Release Kinetics of Nicotinamide from Fatty Acid–Nicotinamide Equimolar Complexes. I.[1] Release Characteristics of Fatty Acid Complexes

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The rates of release of nicotinamide (NAA) from fatty acid (FA)–NAA complexes, FA–NAA, were determined in a JP XI dissolution test apparatus in 500 ml of JP XI disintegration test medium No. 1 at 37°C. The release rate constant (k) and the activation Gibbs energy ($\Delta G^{\pm}$) for the release of NAA from FA–NAA were estimated. The results obtained for FA–NAA were compared with previous results obtained for the thiamine disulfide (TDS) complex, $(FA)_6$-(TDS).

The plots of log k against the carbon number of the constituent FA (n) presented a zig-zag line which indicates a downward convex at an odd-numbered position. The plots of $\Delta G^{\pm}$ against n showed a zig-zag line with an upward convex at an odd-numbered position, though the positive value of $\Delta G^{\pm}$ increased rather regularly with an increase of n for either even-numbered or odd-numbered FA.

The phenomena that the plots of log k *vs.* n and $\Delta G^{\pm}$ *vs.* n show zig-zag lines due to the difference between even- and odd-numbered FA were the same as observed previously for the release of TDS from $(FA)_6$ (TDS).

Keywords nicotinamide; complex; fatty acid; odd-even effect; release; release rate constant; activation Gibbs energy

Higher saturated fatty acids (FA) form crystalline complexes with water-soluble drugs in 1,2-dichloroethane[2]: for example, thiamine disulfide (TDS) complex $(FA)_6$-(TDS)[2a] whose molar ratio of FA to TDS is 6:1, and nicotinamide (NAA) complex FA–NAA[2b] whose molar ratio of FA to NAA is 1:1. The release rate of TDS from $(FA)_6$ (TDS) has already been determined.[3] In the release study of TDS from $(FA)_6$ (TDS), the plot of the release rate constant (k) of TDS against the carbon number of the constituent FA (n) showed a zig-zag line which was represented by an alternative convex at an odd-numbered position, and k decreased rather regularly with an increase of n for either even-numbered or odd-numbered FA. This is considered due to the greater stability of the TDS complex formed with odd-numbered FA compared with the complex formed with even-numbered FA. This is also reflected in the melting points[2a] of $(FA)_6$ (TDS). It is very interesting to see whether the zig-zag patterns as observed for $(FA)_6$-(TDS) will be seen with other drug complexes formed with FA.

By contrast, the results of the heat of dissolution of $(FA)_6$-(TDS)[4] and the association of FA in 1,2-dichloroethane[5] suggested that $(FA)_6$ (TDS) has an inclusion compound property. Determining a common feature among FA–drug complexes by measuring the release kinetics gives an important clue to the application of FA–drug complexes in pharmaceutical and other fields. In the previous paper,[6] the times required for 50% and 80% release of NAA from FA–NAA were shown, and it was suggested that FA–NAA may be applicable to the preparation of a sustained-release drug formulation. This paper presents the release rate constant and the activation Gibbs energy for the release of NAA from FA–NAA. Furthermore, the results obtained for FA–NAA are compared with the results[3] obtained for $(FA)_6$ (TDS), and the effects of the difference in FA will be discussed.

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.[2b,6] FA–NAA was prepared as follows: FA and NAA were dissolved in warm 1,2-dichloroethane, and the solution was set aside to crystallize.[2b] The purity of each FA–NAA was examined by measuring the melting point of FA–NAA.[6] 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[6] 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 paper.[6] About 30 mg of FA–NAA was used in the test. Experiments were carried out at 37 °C.

Quantitative Analysis of NAA The concentration of released NAA was determined spectrophotometrically as previously described.[6]

Results

Rate Constants for the Release of NAA from FA–NAA FA–NAA, FA and NAA are in equilibrium in an aqueous solution (pH 1.2) as follows:

$$\text{FA–NAA solid} \rightleftharpoons \text{FA solid} + \text{NAA}$$

where released NAA is dissolved in the test medium. FA and FA–NAA are almost insoluble in an aqueous acidic medium, and the solubilities of FA–NAA and FA are negligible under the experimental conditions. The percentages of released NAA were calculated with respect to the theoretical total concentration of NAA which is contained in the 1:1 complex, FA–NAA. The equilibrium percent of released NAA was 88—95% under the experimental conditions. The details were shown in the previous paper.[6]

In the equilibrium equation, it is assumed that the concentration change of FA is negligible because of its insolubility. Furthermore, it is assumed that the formation of FA–NAA by the reversed reaction is negligible because the concentration of FA–NAA formed by the reversed reaction is sufficiently lower than that of released NAA. According to the assumptions, the reaction of pseudo first order can be applied in this system. The rate constant for the release of NAA was defined as follows:

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

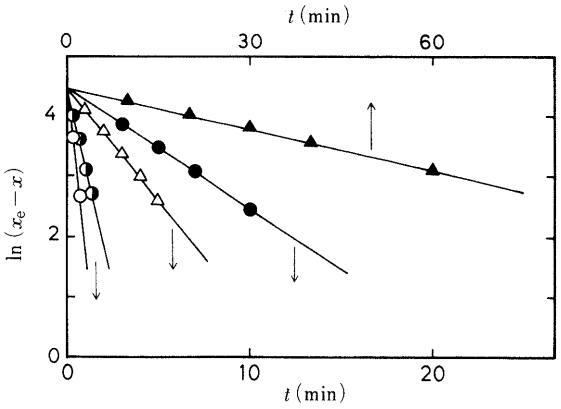


Fig. 1. Effect of FA on the Release of NAA from FA–NAA

Carbon numbers in FA: ○, 14; ◑, 16; ●, 18; △, 15; ▲, 17. Particle size: 48—60 mesh. Temperature: 37 °C.

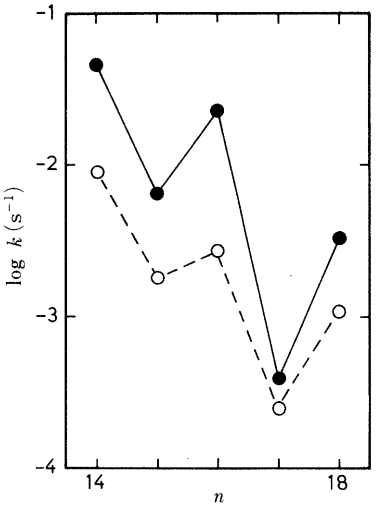


Fig. 2. Effect of FA on the Release Rate Constants (k) of NAA from FA–NAA and TDS[3] from $(FA)_6$(TDS)

Complex: ●, FA–NAA; ○, $(FA)_6$(TDS). Temperature: 37 °C.

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 are presented in Fig. 1. As can be seen in Fig. 1, good linear relationships were obtained in all cases. It was confirmed that the release of NAA can be represented by the first order reaction. The values of release rate constant k were obtained from the slopes shown in Fig. 1. The values of log k obtained for C14–NAA—C18–NAA at 37 °C are plotted against n by closed circles in Fig. 2. The results[3] of the corresponding fatty acid complexes with TDS were also drawn for comparison. Plots of log k against n showed a zig-zag line with a downward convex at an odd-numberd position, which was quite similar to that of the TDS complexes.

Discussion

Activation Gibbs Energy for the Release of NAA from FA–NAA The activation Gibbs energy, $\Delta G^{\ddagger}$, for the release of NAA from FA–NAA can be represented in terms of the release rate constant, k, as follows:

$$\Delta G^{\ddagger} = -RT \ln k + RT \ln(k_B T/h) \quad (2)$$

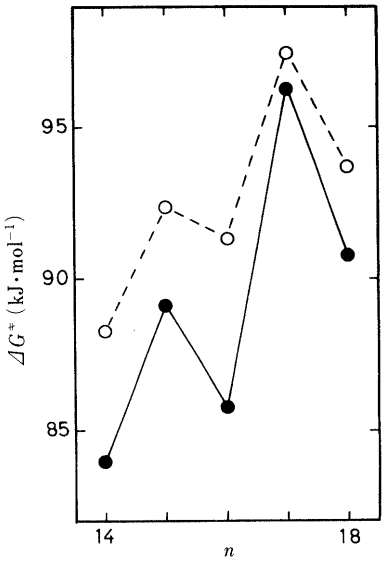


Fig. 3. Effect of FA on the Activation Gibbs Energies ($\Delta G^{\ddagger}$) for the Release of NAA from FA–NAA and TDS[3] from $(FA)_6$(TDS)

Complex: ●, FA–NAA; ○, $(FA)_6$(TDS). Temperature: 37 °C.

where R, k_B and h are the gas constant, Boltzmann constant and Planck constant, respectively. The values of $\Delta G^{\ddagger}$ were estimated from the values of k shown in Fig. 2, and the values of $\Delta G^{\ddagger}$ were plotted against n by closed circles in Fig. 3. The plots of the positive values of $\Delta G^{\ddagger}$ against n showed a zig-zag line with an upward convex at an odd-numbered position, indicating that the release of NAA from FA–NAA formed with odd-numbered FA is more disadvantageous than that from FA–NAA formed with even-numbered FA.

Comparison of k and $\Delta G^{\ddagger}$ between FA–NAA and $(FA)_6$-(TDS) In order to make a comparison between the release behaviors of NAA from FA–NAA and TDS from $(FA)_6$-(TDS), the previously obtained values of k[3] for $(FA)_6$(TDS) were shown by open circles in Fig. 2 together with the values of k for FA–NAA, where the measurement of k for $(FA)_6$-(TDS) was made under the same conditions as applied in this paper. As can be seen in Fig. 2, the absolute values of log k for FA–NAA and $(FA)_6$(TDS) formed with odd-numbered FA are larger than those formed with even-numbered FA whose alkyl chain length is one carbon number longer. The plots of log k *vs.* n show a similar zig-zag pattern in both cases of FA–NAA and $(FA)_6$ (TDS). In addition, it is found that the release rate of NAA from FA–NAA is faster than that of TDS from $(FA)_6$ (TDS). This phenomenon suggests that the binding force between FA and NAA is weaker than that between $(FA)_6$ and TDS. This leads to a further inference that FA–NAA does not consist of one molecule of FA and one molecule of NAA by a strong binding force but consists of n molecules of FA and n molecules of NAA by weakly physical binding modes.

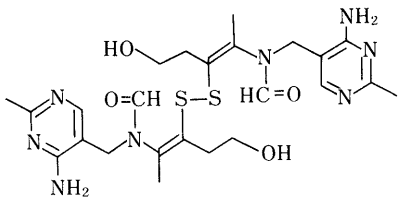
On the other hand, the previously obtained values[3] of $\Delta G^{\ddagger}$ at 37 °C for the release of TDS from $(FA)_6$ (TDS) were shown by open circles in Fig. 3 together with the values of $\Delta G^{\ddagger}$ for FA–NAA. As can be seen in Fig. 3, the positive values of $\Delta G^{\ddagger}$ for FA–NAA and $(FA)_6$ (TDS) formed with odd-numbered FA are larger than those formed with even-numbered FA whose alkyl chain length is one carbon number longer. The plots of $\Delta G^{\ddagger}$ *vs.* n show a similar zig-zag

pattern in the cases of both FA–NAA and $(FA)_6$ (TDS). In addition, it is found that the positive value of $\Delta G^{\neq}$ for FA–NAA is smaller than that for $(FA)_6$(TDS), indicating that the release of NAA from FA–NAA is easier than that of TDS from $(FA)_6$ (TDS).

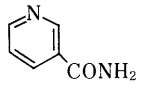
As described above, similar patterns with regard to the release of a drug from an FA–drug complex were found in the cases of both FA–NAA and $(FA)_6$ (TDS). FA–NAA may have a similar structure to $(FA)_6$ (TDS), though the molar ratio of FA to NAA is 1 : 1 for FA–NAA whereas the molar ratio of FA to TDS is 6 : 1 for (FA_6) (TDS).

Considering the weak interaction between FA and TDS estimated from the measurement[4] of the heat of dissolution of $(FA)_6$ (TDS), it was suggested that $(FA)_6$ (TDS) might be an inclusion compound. On the other hand, it was found in the infrared (IR) spectra[2] that the absorption band near 1700 cm^{-1} which is the characteristic of the carbonyl stretching vibration was shifted to higher frequency fields by the formation of either $(FA)_6$ (TDS) or FA–NAA. The similar patterns of IR spectra also imply that FA–NAA has a similar structure to $(FA)_6$ (TDS). Regarding higher and lower frequency shifts for the carbonyl stretching band, Nakai *et al.* reported[7] that the inclusion of *p*-acetoxydiphenyl into the β-cyclodextrin cavity caused a higher frequency shift whereas the formation of hydrogen bonding between *p*-acetoxydiphenyl and β-cyclodextrin caused a lower frequency shift. Taking account of the report[7] with regard to the IR spectra of an inclusion compound and a hydrogen-bonded compound, the IR spectra[2] of FA–NAA and $(FA)_6$ (TDS), the mechanism for the formation of FA–drug complexes in 1,2-dichloroethane,[5] and the release characteristics of $(FA)_6$-(TDS)[3] and FA–NAA, FA–NAA may be an inclusion compound, as may $(FA)_6$ (TDS).[3b,4] Recently, the existence of a new crystalline complex $(C18)_6$ $(NAA)_5$, whose molar ratio of C18 to NAA is 6 : 5, was confirmed.[8] Therefore, the structure formula of 1 : 1 complex FA–NAA may possibly be $(FA)_6$ $(NAA)_6$, in which six molecules of NAA are included in the $(FA)_6$ host structure. This suggestion leads to further inferences that FA–drug complexes formed in 1,2-dichloroethane have a basic structure composed of six molecules of FA, $(FA)_6$,[5] and that the differences in physiochemical properties shown in Figs. 2 and 3 are caused by the difference in the host structure composed of six molecules of odd-numbered FA or six molecules of even-numbered FA, although X-ray crystal structure analysis is necessary to discuss the structure of FA–NAA.

The diameter of the host cavity of $(FA)_6$ was estimated[5] to be 5.1—6.7 Å on the assumption that the host structure consists of six molecules of FA. This suggests a size similar



TDS



NAA

Chart 1

to the host cavity[9] of α- or β-cyclodextrin, although cyclodextrins in general includes a lipophilic compound whereas $(FA)_6$ includes a water-soluble compound. Regarding the inclusion of aromatic guest molecules in cyclodextrin, axial-, equatorial- and lid-type inclusions are known.[10] Taking account of the reports[10] and the structure formulas of TDS and NAA shown in Chart 1, the inclusion mode for NAA may differ from that for TDS: one molecule of TDS may be included axially in $(FA)_6$ whereas six molecules of NAA may be included equatorially in $(FA)_6$.

As described above, the release behavior of NAA from FA–NAA (whose molecular formula may possibly be $(FA)_6$-$(NAA)_6$) was similar to that[3] of TDS from $(FA)_6$ (TDS). In conclusion, it was suggested that the release characteristics of drugs from FA–drug complexes may depend on the basic structure composed of six molecules of FA.

References

1) This study was partly presented at the 111th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1991.
2) *a*) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, and A. Kaneko, *Bitamin*, **61**, 57 (1987); *b*) F. Ueda, T. Higashi, Y. Ayukawa, A. Takada, T. Fujie, A. Kaneko, and S. Yokoyama, *ibid.*, **62**, 669 (1988).
3) *a*) F. Ueda, T. Higashi, Y. Ayukawa, T. Fujie, and S. Yokoyama, *Chem. Pharm. Bull.*, **37**, 2545 (1989); *b*) S. Yokoyama, F. Ueda, and T. Fujie, *ibid.*, **38**, 1819 (1990).
4) S. Yokoyama and T. Fujie, *Chem. Pharm. Bull.*, **38**, 2347 (1990); S. Yokoyama, F. Ueda, A. Kaneko, and T. Fujie, *ibid.*, **39**, 1573 (1991).
5) S. Yokoyama and T. Fujie, *Chem. Pharm. Bull.*, **38**, 2249 (1990).
6) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, in press.
7) Y. Nakai, A. El-Said Aboutaleb, K. Yamamoto, S. I. Saleh, and M. O. Ahmed, *Chem. Pharm. Bull.*, **38**, 728 (1990).
8) S. Yokoyama, F. Ueda, and T. Fujie, *Chem. Pharm. Bull.*, **39**, 1634 (1991).
9) J. C. Harrison and M. R. Eftink, *Biopolymers*, **21**, 1153 (1982); W. C. Cromwell, K. Bystrom, and M. R. Eftink, *J. Phys. Chem.*, **89**, 326 (1985).
10) K. Harata and H. Uedaira, *Bull. Chem. Soc. Jpn.*, **48**, 375 (1975); N. Kobayashi, S. Minato, and T. Osa, *Makromol. Chem.*, **184**, 2123 (1983); N. Kobayashi, *J. Chem. Soc., Chem. Commun.*, **1988**, 918; *idem*, *ibid.*, **1989**, 1126.