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New Crystalline Complexes Composed of a Fatty Acid and Nicotinamide

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Synopsis. New crystalline complexes composed of a fatty acid (FA) and nicotinamide (NAA) at a molar ratio of 6:5, $(FA)_6(NAA)_5$, have been isolated. The melting points of $(FA)_6(NAA)_5$ were higher than those of the corresponding equimolar complexes, $(FA)_6(NAA)_6$.

We previously reported[1] that a fatty acid (FA) forms crystalline complexes with nicotinamide (NAA), 3-pyridine carboxamide, at a molar ratio of 1:1. These FA-complexes were obtained only in 1,2-dichloroethane.[1] A fatty acid forms an association complex similar to a reversed micelle in 1,2-dichloroethane.[2] The aggregation number in the association, though not yet determined, appears to be 6.[2] Association of FA molecules in 1,2-dichloroethane may be the first step for the crystalline FA-NAA complex formation. Further, the diameter of the host cavity of $(FA)_6$ is 5.1—6.7 Å if the host structure consists of six molecules of FA.[2] This cavity size is similar to that of α or β-cyclodextrin, though cyclodextrins generally include lipophilic compounds whereas $(FA)_6$ includes water-soluble compounds.

The FA–NAA equimolar complex is suggested to be of a formula $(FA)_6(NAA)_6$, in view of the formation mechanism of FA-complexes in 1,2-dichloroethane, though the actual molecular formula of the complex has not yet been determined. The FA–NAA complex is obtained as a solid, and the complex is decomposed to FA and NAA when dissolved in solvents. The complex is partially dissociated even when it is dissolved in 1,2-dichloroethane: this is because FA forms an association complex similar to a reversed micelle in 1,2-dichloroethane and that FA is in association equilibria, monomer$\rightleftarrows$dimer$\rightleftarrows$trimer$\rightleftarrows$hexamer, in this solvent.[2] Therefore, the molecular weight of the complex cannot be determined by a general method, namely vapor pressure or freezing point depression. Though X-ray crystal structure analysis is currently envisaged, it takes a long time to attain a clear result. In the meantime, we have isolated a new crystalline complex composed of octadecanoic acid (C18) and NAA from a 1,2-dichloroethane solution.[3] The formula of the new complex was $(C18)_6(NAA)_5$, and the C18-NAA equimolar complex is transformed into $(C18)_6(NAA)_5$ at temperatures below 22 °C by releasing 16% (≒ 1/6) of NAA, when cooled in acidic aqueous medium at temperature intervals of 5 °C from 37 °C.[3] This verified that the formula of the C18-NAA equimolar complex was $(C18)_6(NAA)_6$. Hereafter we denote the FA-NAA equimolar complex as $(FA)_6(NAA)_6$.

The melting point of $(C18)_6(NAA)_5$ was higher than that of $(C18)_6(NAA)_6$.[3] In view of this, the 6:5 complexes, $(FA)_6(NAA)_5$, with various alkyl chain length were prepared, and their melting points were systematically investigated in this work. The differences in the melting point between $(FA)_6(NAA)_5$ and $(FA)_6(NAA)_6$ 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 in previous work.[1] 1,2-Dichloroethane, ethanol, and a 0.1 M KOH ($M=mol\,dm^{-3}$) ethanol solution were the same as those used previously.[1,3]

Preparation of New Complexes. FA and NAA were dissolved at a molar ratio of about 1.4:1 in warm 1,2-dichloroethane, and the solutions were left standing at 20—25, 15—20, or 5—10 °C. Crystals were then obtained by filtration and dried under reduced pressure at room temperature.

Measurement of Melting Points. Melting points were determined with an apparatus equipped with a microscope (×100).

Quantitative Analysis of FA in the Complexes. Complexes with a unique melting point were chosen for quantitative analysis. Complexes were dissolved in ethanol, and the FA contained in the solution was titrated with a 0.1 M KOH ethanol solution.[1]

Elemental Analysis. Elemental analysis of the complex for C, H, and N was carried out by the thermal conductivity method.

Results

Conditions for Preparing New Complexes. It was difficult to obtain the new crystalline complexes in pure form. Occasionally FA, NAA, or $(FA)_6(NAA)_6$ was coprecipitated by changing the experimental conditions. The preparation conditions when the new complexes were obtained pure are summarized in Table 1, though these conditions are not necessarily the most appropriate ones.

Melting Points of the New Complexes. Since the melting point of $(C18)_6(NAA)_5$ is higher than that of $(C18)_6(NAA)_6$,[3] a compound with a melting point higher than that of $(FA)_6(NAA)_6$ was regarded as a new complex. The melting points of the new complexes are summarized in Table 2.

Table 1. Conditions for $(FA)_6(NAA)_5$ Preparation

Starting material[a)]		Solvent	Crystallization[b)]
NAA/g	FA/g	1,2-Dichloroethane/ml	temperature/°C
1.0	C18 3.25	200	20—25
1.0	C17 3.10	180	20—25
1.0	C16 3.10	60	15—20
1.0	C15 2.80	80	5—10
1.0	C14 2.55	100	5—10

a) Molar ratios of FA to NAA are approximately 1.4:1.
b) Crystallization time is 7 h in each case.

Table 2. Melting Points of $(FA)_6(NAA)_5$

$(FA)_6(NAA)_5$	Melting point/°C
$(C18)_6(NAA)_5$	87—89
$(C17)_6(NAA)_5$	89—91
$(C16)_6(NAA)_5$	83—85
$(C15)_6(NAA)_5$	85—87
$(C14)_6(NAA)_5$	78—80

Table 3. Quantitative Analysis of FA in the New Complexes

FA	Number of determinations	FA to NAA Molar ratio[a]
C18	6	1.20±0.00
C17	3	1.20
C16	6	1.19±0.02
C15	3	1.20
C14	6	1.19±0.01

a) Mean±SD.

Quantitative Analysis of FA in the New Complexes. The molar ratio of FA to NAA in the complex was determined by quantitative analysis of FA, and the results are shown in Table 3. As is seen, the molar ratio of FA to NAA is 1.2:1 for each case. This is in line with a molecular formula of $(FA)_6(NAA)_5$.

The starting mixing ratio of FA to NAA was 1.4:1, while the molar ratio of FA to NAA in the complex was 1.2:1. This is because FA exists partly as a monomer, dimer, or trimer in 1,2-dichloroethane.[2]

Elemental Analysis of the New Complexes. The results of elemental analyses of the new complexes are given in Table 4. The experimental values are well consistent with the theoretical values based on the molecular formula $(FA)_6(NAA)_5$. This further indicates that the new complexes are of the formula $(FA)_6(NAA)_5$.

Discussion

Comparison of $(FA)_6(NAA)_5$ with $(FA)_6(NAA)_6$. The melting points of $(FA)_6(NAA)_5$, $(FA)_6(NAA)_6$, and FA are shown in Fig. 1 against the carbon number (n) of the constituent FA. The melting point of an odd-numbered FA is lower than that of an even-numbered FA with an alkyl chain longer by one carbon atom, and the relationship between the melting point of FA and n takes a zig-zag form. The melting points of $(FA)_6(NAA)_6$ are higher than those of FA, especially with odd-numbered FA, and the melting point of $(FA)_6(NAA)_6$ changes roughly linearly with n. The melting points of $(FA)_6(NAA)_5$ are higher than those of $(FA)_6(NAA)_6$, and the difference is larger for compounds with odd-numbered FA. The zig-zag form of the melting point curve is neatly reversed between FA and $(FA)_6(NAA)_5$: the difference in melting point between $(FA)_6(NAA)_5$ and $(FA)_6(NAA)_6$ is 4—5 °C for even-numbered FA, and 8—9 °C for odd-numbered FA. This suggests that $(FA)_6(NAA)_5$ with odd-numbered FA is more thermostable than $(FA)_6(NAA)_5$ with even-numbered FA, and is related to an observation that pure $(FA)_6(NAA)_5$ with odd-numbered FA was formed more easily than pure $(FA)_6(NAA)_5$ with even-numbered FA: namely, coprecipitation of $(FA)_6(NAA)_6$ was to a lesser extent for odd-numbered FA.

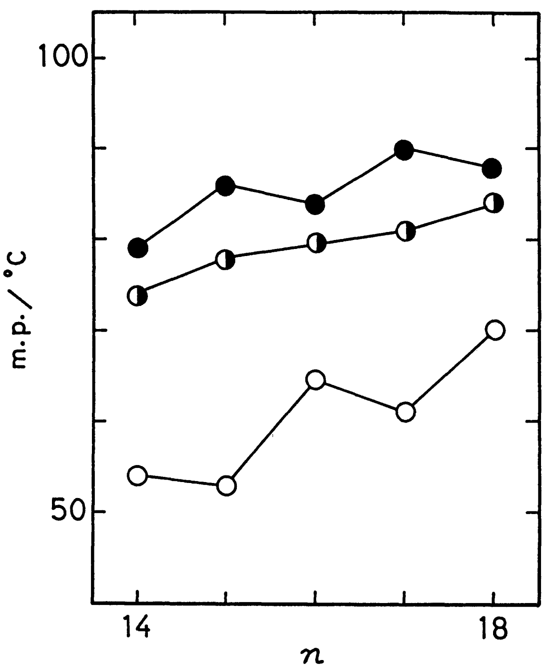

Fig. 1. Relationships between the melting point and n for $(FA)_6(NAA)_5$, $(FA)_6(NAA)_6$, and FA ●, $(FA)_6(NAA)_5$; ◑, $(FA)_6(NAA)_6$; ○, FA.

We now compare $(FA)_6(NAA)_5$ and $(FA)_6(NAA)_6$ for the preparation conditions. In preparing $(FA)_6(NAA)_5$, the mixing ratio of FA to NAA is slightly larger and the temparature for crystallization is lower. The complex formation between a FA and a water-soluble compound in 1,2-dichloroethane presumably begins with the solubilization of the water-soluble compound in the reversed micellar FA hexamer.[2] The amount of FA hexamer

Table 4. Elemental Analysis of $(FA)_6(NAA)_5$

Formula	Analysis/% Found (Calcd)		
	C	H	N
$(C_{18}H_{36}O_2)_6(C_6H_6N_2O)_5$	71.63 (71.52)	10.65 (10.70)	6.04 (6.05)
$(C_{17}H_{34}O_2)_6(C_6H_6N_2O)_5$	70.95 (70.99)	10.58 (10.56)	6.28 (6.27)
$(C_{16}H_{32}O_2)_6(C_6H_6N_2O)_5$	70.31 (70.41)	10.33 (10.41)	6.59 (6.52)
$(C_{15}H_{30}O_2)_6(C_6H_6N_2O)_5$	69.80 (69.79)	10.21 (10.25)	6.79 (6.78)
$(C_{14}H_{28}O_2)_6(C_6H_6N_2O)_5$	69.03 (69.12)	10.02 (10.08)	7.12 (7.07)

increases with increasing its concentration. This may have decreased the amount of NAA per FA hexamer $(FA)_6$ and have led to the formation of $(FA)_6(NAA)_5$.

The temperature also plays an important role in the crystallization of the two kinds of complexes. The temperature for crystallization may yield a difference in the tilting angle of FA molecules in the crystal structure of $(FA)_6$ which serves as a host. For example, even-numbered FA occur in three polymorphic modifications, A, B, and C.[4–6] In none of them do the chains rotate: they differ in the angle of the chains with respect to the plane of the carboxyl groups, A=chains vertical; B=chains tilted at 74°40′; C=chains tilted at 59°12′.[4] The latter two can be easily crystallized. Further, the polymorph B is obtained by slow crystallization at room temperature whereas the polymorph C is obtained by rapid crystallization at lower temperatures.[5]

The tilting angle of $(FA)_6$ in the crystal of $(FA)_6(NAA)_5$ may be different from that in $(FA)_6(NAA)_6$, similarly to the difference between the polymorphs B and C. Further, the tilting angle of $(FA)_6$ may depend on the temperature for crystallization. In view of the conditions for preparing $(FA)_6(NAA)_5$ and $(FA)_6(NAA)_6$, $(FA)_6(NAA)_5$ probably corresponds to the polymorph C of FA, while $(FA)_6(NAA)_6$ to the polymorph B. The heat of solution of the polymorph B is larger than that of the polymorph C.[5] The melting point of $(FA)_6(NAA)_5$ is higher than that of $(FA)_6(NAA)_6$, as seen in Fig. 1. These lead us to speculate that five NAA molecules are fit into the more tilted $(FA)_6$ more favorably than six NAA molecules into the less tilted $(FA)_6$, and hence $(FA)_6(NAA)_5$ is stabilized over $(FA)_6(NAA)_6$.

The reason why the thermostable $(FA)_6(NAA)_5$ was not obtained first, is related to the solubility of FA. Especially with C18, the preparing a pure complex is easier at higher temperatures, where coprecipitation of FA is well suppressed, than at lower temperatures, and the higher temperature thus favored the formation of $(FA)_6(NAA)_6$.

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