Controlled Expansion of a Molecular Cavity in a Steroid Host Compound

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Abstract: Expansion of a molecular cavity is described by using elongation of the side chain of a bile acid host compound. Bishomocholic acid (**2**), which has a side chain that is longer by two methylene unit than cholic acid (**1**), includes many organic substances at 1:1 host:guest ratios. X-ray crystallographic studies revealed that **2** has two types of open host frameworks: a bilayer type and a crossing type. Both of them are isostructural to those of **1**, indicating that they are robust against the elongation of the side chain. In the former type, the increment of the width of the host channel corresponds to that of the length of the molecular structures. Larger aromatic guest components such as 1-methylnaphthalene and 1-tetralone, are included in **2**, but not in **1**.

Introduction

Precise control of host-cavities-directed guest recognition is one of the ultimate goals for supramolecular chemistry. Chemical transformations of known host compounds are basic strategies for designing and controlling the host cavities. For example, expansions of ring sizes in macrocyclic host compounds enlarge sizes of the host cavities, which exhibit expected guest recognition.[1] On the other hand, in crystalline inclusion compounds,[2] it is still hard to manipulate open host frameworks because of the impossibility of prediction and control of crystal structures,[3] despite the recent progresses of design of open host frameworks by multiple hydrogen-bonded networks[4] or metal-to-ligand coordination polymers.[5] In particular, expansions of spacers between connectivities of the open host frameworks often lead to a change in the host frameworks themselves or the multiplicity of interpenetration.[6] This induces an unpredictable deformation of size and shape of the host cavities. Increments of the spacers in the molecular structures hardly correspond to those of the host cavities. As a result, there have been only a few reports on controlled expansion of the host cavities.[7−15] A classical example, the transformation of urea to thiourea, affords the wider

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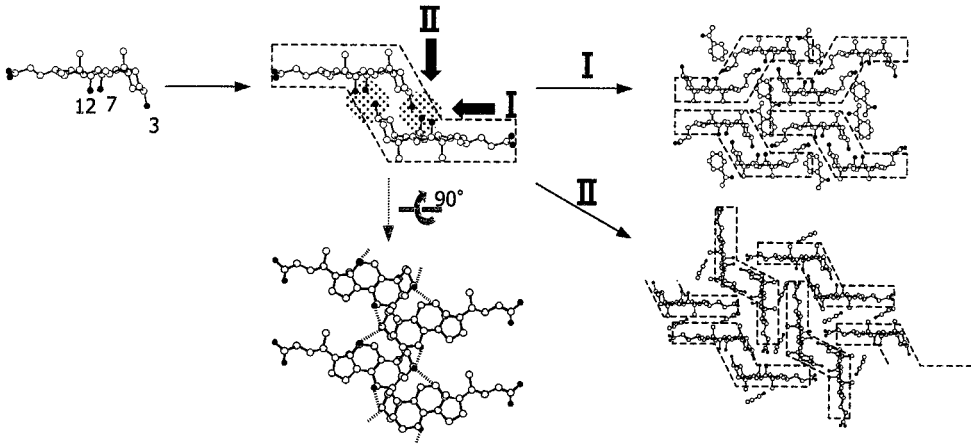
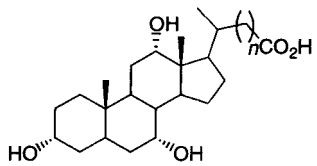


Figure 1. Typical host frameworks of **1** in crystalline state, (I) a bilayer-type structure and (II) a crossing-type structure, respectively.

molecular cavities in the same honeycomb host frameworks as a result of the bond distance that is longer in thiocarbonyl than in carbonyl.[7] Helical tubuland diol host compounds,[8] Dianin's compounds,[9] porphyrin-sponge hosts[4b,c,10], and diamond-type host frameworks[11,12] with various spacing units and connectivities have been reported to control the size of the host cavities. Recently, in the sandwiched-type host frameworks of guanidinium disulfonates, the width and the height of the host cavities were precisely controllable by changing the spacing groups of disulfonate anions.[13] We reported that alkylammonium deoxycholates have the fine-tuned molecular cavities by changing the alkyl parts of the ammonium cations.[14] More recently, variable host cavities based on 3-fold symmetric cyanphenylacetylene silver salts with the pendant groups have been reported.[15]

Cholic acid (**1**) is one of the classical host compounds that form inclusion crystals with various organic compounds.[16,17] A feature of the molecular structure is facial amphiphilicity from three hydroxy groups directed to one face (α-face) and two methyl groups to the other face (*β*-face) on the steroidal plane. In the side chain of the steroidal skeleton, a carboxylic acid is attached at the terminal, and tetramethylene links, between the steroidal nucleus and the carboxylic acid. X-ray crystallographic studies illustrated that **1** forms two major types of the host frameworks: a bilayer type[18] and a crossing type,[19] as shown in Figure 1. The common structural motif in both types is a tape structure formed by hydrogen bonds among the three hydroxy groups. The hydroxy group at the C3 position in one molecule links the two hydroxy groups at C7 and C12 in the other two molecules related by a 2-fold screw axis, which connects the host compounds in an α-face-to-α-face fashion to yield the tape structure. The remaining carboxylic acid at the side chain takes part in the hydrogen bond networks from two different directions (I and II), shown in Figure 1. The former yields the bilayer-type structure, and the latter yields the crossing type. In the former type, the tapes are arranged parallel to the steroidal plane, thus constructing the layer structure. The layers stack by interdigitation of the methyl groups to yield molecular channels, one-dimensional void spaces, in which a wide range of guest components are included. In the latter type, the tapes are arranged in a herringbone fashion, which yields cage-type molecular cavities. Small alcohols and nitriles are included in the crossing-type structure.



n = 2 ; cholic acid (**1**)
n = 4 ; bishomocholic acid (**2**)

Our design of the expansion of the host cavity relies on elongation of the spacing of methylene between the steroidal nucleus and the side-chain terminal. For example, in the bilayer-type structures, the elongation is expected to expand the host

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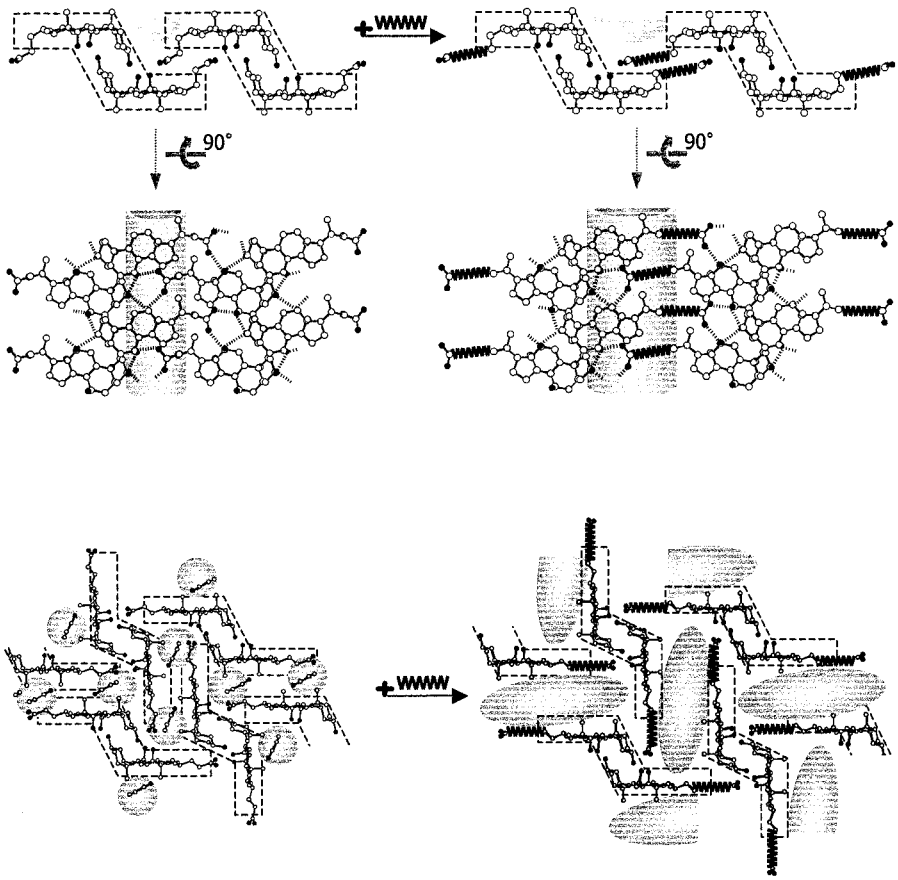

Figure 2. Schematic drawing of an expanded host cavity by elongation of the molecular structure of **1**.

cavity along the directions of the layers, but in the crossing type, the expected host cavity spreads between the lipophilic faces, as shown schematically in Figure 2. To direct the carboxylic acid toward the same manner as **1** and preserve the cyclic hydrogen bond networks, we designed a host compound that has two more methylene units in the spacer as a result of the even−odd rules of alkyl chain packing in the crystalline state.[20] Indeed, elongation and shortening by one methylene from **1** change the orientation of the carboxylic acid and deform the hydrogen bonding.[21] This causes a change in the host frameworks, the host cavities, and the inclusion phenomena. In this report, we describe that bishomocholic acid (**2**) has the same host frameworks as **1** and the expanded host cavities. In particular, the bilayer structure has the expanded host cavity in width, and **2** includes larger guest components than **1**. The increment of the width precisely corresponds to that of the expanded spacer in the molecular structure.

Experimental Section

General Methods. Bishomocholic acid (**2**) was prepared by the previously reported method.[22] All chemicals and solvents were commercially available and used without any purification. Infrared spectra were recorded on a JASCO IR-Report-100 or JASCO IR-810 spectrometer. Thermal gravimetry (TG) was performed on a Rigaku TAS100 system; using ∼5 mg and heating from 40 to 230 °C at a heating rate of 5 °C min^{-1}. X-ray powder diffraction (XRD) patterns were measured by a Rigaku RINT-1100 at room temperature.

Preparation of Inclusion Crystals. The host **2** (20 mg) was dissolved with warming in the liquid guest (usually 1−3 mL), and the resulting solution was allowed to stand at room temperature. In the case of the solid guest, acetone was used as the solvent. The needlelike crystals were collected and dried on filter paper. Inclusion crystals were characterized by TG and XRD. Weight losses in TG, and 2θ angles with relative intensity in parentheses of XRD patterns are summarized as follows. **2**-methanol: weight loss, 5.84%(1:1); XRDP, 6.96 (154), 9.36 (90), 13.30 (230). **2**-ethanol: weight loss, 8.34%(1:1); XRDP, 7.00 (356), 9.42 (123), 13.60 (136). **2**-1-propanol: weight loss, 14.70% (1:1); XRDP, 8.44 (733), 17.12 (175). **2**-2-propanol: weight loss, 11.35% (1:1); XRDP, 7.26 (53), 8.54 (194), 14.7 (49). **2**-1-butanol: weight loss, 15.87% (1:1); XRDP, 7.32 (215), 10.22 (106), 14.80 (162). **2**-2-butanol: weight loss, 14.20% (1:1); XRDP, 6.82 (41), 9.46 (167), 14.14 (167). **2**-1-pentanol: weight loss, 16.27% (1:1); XRDP, 8.50 (252), 17.04 (116). **2**-acetophenone (**c**): weight loss, 21.27% (1:1); XRDP, 6.56 (1499), 8.86 (152), 13.24 (328), 14.50 (151). **2**-2-methylacetophenone: weight loss, 19.91% (1:1); XRDP, 5.88 (107), 9.34 (37), 11.86 (34),12.58 (65). **2**-*o*-xylene: weight loss, 17.36% (1:1); XRDP, 6.14 (107), 9.50 (36), 12.56 (172). **2**-1′-acetonaphthone: weight loss, 41.96% (1:1); XRDP, 5.72 (220), 10.30 (192), 11.52 (162), 12.54(251). **2**-1-tetralone (**b**): weight loss, 35.7% (1:1); XRDP, 5.86 (341), 9.34 (406), 11.84 (331), 12.40 (72). **2**-1-methylnaphthalene (**a**): weight loss, 27.9% (1:1); XRDP, 5.84 (98), 9.66(59), 11.74 (59), 12.70 (180). **2**-acetonitrile (**d**): weight loss, 7.45% (1:1); XRDP, 6.70 (158), 9.22 (330), 13.52 (102). **2**-acrylonitrile (**e**): weight loss, 9.20%(1:1); XRDP, 6.54 (80), 9.10 (107), 13.46 (47). The following compounds yielded guest-free crystals of **2** by recrystallization: acetone, 2-butanone, 2,4-pentadione, 2′-methylacetophenone, isovalerophenone, THF, benzene, toluene, naphthalene, 2-naphthol, coumarin, 2′-acetonaphthone, chalcone, 2-acetylfluorene, anthraquinone, anthrone, 2-bromofluorene, *n*-hexyl benzoate, ethyl acetate, isobutyl benzoate, and dibenzyl ether. **2** (guest-free): weight loss, 0.5%; XRDP, 4.62 (252), 9.34 (329), 16.08 (221), 17.58 (211).

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Table 1. Crystallographic Parameters of Crystals of 2

compd	**2a**	**2b**	**2c**	**2d**	**2e**	**2**
form	$C_{37}H_{54}O_5$	$C_{36}H_{52}O_6$	$C_{34}H_{52}O_6$	$C_{28}H_{47}O_5N$	$C_{29}H_{47}O_5N$	$C_{26}H_{44}O_5$
form wt	578.83	580.80	556.78	477.68	489.69	436.63
crystal syst	monoclinic	monoclinic	orthorhombic	orthorhombic	orthorhombic	orthorhombic
space group	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	14.02(1)	14.101(2)	14.718(3)	17.829(10)	17.784(3)	9.886(1)
b (Å)	7.933(2)	8.036(2)	26.610(5)	18.906(4)	19.166(4)	37.500(4)
c (Å)	15.804(4)	15.75(1)	8.294(1)	8.282(3)	8.400(1)	6.5844(7)
β (deg)	109.07(5)	114.144(4)	90	90	90	90
V (Å^3)	1660(1)	1628.3(9)	3247.3(8)	2791.0(1)	2863.1(7)	2441.0(4)
Z	2	2	4	4	4	4
D_c (g/cm^3)	1.137	1.185	1.139	1.132	1.136	1.188
No. of unique reflections	1886	1832	2584	2228	2158	1970
No. of observed reflections	1573	1637	2394	2115	2011	1734
R_1,wR_2[a]	0.096; 0.254	0.101; 0.250	0.085; 0.229	0.060; 0.155	0.115; 0.260	0.067; 0.115
GOF	1.02	1.40	1.22	1.30	2.20	1.55
2 θ max (deg)	49.9	50.0	50.0	50.0	50.0	50.0
R/*P*	5.62	4.32	6.63	6.89	6.55	6.19
temp (°C)	−63.4	−60.0	−60.5	15.0	15.0	−60.4
host framework	bilayer I	bilayer II	crossing(CII)	crossing(CI)	crossing(CI)	GF

[a] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$ (for all data).

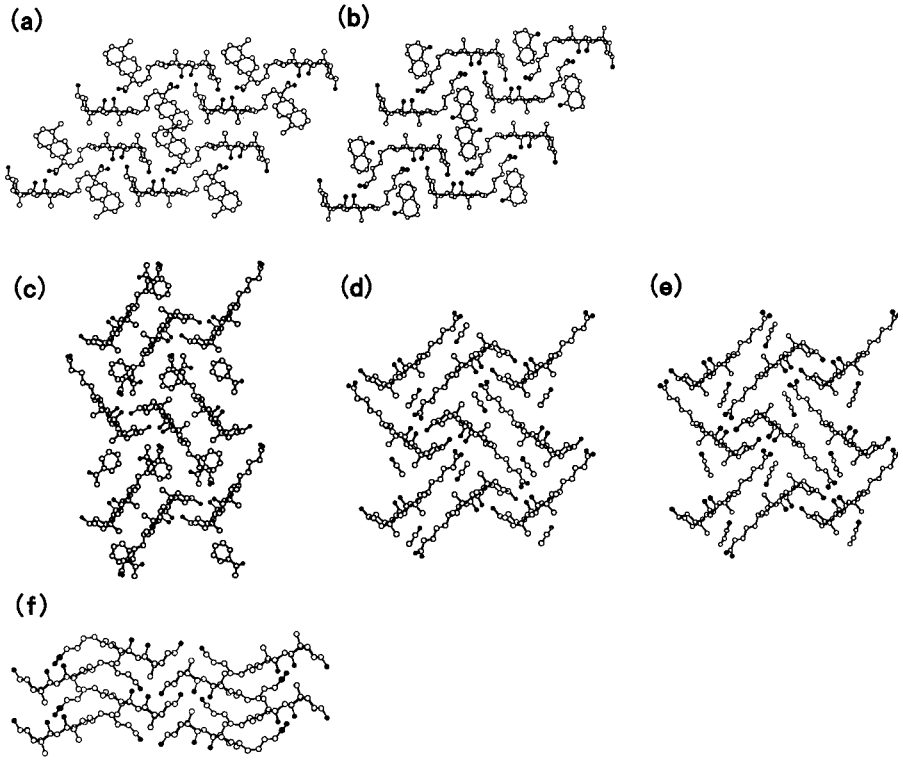

Figure 3. Molecular packing diagrams of (a) **2a**, (b) **2b**, (c) **2c**, (d) **2d**, (e) **2e**, and (f) guest-free **2**, respectively. The figures are viewed down along the crystallographic *b*-axis. Carbon, nitrogen, and oxygen atoms are represented by open, filled, and filled circle, respectively. Hydrogen atoms are omitted for clarity.

Crystal Structure Determinations. X-ray diffraction data were collected on either a Rigaku RAXIS-IV diffractometer or a Rigaku RAPID diffractometer equipped with a 2D area detector with graphite-monochromatized Mo Kα radiation. Lattice parameters were obtained by least-squares analysis from 3 oscillation images in the 2D area detector. Direct methods (SHELEX86 or SIR92) were used for the structure solution. The structure was refined by the full matrix least-squares procedure using the program TEXSAN.[23] Non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were placed in idealized positions, and no further refinement was applied. The measurement condition and structural details are listed in Table 1.

Molecular Graphics. Cross sections of host channels were depicted by using the MODRASTE.[24] The atomic radii of hydrogen, carbon, nitrogen, and oxygen in the cross-sectional views are fixed at 1.20, 1.60, 1.50, and 1.45 Å, respectively.

Results and Discussion

The host **2** includes many organic guest components. We have structurally characterized five host−guest complexes of **2** and one guest-free crystal. The crystallographic data and the packing diagrams are summarized in Table 1 and Figure 3. Hydrogen bond networks are depicted in Figure 4. The crystal structures of the five host−guest compounds might be classified into two

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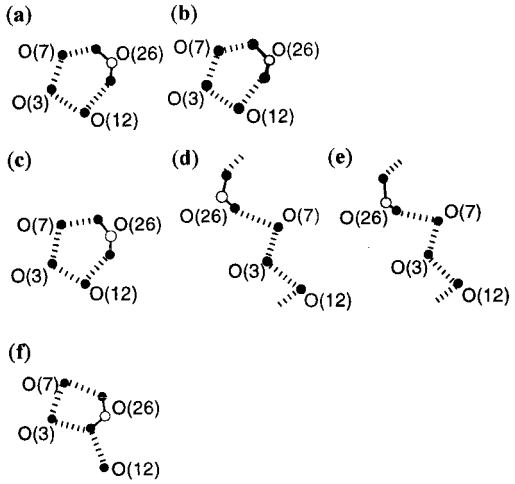

Figure 4. Hydrogen bond networks of (a) **2a**, (b) **2b**, (c) **2c**, (d) **2d**, (e) **2e**, and (f) guest-free **2**. Carbon and oxygen atoms are represented by open, and filled circles, respectively. Hydrogen atoms are omitted for clarity.

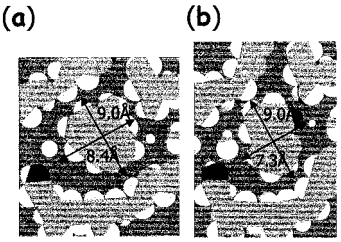

Figure 5. Cross sections of the host channels, sliced perpendicular to the direction of the channel, of (a) **2a** and (b) **2b**, respectively. The guest molecules are omitted. Carbon, hydrogen, and oxygen atoms are represented in white, gray, and black, respectively.

types on the basis of their molecular arrangements; a bilayer type and a crossing type. Large aromatic compounds are included in the former group, and small aromatic compounds, nitriles, and alcohols are included in the latter.

Expanded Channels in Bilayer Type Structures. Inclusion crystals of **2** with 1-methylnaphthalene (**a**) and 1-tetralone (**b**) are of the bilayer type, as shown in Figure 3. The common structural feature is the bilayer structure that consists of the alternating stacks of the lipophilic and the hydrophilic layers. The tape motif constructed by the intermolecular hydrogen bond networks among the three hydroxy groups is arranged parallel to the steroid plane to yield the layer structures in both of the host frameworks. Molecular cavities are formed in wavy lipophilic layers as a result of the interdigitation of the methyl groups in the lipophilic faces. Although they have similar bilayer architectures, there is some variation in the conformations of the side chain. The torsion angles at C22−C23−C24−C25 for **2a** and **2b** are −51 and 173°, respectively. This conformational difference deforms the host cavities. Cross sections of the host channels are shown in Figure 5a,b. The steric dimensions of the host cavities of **2a** and **2b** are the irregular rectangular channels measuring 9.0 × 8.4 Å and 9.0 × 7.3 Å, respectively. This deformation leads to a change of the orientation of the aromatic guest components in the host cavities; however, in both of the host frameworks, the cross sections are suitable only for the naphthalene ring. Therefore, the bilayer structures are suitable for inclusion of the large aromatic compounds at 1:1 host:guest ratios.

Comparison of the host cavities in the bilayer structure between **1** and **2** yields the fruitful discussion. The bilayer

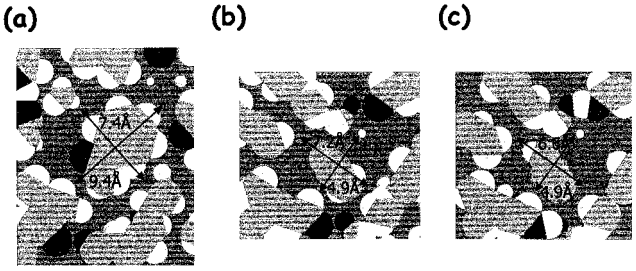

Figure 6. Cross sections of the host channels, sliced perpendicular to the direction of the channel, of (a) **2c**, (b) **2d**, and(c) **2e**, respectively. The guest molecules are omitted. Carbon, hydrogen, and oxygen atoms are represented in white, gray, and black, respectively.

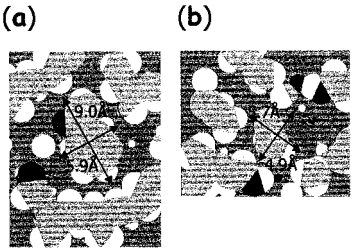

Figure 7. Cross sections of the host channels, sliced perpendicular to the direction of the channel, of (a) **1c** and (b) **1e**, respectively. The guest molecules are omitted. Carbon, hydrogen, and oxygen atoms are represented in white, gray, and black, respectively.

structure of **1**,[16] as shown Figure 1, is similar to those of **2**. They have the same cyclic hydrogen bond networks in the hydrophilic layer and the same form of the interdigitation in the lipophilic layer,[16] although the length of the spacer is different. To compare the steric dimensions of the host cavities, the cross section of **1** with acetophenone (**c**)[18a] is shown in Figure 7a. The host **1** has an irregular square cross section of 9.0 × 5.9 Å. This indicates that **2a** has a cavity that is 2.5 Å wider than **1c**. It is because the side chain extends parallel to the direction of the steroid plane. On the other hand, the depth of the host channel in the unit cells is 7.93 Å for **2a**, which is close to that of **1c** (8.09 Å)[18a] because the depth is restricted by the width of the steroid rings. Moreover, the increment (∼2.5 Å) of the width corresponds to that of the molecular structure.[25] These results indicate that elongation of the spacer between the hydrogen bond functional groups gives rise to precise elongation of the host cavity along one direction. The increments are predictable from the transformation of the molecular structure from **1** to **2**.

Expanded Cage in Crossing-Type Structures. Acetophenone (**c**), acetonitrile (**d**), and acrylonitrile (**e**) are included in the crossing-type host framework of **2,** as shown in Figure 3. The latter two nitriles have the identical host frameworks, termed CI, but the other has CII. The common structural feature is the herringbone arrangements of the host compounds and intermolecular hydrogen bonds among three hydroxy groups that connect the host compounds in a face-to-face manner. Differences between them are a variation in the geometry of the hydrogen bond networks and the crossing angle of the herringbone arrangement. CI type has helical hydrogen bond networks, and CII type has the same cyclic hydrogen bond as those of the bilayer type structure. The former has much wider crossing angles than that of the latter. This leads to a shift in the stacking manner between the lipophilic faces. As the result, the latter have much larger host cavities. Figure 6 shows the

(25) The expanded distance in the molecular structure can be calculated by the following equation; 2.5 Å = 2 × 1.5 Å × sin(109.02°).

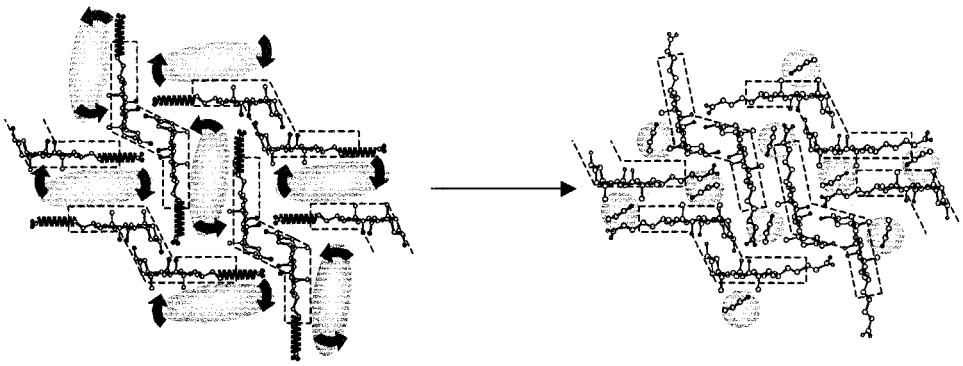

Figure 8. Closing of the void space in the crossing-type host framework of **2**.

cross-sections of **2c**, **2d**, and **2e**. The steric dimensions are 9.4 × 7.4 Å, 7.2 × 4.9 Å, and 6.6 × 4.9 Å for **2c**, **2d**, and **2e**, respectively. The smaller CI type is suitable for small nitriles, and CII is for aromatic compounds. However, both of them are much smaller than those of the bilayer types.

The CI structure of **2** is same as the crossing-type structures of **1**.[18b,19] Figure 7 shows the cross-sections of **1e** sliced at the same position as in Figure 6. The steric dimension of the host cavity of **2e** (6.6 × 4.9 Å) is slightly larger than that of **1e** (5.7 × 4.9 Å)**.** This indicates that the elongation of the spacer is not effective for expansions in the crossing-type structures. In the hypothetical host framework as shown in Figure 8, the large void space would form between the lipophilic faces; however, this ill packing causes the tape motifs to rotate to close the large void space in the similar host arrangement of **1**. The effect of the expanded spacer is canceled by this modification of the host framework. On the other hand, CII type structure has a much larger host cavity than that of **1e**. The herringbone arrangement and the slide between the lipophilic faces expand the host cavity along two directions. This is in good contrast to expansion along one direction in the bilayer structures.

Crystal Structure of the Guest-Free Form of 2. Recrystallization from ethyl acetate gives guest-free (GF) crystals of **2**. The cystal structure is depicted in Figure 3f. This form has the similar tape motif created by the hydrogen bonds among the three hydroxy groups. The most striking structural feature is the fold-back conformation of the side chain. The characteristic torsion angle at C20−C22−C23−C24 is 75° in GF form, but those of other types of **2** are located around 174°. This directs the side chain terminal to the β-face and forms the unique monolayer-type structure that has no more amphiphilic layer structures and no void space between the layers. This is a good contrast to the similarity between the GF form[26] and the crossing form[18b,19] of **1**. The elongation of the spacer increases the flexibility of the side chain, which changes the GF form.

Inclusion Compounds. Comparison of the inclusion properties between **1** and **2** suggests the importance of guest components. Table 2 summarizes the guest compounds, the host−guest ratios, and the classification of the host frameworks. In a series of aliphatic alcohols as guests, both of the hosts construct the crossing host frameworks at constant 1:1 host: guest ratios;[16] however, the ranges of the included alcohols are different: **1** includes methanol, ethanol, and 1-propanol, selectively,[19b] and **2** includes various alcohols from methanol to 1-pentanol. The larger host cavity of **2** allows the including of the larger alcohols, and host−guest hydrogen bonding might stabilize to form the small alcohols in the relative large host cavity. On the other hand, small aliphatic compounds with weak hydrogen bond donors such as ketones and esters are mostly included in the channel-type host framework of **1**,[16b,27] but they are not included in **2** and give guest-free crystals by recrystallization. Large aromatic compounds are included in the channel-type host frameworks of the two hosts;[16b] however, the host: guest ratios of **1** are 2:1 and those of **2** are 1:1. These results indicate that both of the open host frameworks of **2** are larger than that of **1** and that the guest compounds are included in the suitable host cavities.

Table 2. Guest Compounds for **2**

guests	H:G ratio[a]	host framework[b]
methanol	1:1	crossing
ethanol	1:1	crossing
1-propanol	1:1	crossing
2-propanol	1:1	crossing
1-butanol	1:1	crossing
2-butanol	1:1	crossing
1-pentanol	1:1	crossing
acetophenone	1:1	crossing
2-methylacetophenone	1:1	bilayer
o-xylene	1:1	bilayer
1′-acetonaphthone	1:1	bilayer
1-tetralone	1:1	bilayer
1-methylnaphthalene	1:1	bilayer
acetonitrile	1:1	crossing
acrylonitrile	1:1	crossing

[a] Determined by TG. [b] Determined by XRD, see Experimental Section.

Conclusion

We demonstrated the inclusion abilities and the crystal structures of **2**. X-ray crystallographic studies revealed that **2** has the two types of open host frameworks and the guest-free form. It is noteworthy that each of the open host frameworks of **2** is isostructural to the corresponding host framework of **1**. This indicates that both of the host frameworks are robust against this chemical modification. To our knowledge, this pair of the host compounds is the first example that shares the two common robust open host frameworks. This indicates that the guest-dependent isomerizations of the open frameworks do not always become an obstacle to designing host cavities and host frameworks. Guest components suitable for the steric dimensions of the designed host cavities should be required to realize the designed host frameworks.

Moreover, the isostructural host frameworks afford the expansion of the width of the host cavities from **1** to **2**. It should be noted that the increment of the width in the bilayer type corresponds to the expansion of the molecular length. Although

(26) Miki, K.; Kasai, N.; Shibakami, M.; Chirachanchai, S.; Takemoto, K.; Miyata, M. *Acta Crystallogr.* **1990**, *C46*, 2442−2445.

(27) Caira, M. R.; Nassimbeni, L. R.; Scott, J. L. *J. Chem. Soc., Perkin Trans. 2* **1994**, 623−628.

this strategy appears to be simple at a glance because of a simple modification of the molecular structure, it is very hard to preserve the host frameworks and hydrogen bond networks against chemical modifications. Robustness in the hydrogen bond networks, as well as in the association of the non-hydrogen bond parts, is required. In this work, two-methylene elongation enables the carboxylic acid group to be directed toward the same directions, which prompts the formation of the identical hydrogen bond networks. The robust interdigitations between methyl groups in the lipophilic layers enablethe formation of the robust motifs in the lipophilic layer.[14,16b] Therefore, orientation of the hydrogen bond functional groups, as well as design of the lipophilic parts, plays an important role for designing the robust host frameworks against the chemical modifications by using hydrogen bond networks as connectivities.

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Supporting Information Available: X-ray crystallographic details with positional parameters, bond lengths, and bond angles for all compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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