, 17; ●, 18.

TABLE I. Activation Energies for the Release of NAA from FA–NAA

	C14–NAA	C15–NAA	C16–NAA	C17–NAA	C18–NAA
E^* (kJ mol^{-1})	13.9	54.4	22.2	92.7	85.2

Activation Thermodynamic Quantities for the Release of NAA from FA–NAA The values of activation Gibbs energy (ΔG^*) for the release of NAA from FA–NAA were estimated from the values of k as previously described.[4] The values of ΔG^* were graduated at ordinate in Fig. 13. All the values of ΔG^* are positive.

Next, we investigated which activation thermodynamic parameter contributes to the positive value of ΔG^*. ΔG^* is related to activation enthalpy (ΔH^*) and activation entropy (ΔS^*) as follows:

$$\Delta G^* = \Delta H^* - T\Delta S^* \quad (3)$$

According to Eq. 3, the values of ΔG^* were plotted against T, and the relationship is shown in Fig. 13.

As can be seen in Fig. 13, the relationship between ΔG^* and T can be represented by a single line for each complex with a different chain length of FA. The values of ΔS^* were, therefore, obtained from the values of the slope. ΔH^* was approximately estimated from the intercept, which agreed well with the value from the slope of $\Delta G^*/T$ *vs.* $1/T$ and nearly with the approximate evaluation, $E^* - RT$. The results are summarized in Table II. As can be seen in Table II, the value of ΔH^* is positive and the value of ΔS^* is negative. This indicates that the release of NAA from FA–NAA is disadvantageous not only enthalpically but also entropically. These are the same tendencies as the results obtained for $(FA)_6$(TDS).[4]

Effect of FA on the Activation Thermodynamic Quantities The values of ΔG^* at 310.15 K, ΔH^* and ΔS^* for the release of NAA from FA–NAA are represented graphically against n in Fig. 14. As can be seen in Fig. 14, the plots of positive values of ΔH^* *vs.* n indicate a zig-zag line with an upward convex at an odd-numbered position, while the plots of negative values of ΔS^* *vs.* n indicate a zig-zag line with a downward convex at an odd-numbered position. This indicates that the release of NAA from FA–NAA formed with odd-numbered FA is more disadvantageous enthalpically but more advantageous entropically as compared with that formed with even-numbered FA. Furthermore, the positive value of ΔH^* increases and the negative value of ΔS^* decreases with an increasing n for either even-numbered or odd-numbered FA. This indicates that the release of NAA from FA–NAA with a longer alkyl chain of FA is more disadvantageous enthalpically but more advantageous entropically. However, the positive value of ΔG^* increases with an increasing n for either even-numbered or odd-numbered FA, and the plots of ΔG^* *vs.* n indicate a zig-zag line with an upward convex at an odd-numbered position.

The comparison of the magnitude of $|\Delta H^*|$ with $|T\Delta S^*|$ were summarized in Table III. $|\Delta H^*|$ was larger than $|T\Delta S^*|$ for FA–NAA formed with odd-numbered FA. In addition, $|\Delta H^*|$ was larger than $|T\Delta S^*|$ for FA–NAA formed with even-numbered FA whose alkyl chain length is longer, while $|\Delta H^*|$ was smaller than $|T\Delta S^*|$ for FA–NAA formed with even-numbered FA whose alkyl chain length is shorter. This is the only difference from the results[4] that $|\Delta H^*|$ is larger than $|T\Delta S^*|$ for all of $(FA)_6$-(TDS). One reason for this cause is considered to be related to the extremely small values of ΔH^* for C14–NAA and C16–NAA as compared with the value of ΔH^* for $(FA)_6$-

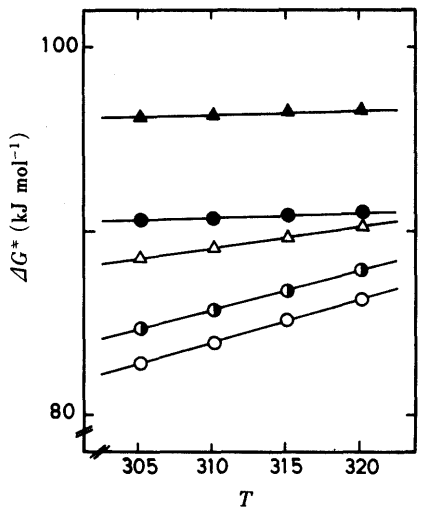

Fig. 13. Relationship between Activation Gibbs Energy and Temperature

Symbols are the same as in Fig. 12.

Table II. Activation Thermodynamic Quantities for the Release of NAA from FA–NAA

	ΔG^* (kJ mol^{-1})[a]	ΔH^* (kJ mol^{-1})	ΔS^* (J K^{-1} mol^{-1})
C14–NAA	84.0	11.6	−233
C15–NAA	89.1	51.9	−120
C16–NAA	85.8	19.3	−214
C17–NAA	96.3	90.1	−20.0
C18–NAA	90.8	83.0	−25.0

a) At 310.15 K.

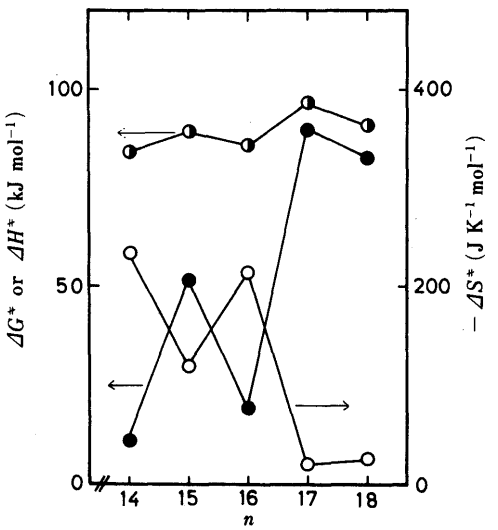

Fig. 14. Effect of FA on the Activation Thermodynamic Quantities for the Release of NAA from FA–NAA

Thermodynamic parameter: ◑, ΔG^*; ●, ΔH^*; ○, ΔS^*.

Table III. Comparison of the Magnitude of $|\Delta H^*|$ with $|T\Delta S^*|$

C14–NAA	$\|\Delta H^*\| < \|T\Delta S^*\|$
C15–NAA	$\|\Delta H^*\| > \|T\Delta S^*\|$
C16–NAA	$\|\Delta H^*\| < \|T\Delta S^*\|$
C17–NAA	$\|\Delta H^*\| > \|T\Delta S^*\|$
C18–NAA	$\|\Delta H^*\| > \|T\Delta S^*\|$

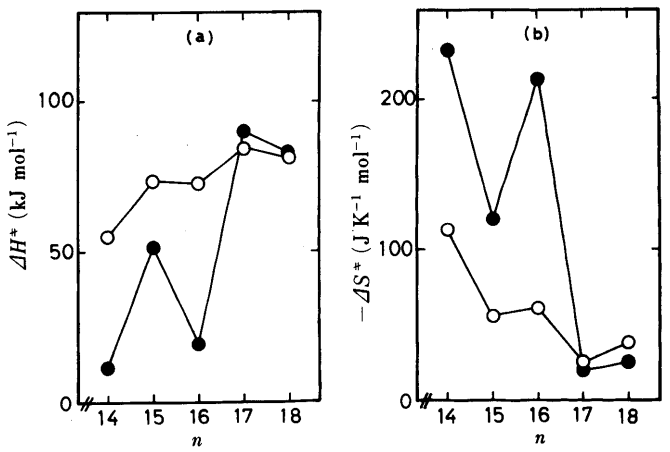

Fig. 15. Comparison of ΔH^* and ΔS^* between FA–NAA and $(FA)_6$-(TDS)

(a) Plots of ΔH^* *vs. n*. (b) Plots of ΔS^* *vs. n*. Complex: ●, FA–NAA; ○, $(FA)_6$-(TDS).

(TDS). Taking into account the change in the magnitude of $|\Delta H^*|$ and $|T\Delta S^*|$ ($|\Delta H^*| > |T\Delta S^*|$ or $|\Delta H^*| < |T\Delta S^*|$), it is reasonable to regard that FA–NAA is composed of *m* molecules of FA and *m* molecules of NAA, where *m* is not unity ($m > 1$).

Regarding the formation of complexes, it has been reported[5] that complexes formed by hydrophobic interactions have an approximate zero of ΔH^* and a positive value of ΔS^* and that complexes formed by van der Waals forces have a negative value of ΔH^* and a negative value of ΔS^*. According to the report,[5] it is suggested that hydrophobic interactions are dominant for the formation of FA–NAA composed of even-numbered FA whose alkyl chain length is shorter and that van der Waals forces are dominant for the formation of FA–NAA composed of even-numbered FA whose alkyl chain length is longer or composed of odd-numbered FA. This tendency for FA–NAA is similar to $(FA)_6$(TDS).

Comparison of the Activation Thermodynamic Quantities between FA–NAA and $(FA)_6$(TDS) In order to make a comparison between the release characteristics of NAA from FA–NAA and TDS from $(FA)_6$(TDS), the values of ΔH^* and $-\Delta S^*$ for FA–NAA were shown by closed circles in Fig. 15 together with the values[4] for $(FA)_6$-(TDS) which were shown by open circles. The plots of ΔH^* *vs. n* show zig-zag lines with an upward convex at odd-numbered positions. It is found that the relationship between ΔH^* and *n* for FA–NAA is similar to that for $(FA)_6$(TDS). However, the variation of ΔH^* for FA–NAA owing to the difference in *n* is larger than that for $(FA)_6$(TDS). Namely, the positive value of ΔH^* for FA–NAA is evidently smaller compared with that for $(FA)_6$(TDS) in the case of $14 \leqq n \leqq 16$, while the value of ΔH^* for FA–NAA becomes slightly larger than that for $(FA)_6$(TDS) in the case of $n \geqq 17$.

On the other hand, the polts of ΔS^* *vs. n* show zig-zag lines with a downward convex at odd-numbered positions. The relationship between ΔS^* and *n* for FA–NAA is similar to that for $(FA)_6$(TDS). The variation of ΔS^* for FA–NAA owing to the difference in *n* is larger than that for $(FA)_6$(TDS). Namely, the negative value of ΔS^* for FA–NAA is evidently larger as compared with that for $(FA)_6$(TDS) in the case of $14 \leqq n \leqq 16$, while the negative value of ΔS^* for FA–NAA becomes slightly smaller than that for $(FA)_6$(TDS) in the case of $n \geqq 17$. As described above, it is evident that FA–NAA has a similar physicochemical property to $(FA)_6$(TDS) and that the variation of physicochemical property of FA–NAA owing to the difference in *n* is larger than that of $(FA)_6$(TDS). This may be considered to the due to that FA–NAA is composed of *m* molecules of NAA and $(FA)_m$ in contrast to that $(FA)_6$(TDS) is composed of one molecule of TDS and $(FA)_6$. It is considered that FA–NAA with a longer alkyl chain of FA is more greatly stabilized than that with a shorter alkyl chain of FA as compared with the stability of $(FA)_6$(TDS) if the *m* molecules of NAA are included in $(FA)_m$. Recently, it was found that the molecular formula of FA–NAA is $(FA)_6(NAA)_6$. The content was promptly reported.[6]

$(FA)_6$(TDS) seems to be an inclusion compound.[4,7] The similar physicochemical properties between FA–NAA and $(FA)_6$(TDS) suggest that FA–NAA also may be an inclusion compound.

The structure formulas of NAA and TDS were shown in the previous paper.[1] NAA and TDS have the structure of a six-membered ring. NAA has a pyridine-ring, while TDS has two pyrimidine-rings which are linked by long side chains. It is therefore suggested that one molecule of TDS may be included axially in the $(FA)_6$ host structure, whereas six molecules of NAA may be included equatorially in $(FA)_6$. This may reflect the larger variation of ΔS^* and ΔH^* for FA–NAA owing to the difference in *n*.

Regarding the effect of polar groups, it has been found[7b] from the measurement of the heat of dissolution of $(FA)_6$-(TDS) that the polar groups ($-NH_2$, -OH and -CHO) do not contribute much to the binding force between $(FA)_6$ host and guest molecule. It is thought that the polar groups of the guest molecule contribute as a driving force for inclusion in the $(FA)_6$ host structure from the bulk phase, 1,2-dichloroethane solution.

Conclusion

The values of ΔH^* and ΔS^* for the release of NAA from FA–NAA were positive and negative, respectively. The plots of ΔH^* *vs. n* showed a zig-zag line with an upward convex at an odd-numbered position, while the plots of ΔS^* *vs. n* showed a zig-zag line with a downward convex at an odd-numbered position. These phenomena were similar to those observed for $(FA)_6$(TDS).

It is suggested by comparison of ΔH^* and ΔS^* among FA–NAA with various alkyl chains that FA–NAA is formed at least by van der Waals forces and hydrophobic interactions and that van der Waals forces are dominant for the formation of FA–NAA formed with odd-numbered FA and hydrophobic interactions are dominant for the formation of FA–NAA formed with even-numbered FA. These are also the same tendencies as estimated[4] for the formation of $(FA)_6$(TDS). It is suggested that FA–NAA may be an inclusion compound as well as $(FA)_6$(TDS).

Acknowledgement We are pleased to acknowledge the experimental assistance of Miss Y. Saitoh.

References

1) Part I: S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*,

39, 2696 (1991).
2) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, A. Kaneko, and S. Yokoyama, *Bitamin*, **62**, 669 (1988).
3) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 3075 (1991).
4) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **38**, 1819 (1990).
5) *a*) J. Martinle, J. Michon, and A. Rassat, *J. Am. Chem. Soc.*, **97**, 1818 (1975); *b*) M. Komiyama and M. L. Bender, *ibid.*, **100**, 2259 (1978); *c*) M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Perlmutter, and D. S. Kristol, *ibid.*, **111**, 6765 (1989).
6) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 1634 (1991).
7) *a*) S. Yokoyama and T. Fujie, *Chem. Pharm. Bull.*, **38**, 2249 (1990); *b*) S. Yokoyama, F. Ueda, A. Kaneko, and T. Fujie, *ibid.*, **39**, 1573 (1991).