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Preparation and Physicochemical Properties of New Crystalline Complexes Composed of Fatty Acids and 3-Aminopyridine

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New crystalline complexes composed of fatty acids (FA) and 3-aminopyridine (3AP), FA–3AP, were prepared, and the physicochemical properties of FA–3AP were investigated by elemental analysis, differential scanning calorimetry and infrared (IR) spectroscopy and compared with those of FA–nicotinamide (NAA) complexes, FA–NAA.

The molar ratio of 3AP to FA in the FA–3AP was 1 : 1, the same as FA–NAA. The melting points of FA–3AP were lower than that of the corresponding FA–NAA and FA alone. The relationship between the melting points of FA–3AP and the carbon number (*n*) of the constituent FA took a linear form as shown in FA–NAA, whereas the relationship between the melting points of FA and *n* took a zig-zag one. In the IR spectrum, 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 FA–3AP as observed for FA–NAA. The binding of 3AP to FA seemed to be similar to that of NAA.

Keywords 3-aminopyridine; fatty acid; complex; infrared spectroscopy; differential scanning calorimetry; elemental analysis

It has been found[1] that nicotinamide (NAA) forms a crystalline complex with saturated higher fatty acid (FA) with 1 : 1 molar ratio of FA to NAA, FA–NAA. The release behavior of NAA from FA–NAA has been determined, and studies suggested[2a] 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 having minimal side effects. It was further suggested that docosanoic acid–NAA might be applicable to a temperature-respondent drug delivery system.[2b] FA–drug complexes are useful in the pharmaceutical field, so determination of the possibility of formation of FA complex with the other drug can be valuable. On the other hand, it has been suggested[3] that FA–NAA may be an inclusion compound because of the weak binding force, hydrophobic interaction and/or van der Waals force, between FA and NAA. It is of interest what kind of drug is included in the FA host structure. Mod *et al.*[4] reported in a study of binary freezing-point diagram that hexadecanoic acid (C16) interacted with 3-aminopyridine (3AP). However, the physicochemical property of the C16–3AP interaction compound was not determined, and the interaction of the other FA with 3AP has not yet been studied.

We therefore were interested in the formation of a new complex composed of FA and 3AP. The physicochemical properties of the complex, FA–3AP, were investigated and compared with those of FA–NAA.

Experimental

Materials 3AP was purchased from Tokyo Kasei Kogyo Co., Ltd. Tetradecanoic acid (C14), pentadecanoic acid (C15), hexadecanoic acid (C16), heptadecanoic acid (C17) and octadecanoic acid (C18) were the same as those used in the previous work.[1] 1,2-Dichloroethane, ethanol and a 0.1 M KOH ethanol solution were also the same as used previously.[1]

Preparation of FA–3AP FA and 3AP were dissolved at a molar ratio of about 0.8—0.9 : 1 in warm 1,2-dichloroethane, and the solutions were allowed to stand at 25—30, 20—25, or 15—20 °C. Crystals were then obtained by filtration and dried under reduced pressure at room temperature.

Differential Scanning Calorimetry (DSC) DSC heating curve was determined under air with a thermogravimetric and differential scanning calorimeter (TG-DSC) of Rigaku Denki Co., Ltd. using 5 mg of sample. The scanning speed was 5 °C/min, and an aluminum plate was used as a reference. Melting points were determined from the DSC curves.

Quantitative Analysis of FA in the FA–3AP FA–3AP was 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 FA–3AP for C, H, N was carried out by the thermal conductivity method.

Infrared (IR) Spectroscopy The transmission IR spectra of the samples were obtained by KBr disk method using JASCO FT/IR-5300.

Results and Discussion

Conditions for Preparing FA–3AP The preparation conditions under which pure FA–3AP was obtained are listed in Table I.

DSC Heating Curve The DSC heating curves of 3AP, C14, C15, C17, C14–3AP, C15–3AP and C17–3AP are

TABLE I. Conditions for FA–3AP Preparation

Starting material[a] 3AP (g)	Starting material[a] FA (g)	Solvent[b] (ml)	Crystallization[c] temperature (°C)
1.0	C18 2.4	7.1	25—30
1.0	C17 2.3	7.7	20—25
1.0	C16 2.2	4.1	25—30
1.0	C15 2.0	5.2	15—20
1.0	C14 2.2	2.4	15—20

a) Molar ratios of FA to 3AP are approximately 0.8—0.9 : 1. *b*) 1,2-Dichloroethane. *c*) Crystallization time is 18 h in each case.

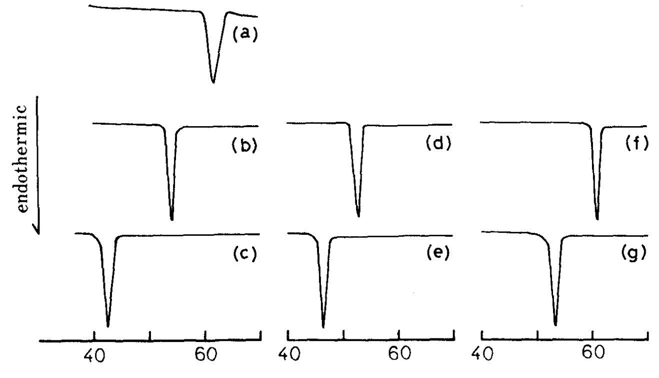

Fig. 1. DSC Heating Curves of 3AP, FA and FA–3AP

(a), 3AP; (b), C14; (c), C14–3AP; (d), C15; (e), C15–3AP; (f), C17; (g), C17–3AP.

shown in Fig. 1. The DSC curve of each FA–3AP showed a single endothermic peak, but no peaks corresponding to FA or 3AP were found in these curves. The DSC curve of FA–3AP indicates the existence of new molecular compounds and their purities. An impurely obtained complex, whose molar ratio of FA to 3AP is 1.3 : 1 or 1 : 1.3, showed another endothermic small peak corresponding to FA or 3AP, in addition to the independent main endothermic peak corresponding to FA–3AP. It is therefore reasonable to assume that FA–3AP is formed with a 1 : 1 molar ratio of FA to 3AP.

Next, the melting points of FA–3AP were determined from the DSC curves, and are listed in Table II. The melting points of FA–3AP, FA–NAA and FA are shown in Fig. 2 against the carbon number (*n*) of the constituent FA. The melting point of an odd-numbered FA is lower than that of

Table II. Melting Points of FA–3AP

FA–3AP	Melting point (°C)
C18–3AP	56.5—58.5
C17–3AP	52.1—54.5
C16–3AP	49.0—51.5
C15–3AP	45.4—47.9
C14–3AP	41.2—44.0

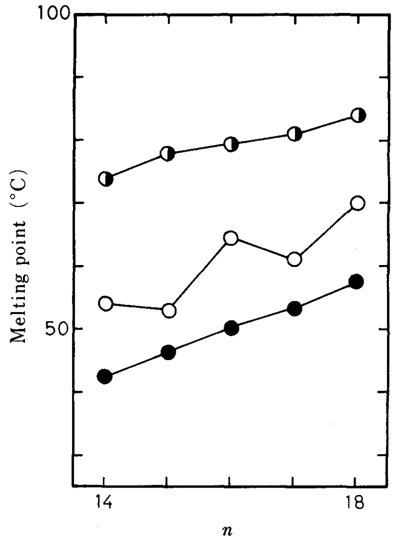

Fig. 2. Relationships between the Melting Point and *n* for FA–3AP (●), FA–NAA (◑), and FA (○)

Table III. Quantitative Analysis of FA in FA–3AP

FA	Number of determinations	FA to 3AP molar ratio[a]
C18	9	0.99±0.01
C17	3	1.00
C16	7	0.99±0.02
C15	3	1.00
C14	4	0.99±0.03

a) Mean±S.D.

Table IV. Elemental Analysis of FA–3AP

Formula	Analysis % Found (Calcd)		
	C	H	N
$(C_{18}H_{36}O_2)(C_5H_6N_2)$	72.92 (72.97)	11.14 (11.18)	7.44 (7.40)
$(C_{17}H_{34}O_2)(C_5H_6N_2)$	72.45 (72.48)	11.04 (11.06)	7.70 (7.68)
$(C_{16}H_{32}O_2)(C_5H_6N_2)$	71.92 (71.95)	10.89 (10.93)	8.04 (7.99)
$(C_{15}H_{30}O_2)(C_5H_6N_2)$	71.40 (71.38)	10.74 (10.78)	8.33 (8.33)
$(C_{14}H_{28}O_2)(C_5H_6N_2)$	70.70 (70.76)	10.57 (10.63)	8.75 (8.69)

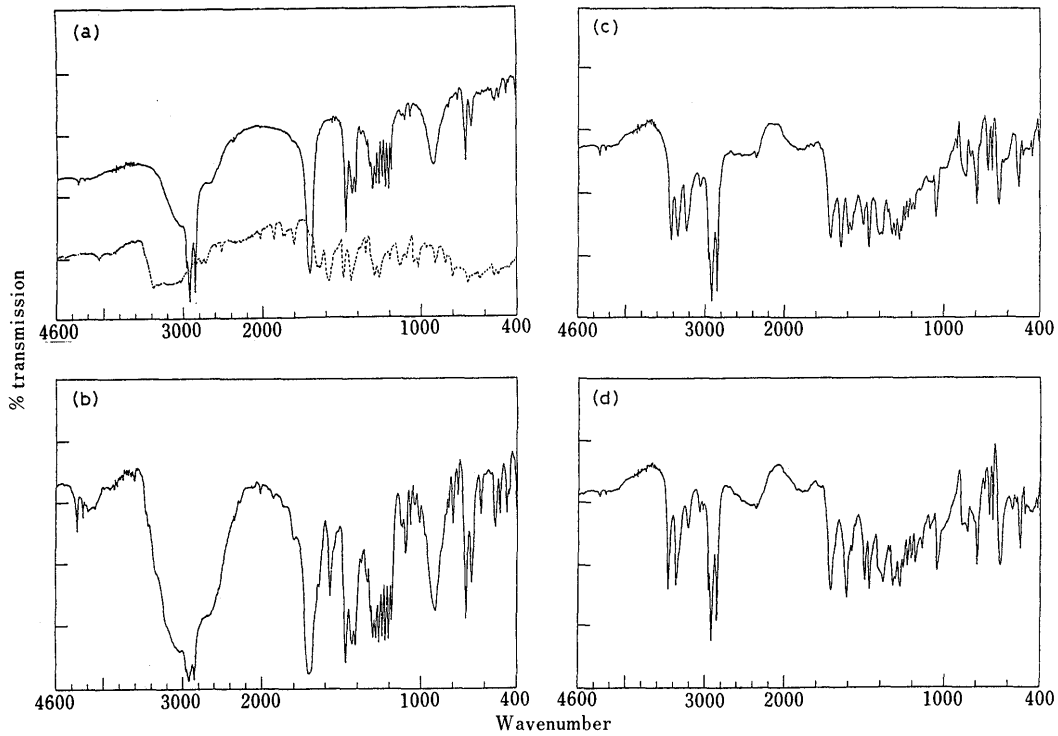

Fig. 3. IR Spectra of FA, 3AP, (FA+3AP) Mixture and FA–3AP

(a) solid line, C17; dotted line, 3AP, (b) (C17+3AP) mixture in 1 : 1 molar ratio, (c) C17–3AP, (d) C14–3AP.

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–NAA are higher than those of FA, especially with odd-numbered FA, and the melting point of FA–NAA changes roughly linearly with *n*, whereas the melting points of FA–3AP are lower than those of FA. However, the relationship between the melting point of FA–3AP and *n* takes a linear form as observed for FA–NAA.

Quantitative Analysis of FA in the FA–3AP The molar ratio of FA to 3AP in the purely obtained FA–3AP was determined by quantitative analysis of FA, and the results are shown in Table III. As seen, the molar ratio of FA to 3AP is 1.0 : 1 in each case.

Elemental Analysis of FA–3AP The results of elemental analyses of purely obtained FA–3AP are given in Table IV. The experimental values are well consistent with the theoretical values based on the stoichiometry of FA–3AP being 1 : 1.

IR Spectrum The IR spectra of C17 alone and 3AP alone are shown in Fig. 3a by solid and dotted lines, respectively, and the IR spectrum of the powder mixture (C17+3AP) in 1 : 1 molar ratio is shown in Fig. 3b. The IR spectrum of C17–3AP is shown in Fig. 3c. This latter spectrum is different from that of the mixture (C17+3AP): the absorption band near 1700 cm^{-1} which is characteristic of the carbonyl stretching vibration and the absorption band near 3400 cm^{-1} which is characteristic of the N–H stretching vibration are shifted to higher frequency fields by the formation of the complex. A similar tendency was found not only in C17–3AP but also the other FA–3AP. The higher frequency shift for the carbonyl stretching band has been found in the formation of FA–NAA.[1] Based on the IR spectra of FA–3AP and FA–NAA, and the mechanism for the formation of FA–drug complex in 1,2-dichloroethane,[5] FA–3AP is recognized to have a similar structure to FA–NAA.

The IR spectrum of C14–3AP is shown in Fig. 3d. Comparing Figs. 3c and 3d, it is found that the absorption bands near 1600 and 3000—3200 cm^{-1} of C14–3AP are different from those of C17–3AP and that the relative strength of the absorption band at 3230 cm^{-1} against 3350 or 3450 cm^{-1} of C14–3AP is less than that of C17–3AP, suggesting that the crystal structure of FA–3AP formed with odd-numbered FA is a little different from that of FA–3AP formed with even-numbered FA. The absorption bands near 1600 and 3000—3200 cm^{-1} are the N–H ($-\mathrm{NH_2}$) in-plane bending vibration and the hetero-aromatic C–H stretching vibration, respectively; both are derived from 3AP. The IR spectrum pattern of C15–3AP was the same as that of C17–3AP, and the IR spectrum patterns of C16–3AP and C18–3AP the same as that of C14–3AP, although the IR spectra of C15–3AP, C16–3AP and C18–3AP are not given here. It is thus suggested that the interaction of 3AP with odd-numbered FA differs slightly from that of 3AP with even-numbered FA.

As described above, 3AP formed a crystalline complex with FA in 1 : 1 molar ratio as determined for FA–NAA. The relationship between the melting point of FA–3AP and *n* indicated a linearity as was observed for FA–NAA. In conclusion, it is suggested that FA–3AP has a similar structure to FA–NAA.

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