A Novel Three-component Pseudo-polymorphism in the Cholamide Inclusion Crystals Promoted by the Combination of Organic Guest and Water

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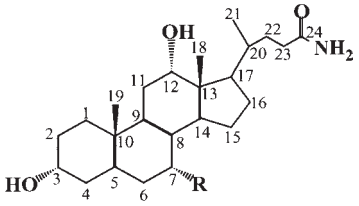
Cholamide (**1**) exhibits a novel pseudopolymorphism in a three-component system composed of **1**, acetonitrile, and water. Recrystallization of **1** from a guest solution composed of an equal amount of acetonitrile and water gave one polymorph (triangular, 1 : 1 : 1 molar ratio of **1** : acetonitrile : water). Diminished water in the guest solution provided the other polymorph (bilayer, 1 : 1 : 2).

Pseudopolymorphisms are defined for crystal structures in which their components are different in the species and/or stoichiometries.[1] The phenomena have been widely investigated due to their important roles in physical and chemical properties. They are usually found in one-component systems, but rare in two-component systems like inclusion compounds.[2] Here, we present a novel pseudopolymorphism in a three-component system composed of cholamide (3α,7α,12α-trihydroxy-5β-cholan-24-amide, **1**),[3] acetonitrile, and water. The inclusion crystals have different molar ratios and molecular assembly modes.

1 was prepared via the conventional condensation reaction from cholic acid and ammonia by mixed anhydride method at $-20\,^{\circ}$C.[4] Direct recrystallization of **1** from a solution of 1 : 1 acetonitrile and water gave needle-like crystals (Form I), while recrystallization from a solution of 25 : 1 (acetonitrile : water) provided platelet-like crystals (Form II). Each crystal of the two forms was collected and dried on filter papers before characterized by TG-DTA, IR and ^{1}H NMR spectroscopy, as well as X-ray powder diffraction (XRD) and single X-ray crystallographic analyses.



1: R = OH
2: R = H

Scheme 1.

Both of the crystals showed two-step guest release on TG analysis. Form I and II show three and four endothermic peaks in DTA spectra, respectively. The peak at the highest temperature (227 °C) corresponds to the melting point of the pure compound **1**. Acetonitrile guests were released at 88 and 74 °C in Form I and II, respectively. The other peaks correspond to loss of water from the host lattices. In their IR spectra, both exhibit similar patterns with two absorption peaks at 1612 and 1658 cm^{-1} in the region of amide group. The incorporation of organic guest as well as water was confirmed by ^{1}H NMR. Form I crystal consists of a three-component system in a 1 : 1 : 1 molar ratio of **1** : acetonitrile : water, while Form II does in a 1 : 1 : 2 ratio.

X-ray crystallographic studies revealed that **1** forms completely different crystal systems,[5,6] indicating the existence of pseudopolymorphism of the inclusion crystals in the three component system. The needle-like crystal (Form I) belongs to the trigonal crystal system, space group $P3_1$. The host molecules arrange along a three-fold screw axis to yield a triangular pillar with a hydrophilic core and lipophilic surface (Figure 1a). The acetonitrile guests are included among the pillars, while the water molecules are included in the core. It should be noted that this crystal structure is similar to the inclusion crystal of deoxycholamide(**2**) with acetic acid and water.[7]

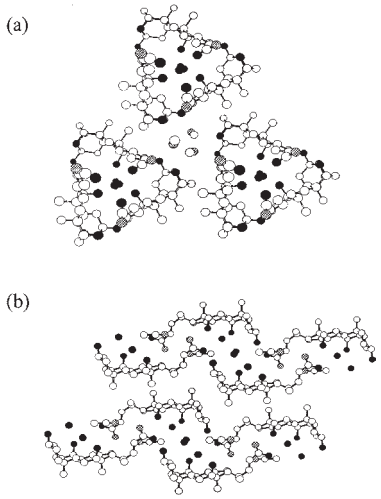


Figure 1. The crystal strutures of **1** with acetonitrile and water (a) Form I and (b) Form II as viewed down the crystallographic *c* and *b* axes, respectively. White, gray and black circles represent carbon, nitrogen and oxygen atoms, respectively. Hydrogen atoms are omitted for clarity.

The host molecules are connected together via the hydrogen bond, as shown in Figures 2a and 2b. In the hydrophilic core, water molecules participate in the host-to-host hydrogen bond as depicted in Figure 2a. The cyclic hydrogen bond network has a sequence of OH[water]···OH[C(12)]··OH[water]···O=C(24)···HO[water] with distances of 2.773, 2.762, 2.880, and 2.958 Å, respectively. Two rectangular loops are connected together via hydrogen bonds involving water molecules as donors and acceptors. Figure 2b shows the linear hydrogen bond

network in the lipophilic surface as a sequence of NH(C24)···N[guest]···HO[C(7)]. The nitrile guest forms the bifurcated hydrogen bond with NH(C24) and OH[C(7)] in the distance of 2.739 and 2.823 Å, respectively. One amide proton at the side chain is bridged to the OH[C(3)].

On the other hand, the platelet-like crystal (Form II) belongs to the monoclinic crystal system, space group $P2_1$. The crystal structure is shown in Figure 1b. The bilayer structure is constructed by alternating stack of hydrophilic and lipophilic layers. Such a structure is different from the usual bilayer structure in which acetonitrile molecules are included in the lipophilic layers.[2d] Moreover, the crystal packing shows two types of cavities; cages and channels. Acetonitrile molecules are held in the cages created by the stacking of the pleated bilayers, while water molecules are inserted in the channels.

Figure 2c shows the hydrogen bond network of the bilayer structure. One of water molecules joins in the cyclic hydrogen bond network of NH(C24)···OH[C(12)]···OH[water1]···O=C(24) with distances of 2.949, 2.843, and 2.726 Å, respectively. Water1 donates one hydrogen bond to water2, and accepts one hydrogen bond from hydroxy group at C7 position. Water2 donates two hydrogen bonds to the hydroxy groups at C7 and C3 positions. The nitrile guest forms one hydrogen bond with amide side chain of **1**. This result supports the lower releasing temperature in the DTA spectra than Form I, which has bifurcated hydrogen bond.

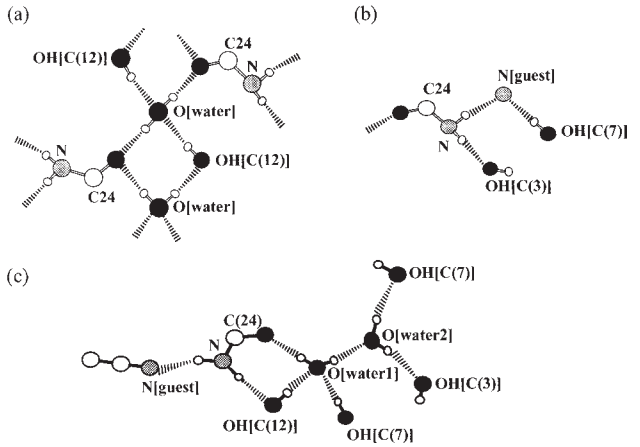


Figure 2. Hydrogen bonding networks of **1** with acetonitrile and water of Form I (a) in the hydrophilic core, (b) lipophilic surface, and (c) Form II. Carbon, nitrogen, and oxygen atoms are represented by white, gray, and black circles, respectively. Hydrogen atoms are represented as small circles.

We have demonstrated the pseudopolymorphism of the inclusion crystals of **1** with acetonitrile and water, as depicted in triangular pillar Form I and bilayered Form II. It should be noted that we tried various ways for obtaining polymorphic inclusion crystals of **1** with other guests but we do not get such polymorphic crystals yet. It is considered that acetonitrile molecules disturb the host framework construction through the weak hydrogen bonds between the host and nitrile guest, and that water molecules increase the ability to form host-to-guest hydrogen bond network by acting as hydrogen bond donors and acceptors. Therefore, water molecules may support the formation of the flexible host frameworks in the presence of acetonitrile.

In conclusion, this study indicates that various combinations between organic guest and water may give us a new insight to the construction of the host framework in crystal engineering of inclusion compounds.

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References and Notes

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5 Crystal data for **1** with acetonitrile and water (1 : 1 : 1) (Form I): $C_{24}H_{41}O_4N+C_2NH_3+H_2O$, fw = 465.65, trigonal, space group $P3_1$, $Z = 3$, $a = 13.907(2)$, $c = 11.394(2)$ Å, $V = 1908.8(4)$ Å^3, $D_{calcd} = 1.22$ gcm^{-3}. Total number of reflections measured: 3251. $R = 0.091$, $wR = 0.249$. XRDP: 7.22(39), 10.58(38), 12.58(73), 14.58(59), 14.78(80)°.

6 Crystal data for **1** with acetonitrile and water (1 : 1 : 2) (Form II) $C_{24}H_{41}O_4N+C_2NH_3+(H_2O)_2$, fw = 484.67, monoclinic, space group $P2_1$, $Z = 2$, $a = 13.074(4)$, $b = 8.007(4)$, $c = 13.884(3)$ Å, $\beta = 107.35(3)°$, $V = 1387.28(0)$ Å^3, $D_{calcd} = 1.160$ gcm^{-3}. Number of reflections measured: 2745. $R = 0.042$, $wR = 0.050$. XRDP: 7.2(9), 8.14(12), 10.7(17), 11.08(80), 12.66(23), 13.16(44), 13.72(31), 14.24(36), 14.88(30), 15.66(34)°.

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