Topological and Nontopological Rearrangement in Crystal Lattice of Cholic Acid Inclusion Complex Induced by Guest Exchange

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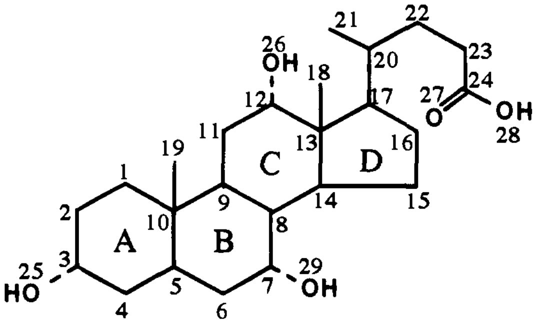
Received November 21, 1994[⊗]

Abstract: This article describes single-crystal to single-crystal transformations in the crystal lattice of the multimolecular inclusion complex of cholic acid (CA). These transformations are induced by the guest-exchange method, i.e., soaking the crystals of CA complex in liquid guest. In the present study, 2-, 3-, and 4-fluorobenzyl alcohol (2-, 3-, and 4-FBzOH, respectively) and water were used as guest molecules. The guest exchange from 2- to 4-FBzOH retained essentially both the amphiphilic bilayered structure and space group $P2_1$ of the starting complex. Similarly, the exchange from 3- to 4-FBzOH retained the bilayered structure and space group $P2_1$; in CA−3-FBzOH, the guest molecules in the channel are not related by 2_1 symmetry; if the crystals are soaked in 4-FBzOH, exchange of guests takes place, associated with the appearance of 2_1 symmetry between the guest molecules. The exchange from 3-FBzOH to water caused a drastic structural change accompanied by space group change from $P2_1$ to $P6_522$. The exchange from 2-FBzOH to water afforded two types of CA−H_2O structure: one has space group $P6_522$ and the other has the bilayered structure with space group $P2_1$. In contrast to CA−2- and −3-FBzOH, the crystal of CA−4-FBzOH did not undergo any transformation. Several transformations accompany the conspicuous change in the hydrogen bond network which plays an important role in constructing the crystal lattice. Such phenomena indicate the crystal flexibility of the CA inclusion complex.

Introduction

For several years, we and other workers have been studying the crystal structures of multimolecular inclusion complexes of cholic acid (CA), a naturally occurring bile acid. Of particular structural interest is the polymorphism observed in the crystal lattice. Namely, complexation of CA with an aromatic substance or a cyclic lactone affords the amphiphilic bilayered structure containing channel-type spaces with space group $P2_1$.[1−5] In contrast, the CA assembly has space group $P2_12_12_1$ when it accommodates guest alcohols into the cage-type spaces, where a bilayered structure is not observed.[6−8] At least six different space groups have hitherto been reported in CA complexes.[9]



Cholic acid

Our interest in this polymorphism prompted us to explore the topological rearrangement within a single crystal of a CA complex when guest molecules are replaced with another species.[10] It is well-known that some inorganic crystals such as clay and graphite reveal layer-to-layer transformation, i.e., intercalation phenomena,[11] and, recently, Abrahams et al. have reported the topological single-crystal to single-crystal transformation of cadmium cyanide complex induced by guest exchange.[12] In contrast to inorganic compounds, such phenomena are rarely observed in organic crystals.[13] The components of organic crystals generally bind to each other through relatively weak interactions, e.g., hydrogen bonds and van der Waals and electrostatic interactions as compared with covalent bonds in inorganic crystals. Owing to such a property, most organic inclusion crystals disintegrate if one attempts to exchange guest molecules.

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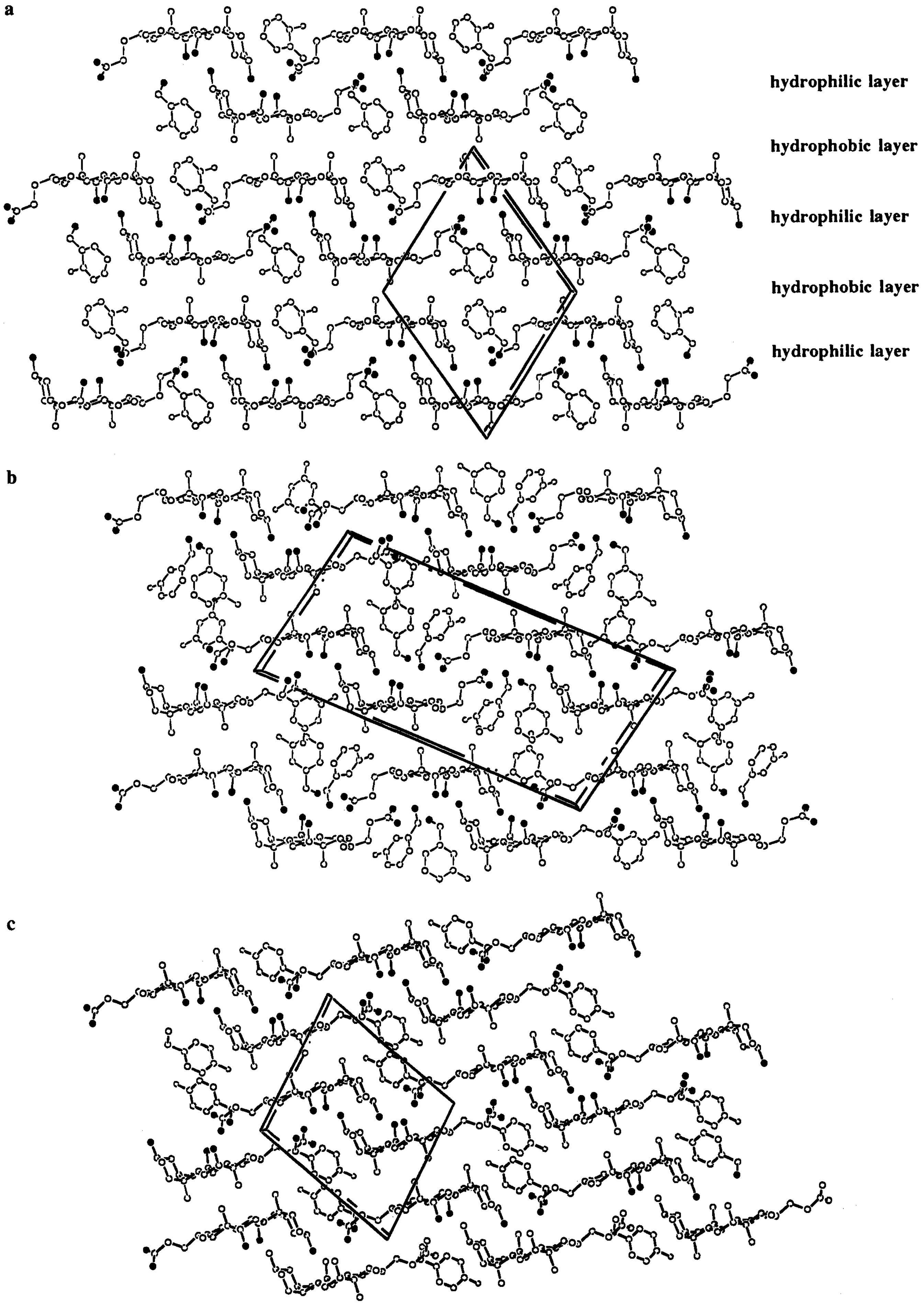
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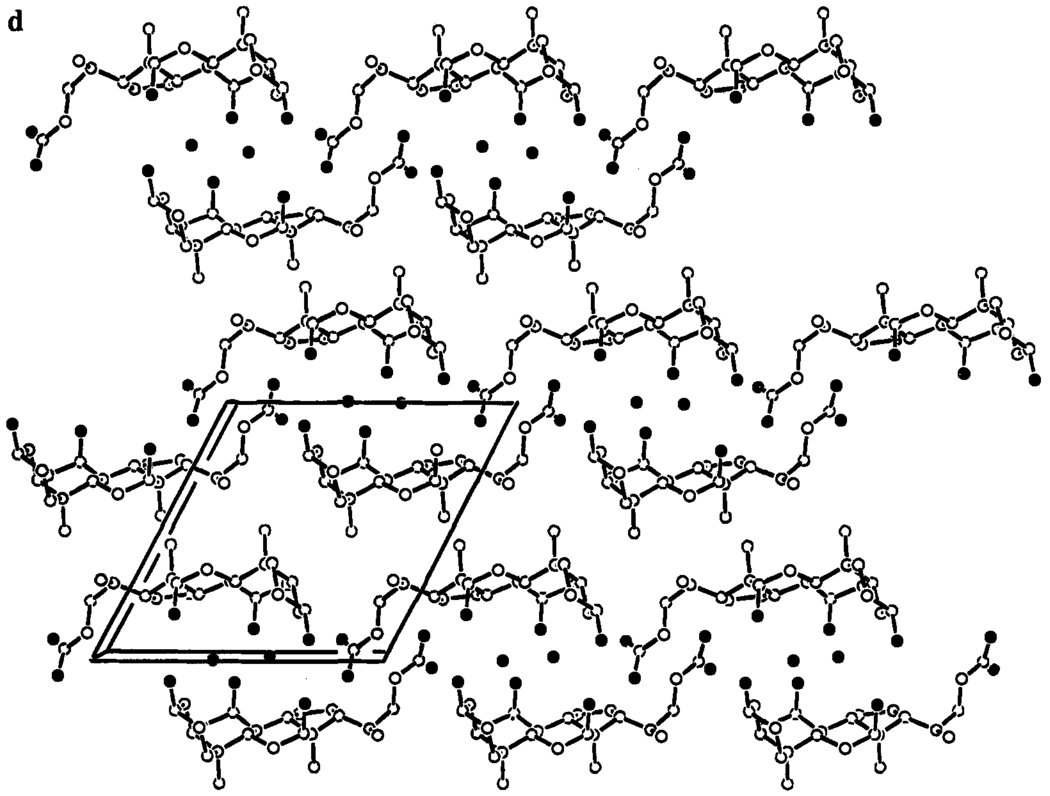


Figure 1. The crystal structure of CA inclusion complexes viewed down the *b*-axis: (a) CA−2-FBzOH, (b) CA−3-FBzOH, (c) CA−4-FBzOH, and (d) CA−H_2O (type I). H atoms are omitted for clarity. Carbon and oxygen atoms are represented by empty and filled circles, respectively. Fluorine atoms are also represented by empty circles.

Table 1. Crystal Data for CA Inclusion Complexes

complex	CA−2-FBzOH[a]	CA−2-FBzOH[b]	CA−3-FBzOH	CA−4-FBzO[H]	CA−H_2O(I)[c]	CA−H_2O(II)[d]
mol. formula	$C_{31}H_{47}FO_6$	$C_{31}H_{47}FO_6$	$C_{69}H_{101}F_3O_{13}$	$C_{31}H_{47}FO_6$	$C_{32}H_{47}FO_6$	$C_{48}H_{82}O_{11}$
M	534.71	534.71	1195.54	534.71	546.72	835.17
space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P6_522$
Z	2	2	4	2	2	12
a/Å	13.421(5)	13.351(6)	13.459(4)	12.632(3)	12.771(3)	13.739(10)
b/Å	8.510(4)	8.549(6)	8.485(4)	8.610(5)	8.148(4)	13.739(10)
c/Å	13.978(3)	13.966(5)	28.512(5)	13.806(3)	12.856(2)	85.096(7)
β/deg	113.15(2)	113.02(3)	101.30(2)	105.21(2)	117.62(1)	90[e]
V/Å^3	1467(1)	1466(1)	3193(1)	1448.9(9)	1185.4(6)	13910(19)
D_{calc}/g cm^{-3}	1.210	1.210	2.487	1.225	1.532	1.237
μ/cm^{-1}	7.02	7.02	14.71	7.11	8.84	6.67
F(000)	580	580	2584	580	592	5496
crystal size/mm	0.25 × 0.10 × 0.30	0.20 × 0.07 × 0.20	0.20 × 0.02 × 0.40	0.20 × 0.30 × 0.12	0.10 × 0.10 × 0.10	0.40 × 0.30 × 0.40
θ limit/deg	120.3	120.4	120.2	120.1	120.2	120.6
no. of unique reflctns	2361	2351	5131	2336	1915	4328
no. of observed reflctns[f]	1135	1141	3400	1502	1563	1972
no. of variables	343	343	733	343	271	533
R	0.058	0.060	0.066	0.050	0.055	0.062
R_w	0.075	0.080	0.085	0.061	0.081	0.085
goodness of fit indicator	1.67	1.92	2.44	1.88	1.47	1.71

[a,b] The complex was obtained by the recrystallization and absorption methods, respectively. [c] The lattice parameters previously reported are as follows: $a = 12.794(2)$ Å, $b = 8.157(2)$ Å, $c = 12.885(2)$ Å, $\beta = 117.60(1)°$.[20] [d] The complex was obtained from CA−2-FBzOH by the guest-exchange method. [e] The angles of the crystal lattice with space group $P6_522$ are defined as $\alpha = \beta = 90°$, $\gamma = 120°$. [f] Criterion for F_{obs} exclusion: $I > 3\sigma(I)$.

In the present research, we examine the guest-exchange process in a CA complex using X-ray diffraction, infrared spectroscopy, and microscopic analysis. This exchange process is induced by soaking the crystals of the complex in a liquid guest. Here 2-, 3-, and 4-fluorobenzyl alcohol (2-FBzOH, 3-FBzOH, and 4-FBzOH, respectively) and water were used as guest molecules. We report topological and nontopological single-crystal to single-crystal transformations induced by guest exchange in which the crystal lattice, hydrogen bond network, and/or symmetry of the CA complex undergo extensive changes.

Experimental Section

Solubility Measurement. The solubility of CA in the fluorobenzyl alcohols and water was determined from the CA−solvent ratio of the CA−saturated solution measured by ^{1}H-NMR using a JEOL EX-270 after over 18 h of vigorous stirring of the solution kept at 25 ± 0.5 °C in a thermostat-controlled environment. Further stirring caused no change in the solubility. Prior to the measurement, the solution was allowed to stand for 30 min. The solubility data are the means of three measurements.

Preparation of Inclusion Complex by Recrystallization Method. A solution of CA (0.3 g) in fluorobenzyl alcohol (2-, 3-, and 4-FBzOH)

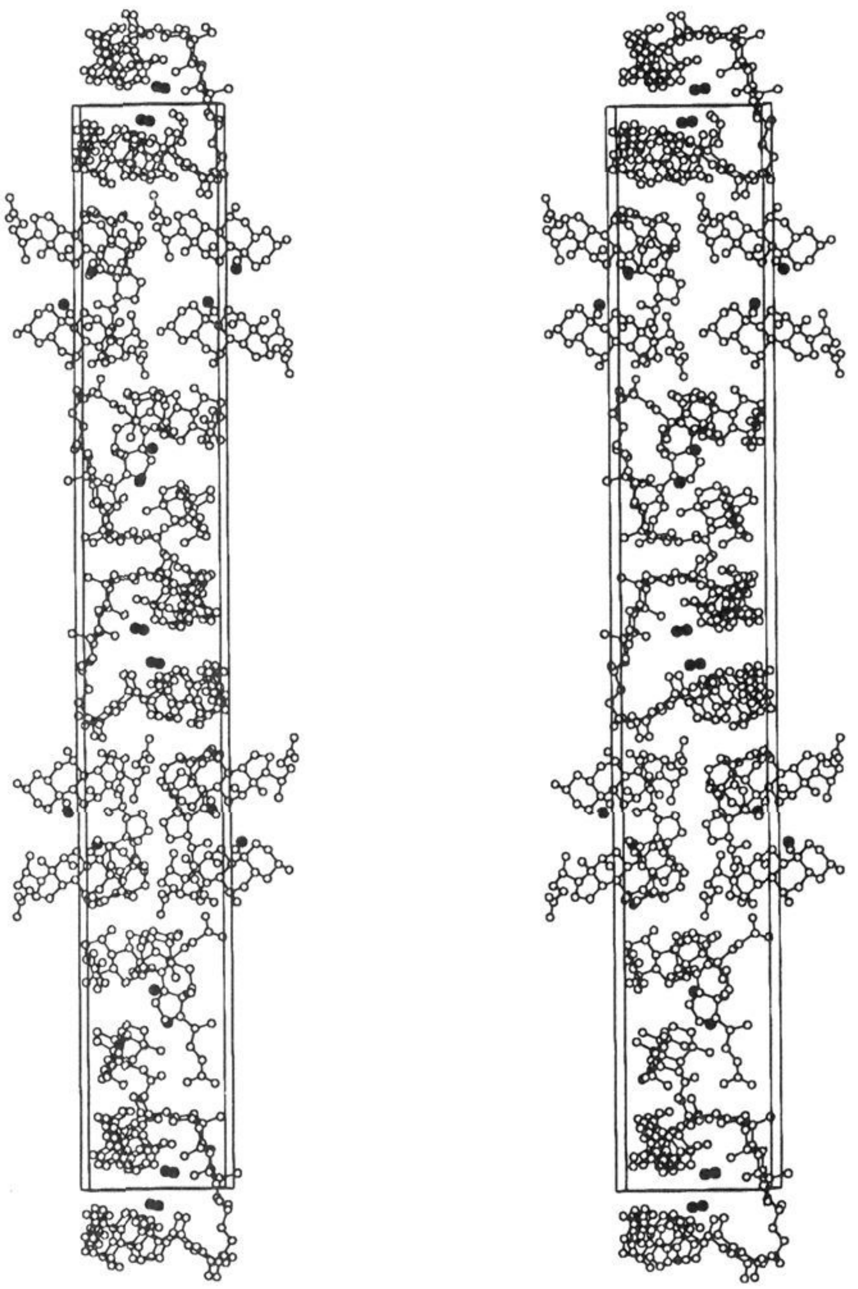


Figure 2. Stereo-drawing of CA−H_2O (type II) crystal structure viewed down the *b*-axis. H atoms are omitted for clarity. The oxygen atoms of the water molecules are represented by filled circles with larger radius.

Table 2. Solubilities of CA in Liquid Guests at 25 °C (in g/100 g Solvent)

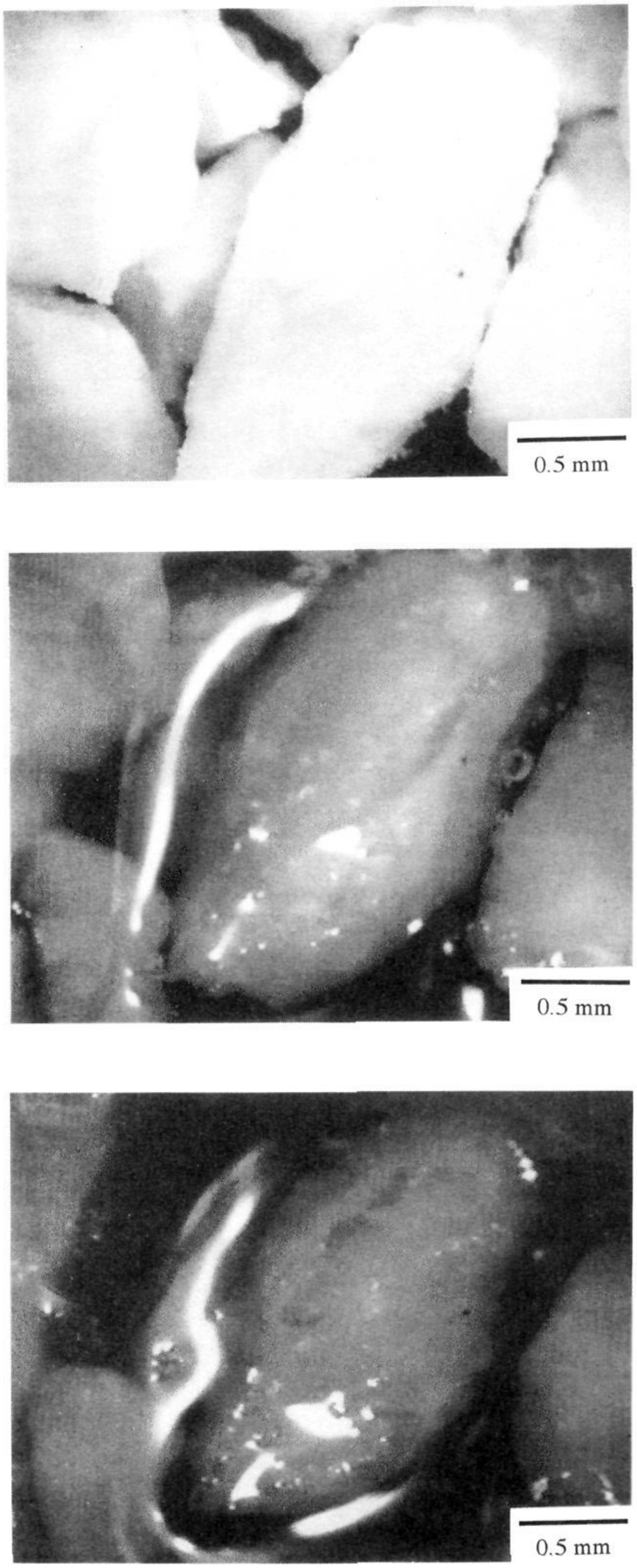
solvent	solubility
2-FBzOH	11.7
3-FBzOH	11.3
4-FBzOH	1.7
H_2O	~0[a]

[a] Solubility at 15 °C: 0.028 g/100 g(H_2O).[23]

Table 3. Lattice Parameters for CA Inclusion Complexes Obtained by the Absorption Method

complex	CA−2-FBzOH[a]	CA−3-FBzOH	CA−H_2O(I)
a/Å	13.351(6)	13.426(6)	12.775(3)
b/Å	8.549(6)	8.502(5)	8.150(1)
c/Å	13.966(5)	28.58(1)	12.862(3)
β/deg	113.02(3)	101.36(4)	117.65(1)
V/Å^3	1466(1)	3198(3)	1186.2(4)

[a] Not only the lattice parameters but also the crystal structure was elucidated, as shown in Table 1.



0.5 mm

0.5 mm

0.5 mm

Figure 3. Time course of the absorption process of 3-FBzOH by CA crystals: (a, top) pure CA crystals before soaking, (b, middle) 5 min after soaking, and (c, bottom) 2 h after soaking.

(2 cm^3) was kept at room temperature for about 12 h, and crystals of the inclusion complex with a host−guest ratio of 1:1 or 1:1.5 were obtained as colorless prisms. Crystals of CA−H_2O (type I) were obtained as colorless prisms by recrystallizing CA from a mixed solution of 4′-fluoroacetophenone−water.

Preparation of Inclusion Complex by Absorption Method. Guest-saturated crystals were obtained by soaking pure CA crystals (100 mg) with size of about 0.2 × 0.2 × 0.2 mm, which had been obtained beforehand by drying crystals of the CA−methanol complex *in vacuo* at 150 °C for 20 h, in fluorobenzyl alcohol or water (25 mg) at 25 ± 0.5 °C for a few hours. To confirm the saturation and crystalline states, infrared spectra, measured using FT/IR-8900 of Japan Spectroscopic Co., Ltd., of powdered crystals, and lattice parameters determined using X-ray diffraction were compared with those of the crystalline complex whose structure had been previously elucidated by X-ray diffraction. The guest saturation process was monitored using the optical microscope Microwatcher VS-30H of Mitsubishi Kasei Co., Ltd.

Preparation of Inclusion Complex by Guest-Exchange Method. Crystals of the CA inclusion complex (100 mg) with size of about 0.1

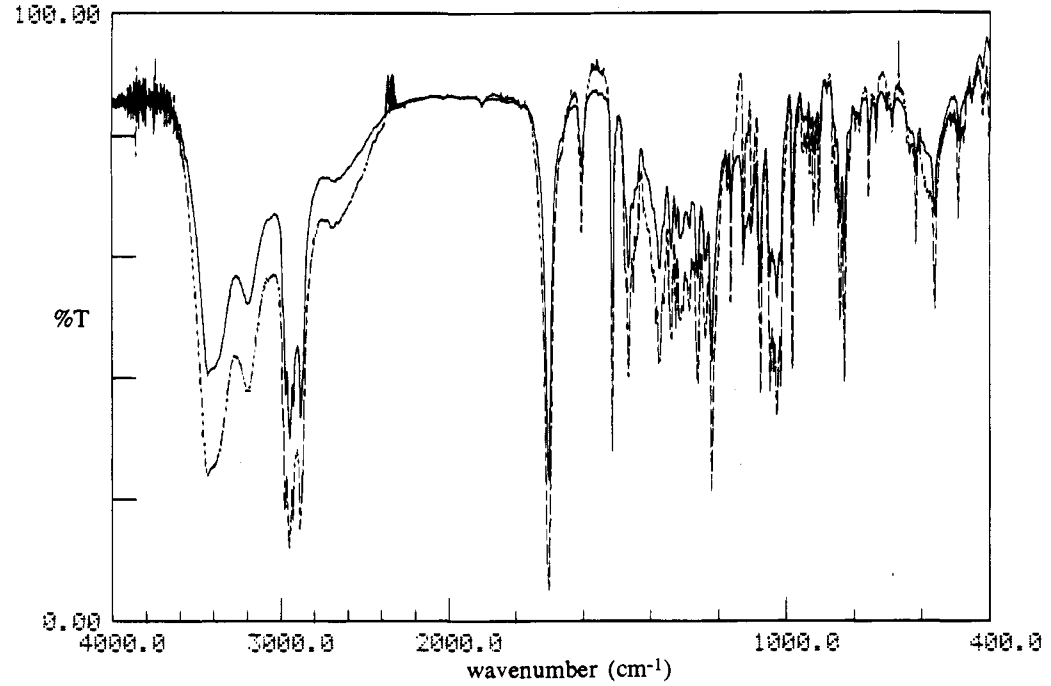


Figure 4. Infrared spectra of CA–4-FBzOH inclusion complexes obtained by the recrystallization method (solid line) and the absorption method (dotted line).

Table 4. Resulting Complexes by the Guest–Exchange Method

	starting complex		
solvent	CA–2-FBzOH	CA–3-FBzOH	CA–4-FBzOH
2-FBzOH		CA–H_2O(II)[a]	no reaction[b]
3-FBzOH	CA–H_2O(I)[a]		no reaction[b]
4-FBzOH	CA–4-FBzOH	CA–4-FBzOH	
H_2O	CA–H_2O(II)	CA–H_2O(II)	no reaction[b]

[a] The water molecules were from impurities in the solvent. [b] This means that the starting complex retains its structure.

× 0.1 × 0.1 mm obtained by the recrystallization or absorption method were soaked in fluorobenzyl alcohol or water (25 mg) at 25 °C. After a few hours, guest-exchanged crystals were obtained. To confirm the exchange and crystalline states, infrared spectra and lattice parameters were compared with those of the authentic crystal. The guest-exchange process was monitored using the Microwatcher.

X-ray Structural Analysis and Refinement. X-ray diffraction measurements were performed on a Rigaku AFC7R diffractometer with graphite-monochromated Cu-Kα (λ = 1.54178 Å) radiation at 293 K. The Rigaku R-AXIS IIC diffractometer with graphite-monochromated Cu-Kα (λ = 1.54178 Å) radiation was used for determining the lattice parameters of the CA–4-FBzOH crystal obtained by the guest-exchange method, since the crystal quality was not suitable for four-circle diffractometry. The data were corrected for Lorentz and polarization effects. An empirical absorption correction using the program *DIFABS*[14] and a correction for secondary extinction were applied. The structures were solved by direct methods: *SAPI91*[15] and *DIRDIF92*[16] for CA–2-FBzOH (by the recrystallization method); *SHELXS86*[17] and *DIRDIF92* for CA–2-FBzOH (by the absorption method), CA–3-FBzOH, CA–H_2O (type I), and CA–H_2O (type II); *MULTAN88*[18] and *DIRDIF92* for CA–4-FBzOH. Some hydroxyl hydrogen atoms were located from the difference Fourier map. Hydrogen atoms except for hydroxyl hydrogen atoms were placed at calculated positions. Non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms were included but not refined. The position of one guest in CA–3-FBzOH was unambiguous, and the C_6H_4 group was refined as a rigid body. The function minimized was $\sum w(|F_o|^2 - |F_c|^2)^2$. The weighting scheme used was $w = 1/\sigma^2(F_o) = 4F_o^2/\sigma^2(F_o^2)$. The absolute configurations conformed to a previously reported structure of CA.[1] All calculations were performed using the *TEXSAN* crystallographic software package.[19] The measurement conditions and structural details are listed in Table 1.

Results and Discussion

Structure of CA Inclusion Complex. The crystal structures of CA–2-FBzOH, –3-FBzOH, –4-FBzOH, and –H_2O(I) inclusion complexes obtained by recrystallization are depicted in Figure 1. CA molecules are arranged so that the OH and CH_3 groups associate to form hydrophilic and hydrophobic layers, respectively. Channel-like spaces are observed in hydrophobic layers. The channel consists of steroidal A rings and side chains and is parallel to the crystallographic *b*-axis. The aromatic guests are accommodated inside these channels, whereas water molecules are accommodated in the hydrophilic layers. The host–guest ratio of CA–3-FBzOH is 1:1.5, unlike the 1:1 of CA–2-FBzOH, –4-FBzOH, and –H_2O(I). The stereo-drawing of the CA–H_2O(II) crystal structure with host–guest ratio of 2:1 is depicted in Figure 2. This assembly pattern differs considerably from all the

Table 5. Lattice Parameters for CA Inclusion Complexes Obtained by the Guest–Exchange Method

complex	CA–H_2O(I)	CA–H_2O(II)[a]	CA–H_2O(II)[b]	CA–H_2O(II)[c]	CA–4-FBzOH[d]	CA–4-FBzOH[e]
space group	$P2_1$	$P6_522$	$P6_522$	$P6_522$	$P2_1$	$P2_1$
a/Å	12.769(3)	13.724(4)	13.73(2)	13.74(9)	12.784	12.748
b/Å	8.149(2)	13.724(4)	13.73(2)	13.74(9)	8.634	8.633
c/Å	12.856(2)	85.04(8)	85.05(2)	85.2(2)	13.820	13.820
β/deg	117.62(1)	90[f]	90[f]	90[f]	105.85	104.90
V/Å^3	1185.3(5)	13880(11)	13879(9)	13921(60)	1467.4	1469.8

[a] The complex was obtained by guest exchange from 3- to 2-FBzOH. The water molecules were from impurities in the solvent. [b] The complex was obtained by guest exchange from 2-FBzOH to H_2O. Not only the lattice parameters but also the crystal structure was elucidated, as shown in Table 1. [c] The complex was obtained by guest exchange from 3-FBzOH to H_2O. [d,e] The complexes were obtained from CA–2-FBzOH and CA–3-FBzOH, respectively. The parameters were not refined. [f] The angles of the crystal lattice with space group $P6_522$ are defined as $\alpha = \beta = 90°$, $\gamma = 120°$.

previously reported crystal structures of bile acid inclusion complexes.[1-8,21] It has no channel, and water molecules are accommodated in the interstices.

Observation of Absorption Process. Until several years ago, all the CA complexes had been obtained only by the recrystallization method. In 1988, Miyata et al. reported the absorption method as another means of preparation.[22] No detailed study, however, has been reported on the absorption process itself.

We have now found that the present complexes can also be obtained by the absorption method. To confirm that each complex remains in the crystalline state during the process, we monitored the guest absorption process with a microscope. As seen in Figure 3a, the pure CA crystals are opaque white polycrystals. Soaking the crystals in 3-FBzOH for 5 min caused them to become translucent [Figure 3b]. During the first 10 min of soaking, we observed the evolution of numerous bubbles from the surface of the crystals, which indicates the absorption of 3-FBzOH molecules by the crystals. After 2 h, the whole crystals changed into a cluster of transparent needle-like crystals [Figure 3c]. A few crystals might be formed from CA molecules dissolved in the liquid guest. It is, however, evident that most of the CA crystals absorbed 3-FBzOH molecules and became a crystalline complex without any transition to the amorphous state, since the polycrystalline cluster maintained its original form throughout the absorption process. We also confirmed that not only the surfaces but also the inside of the crystals became needle-like. Similar absorption processes were observed with 2-FBzOH and H_2O as liquid guests. Table 2 shows the solubilities of CA molecules. For example, a maximum of 3 mg of CA could be dissolved in 25 mg of 3-FBzOH according to the solubilities obtained under the present experimental conditions. This is only 4% of the soaked CA crystals. Consequently, these solubilities also indicate the retention of the crystalline state in the present cases. The lattice parameters of the resulting crystals are tabulated in Table 3, which indicate that the structures of these crystals are isomorphous to those elucidated previously by the X-ray method. Crystals of CA−4-FBzOH obtained by the absorption method were not suitable for investigation by four-circle diffractometry. Infrared spectroscopy indicates, however, the formation of the CA−4-FBzOH complex, as seen in Figure 4.

Guest-Exchange Process and Accompanying Structural Changes. We have now found that the guest-exchange method is an efficient means of forming some CA inclusion complexes. Table 4 shows the relationship between starting materials and resulting complexes. One characteristic is that this method produces the crystalline complexes [CA−4-FBzOH and CA−H_2O(II)] which are difficult to form by the recrystallization or absorption method. During the exchange process from 3- to 4-FBzOH, it was observed that prism-shape of the starting crystals was retained. It is, therefore, evident that the CA−3-FBzOH crystals exchanged guest molecules without any transition to the amorphous state during the process, which is also supported by the solubility values in Table 2. Similar phenomena were observed in the process from 2- to 4-FBzOH. The lattice parameters of the resulting

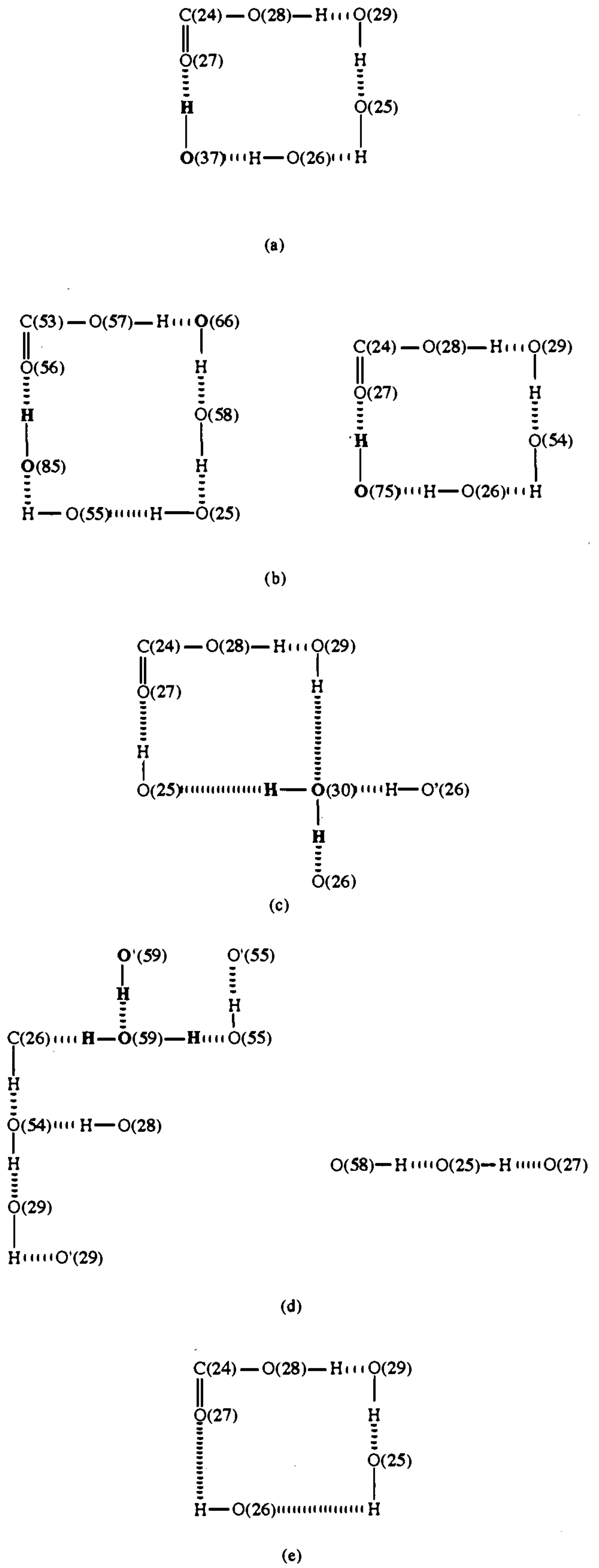


Figure 5. Schematic representations of the hydrogen bond network observed in (a) CA−2-FBzOH and CA−4-FBzOH, (b) CA−3-FBzOH, (c) CA−H_2O(I), (d) CA−H_2O(II), and (e) CA−AP. The hydroxyl groups of the guest molecules are shown in boldface.

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complexes are tabulated in Table 5, indicating that the structures of the resulting complexes are isomorphous to those of the corresponding authentic complexes.

Based on the X-ray results, we discuss the structural change in the crystal lattice which occurred during the guest-exchange process. As shown in Figure 1 (parts b and c), CA−3-FBzOH and −4-FBzOH structures are apparently similar to each other, except for the host−guest ratio. We have found, however, that the cyclic hydrogen bond network changes during the guest-exchange process from 3- to 4-FBzOH. Schematic representations of the networks of the present complexes, together with that of CA−acetophenone (AP) as a conventional channel-type CA complex,[1] are shown in Figure 5; each network plays an important role in the formation of the crystal lattice. In CA−4-FBzOH, a 12-membered ring network is found (Figure 5a). In contrast, two kinds of networks are formed in CA−3-FBzOH: one consists of four OH groups and one CO_2H group, i.e., a 12-membered ring, and another consists of five OH groups and one CO_2H group, i.e., a 14-membered ring (Figure 5b). The rearrangement from the 14- to the 12-membered ring must have occurred during this exchange process, which involves the release of the OH group of 3-FBzOH from the 14-membered ring and the subsequent closure of the ring. In contrast, the guest exchange from 2- to 4-FBzOH retains the 12-membered ring, which involves the substitution of the OH group of 2-FBzOH by that of 4-FBzOH into the network.

X-ray studies have shown that a twofold screw axis symmetry in the guest arrangement inside the channel is a feature of the channel-type CA inclusion complexes.[1−5] As seen in Figure 1 (parts a and c), this axis exists in both CA−2-FBzOH and −4-FBzOH. By contrast, such an axis cannot be observed in CA−3-FBzOH (Figure 1b). Thus it is clear that the exchange from 3- to 4-FBzOH caused the appearance of this symmetry. The channel wall in CA−4-FBzOH also has a twofold screw axis symmetry, but the channel wall in CA−3-FBzOH has no symmetry. Consequently, the same change in symmetry involves the entire crystal structure, guest arrangement, and host lattice, and both exchange processes induced a topological single-crystal to single-crystal transformation. To our knowledge, such a phenomenon has never before been observed in CA complexes.

Comparison of the crystal structures between CA−H_2O(II) and CA−2-FBzOH or −3-FBzOH indicates that a drastic structural change occurred when CA−2-FBzOH or −3-FBzOH was soaked in water. During these processes, the channels disappeared, and the characteristic arrangement of CA molecules was disrupted. This was thought to involve a change in the hydrogen bond network, as shown in Figure 5d. These guest exchanges with water producing CA−H_2O(II) caused a change from the cyclic to linear network. Details of the processes of these structural changes remain unclear.

The water molecules of CA−H_2O(I) and −H_2O(II) crystals shown in the top and second rows in Table 4 were present as impurities in the solvents. Complex formation with water instead of the solvent may occur depending on crystallization conditions or on the relative thermostability between the starting and the resulting complex. The transformation from CA−2-FBzOH to −H_2O(I) essentially led to the retention of the internal crystallographic orientation, i.e., bilayered amphiphilic structure. As shown in Figure 5 (parts a and c), the hydrogen bond network pattern changes somewhat and is rearranged from the 12- to the 10-membered ring. In contrast to the transition between CA−fluorobenzyl alcohol structures, the transition to the CA−H_2O(I or II) complex did not led to a retention of the external morphology: the resulting crystals were colorless prisms (type I) or hexagonal plates (type II). It is noteworthy that all the transformations proceed without any transition to the amorphous state, which is supported by the solubilities in Table 2. In addition, we observed the transition from CA−H_2O(II) to CA−H_2O(I) within a few days with retention of the external hexagonal morphology.[24] We assume, therefore, that CA−H_2O(II) may be a transition state of CA−H_2O(I).

Table 4 shows that CA−4-FBzOH is stable upon soaking in any of the given solvents. This is presumably due to the thermostability of 4-FBzOH inside the crystal lattice compared with the other guests.

Supplementary Material Available: Tables of atomic positional parameters and bond lengths, bond angles, torsion angles and nonbonded contacts (96 pages); tables of observed and calculated structure factors (75 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943767Y

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(23) *The Merck Index*, 11th ed.; Merck & Co., Inc.: NJ, 1989.

(24) The transition was confirmed by infrared spectroscopy and X-ray analysis. The lattice parameters of the resulting crystal are as follows: a = 12.773(4) Å, b = 8.146(1) Å, c = 12.856(2) Å, β = 117.60(2)°.