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Use of Supramolecular Cavities Maintained by Hydrogen-Bonded Network in Molecular Crystals As a Novel Binding Site for Guests in Water. The Solid-State Host-Guest Complexation of a Bisresorcinol Derivative of Anthracene

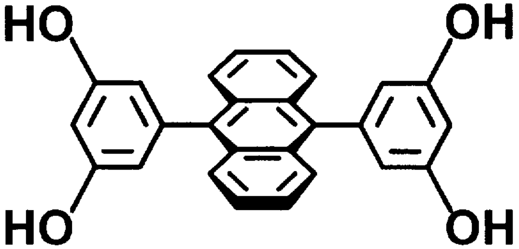
Yasuhiro Aoyama,* Yuki Imai, Ken Endo, and Kenji Kobayashi
Section of Biofunctional Chemistry, Department of BioEngineering, Nagaoka University of Technology, Kamitomioka, Nagaoka, Niigata 940-21, Japan

Abstract: A variety of guest molecules in water can be bound to the supramolecular cavities maintained by hydrogen-bonded network in molecular crystals of an orthogonal resorcinol-anthracene-resorcinol compound **1** as a host. The resulting 1:2 host-guest adducts possess a high degree of single-crystallinity as well as host-guest hydrogen-bonding.

INTRODUCTION

Hydrogen bonding plays an important role to govern the crystal structures of rigid polyhydroxy compounds. They often form lattice inclusion compounds with a variety of guest molecules included in the channel-, layer-, or cage-like cavities.[1-3] We have recently shown that an orthogonal resorcinol-anthracene-resorcinol compound **1** forms molecular crystals consisting of layered molecular sheets which involve an extensive hydrogen-bonded network together with supramolecular cavities (Figure 1a). In each cavity are incorporated two molecules of recrystallization solvent via hydrogen bonding (Figures 1b and 1c).[4,5]

The hydrogen bonding is not an effective force to achieve host-guest complexation in water. At the same time, it is true that hydrogen bonding in water plays an essential role in the maintenance of the structures and functions of biopolymers. The supramolecular cavities in the present crystals of host **1** are also maintained by hydrogen bonds (O-H···O-H). With all of these in mind, we have investigated the solid-state guest-binding



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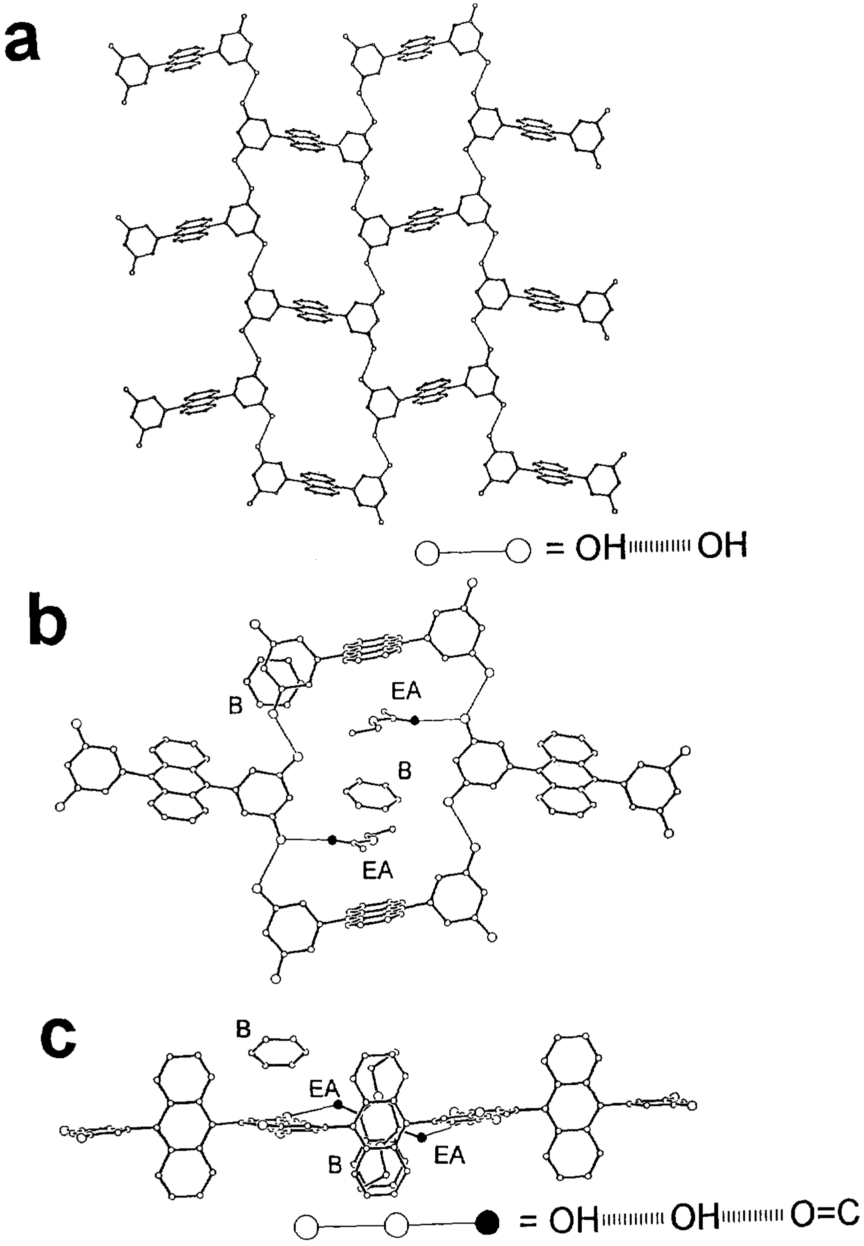

Fig. 1. Crystal structure of adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6): hydrogen-bonded network in a molecular sheet (a), packing geometry for two ethyl acetate (EA) and two benzene (B) molecules incorporated in the cavity (b), and its top view (c).

properties of **1** *in water*. We report here that the supramolecular cavities survive in an aqueous environment and are capable of *extracting* guests from water in a stoichiometric manner.

RESULTS AND DISCUSSION

Guest-Exchange for Adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6). Recrystallization of compound **1** from a mixture of ethyl acetate and benzene afforded single crystals (approximate size, 2 x 1 x 1 mm^3) of a 1:2:2 adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6).[4] It is not soluble in water at all. When dipped in an aqueous solution of guest X, it underwent a very slow solid-state guest-exchange, ultimately giving a 1:2 adduct 1·2(X).[6] The exchangeable guests X include cyclohexanol, cyclohexanediol (1,2-, 1,3-, and 1,4-), alkyl acetate (alkyl = ethyl, propyl, and butyl), and choline ((2-hydroxyethyl)trimethylammonium chloride) and acetylcholine. On the other hand, such guests as sugars and amino acids showed far less pronounced affinities to **1** under similar or even more compelling conditions. Although the crystals became somewhat turbid upon guest exchange, they appeared to retain the shape and size of the original single crystals.

The relative affinities of various guests appeared to be primarily governed by their hydrophobicities. This is, however, not strictly true; the selectivity changes with the progress of exchange. The time-courses of the uptake of choline and acetylcholine under competitive conditions ($[\text{choline}]_{aq}$ = $[\text{acetylcholine}]_{aq}$ = 1.5 M) are shown, as an example, in Figure 2 together with those of the loss of two pre-bound guests, i.e., ethyl acetate and benzene. Several characteristic aspects are noted. (1) Acetylcholine is highly selectively bound at the initial stage, while choline is finally included almost exclusively. (2) The loss of two molecules of ethyl acetate is synchronous and relatively rapid. It is compensated by an uptake of the corresponding amount of newly bound guests; the total amount of ethyl acetate, choline, and acetylcholine is kept constant at ~2 M during the guest exchange. (3) The loss of two molecules of benzene, on the other hand, is asynchronous. One molecule is rapidly lost, while the other more slowly. Interestingly, the amount of benzene left seems to govern the choline/acetylcholine selectivity. This point becomes clearer when the amounts of the two guests incorporated are plotted against that of benzene left (Figure 3). Thus, the selectivity is highly in favor of acetylcholine until one molecule of benzene has been lost (2 > benzene/**1** ≥ 1). After that (1 > benzene/**1** > 0), however, a high preference for choline is observed; the 1:2 choline adduct **1**·2(choline) ultimately results as the sole guest-exchanged product. Another interesting example of benzene-dependent selectivities is the discrimination between stereoisomers of 1,4-cyclohexanediol. The binding of this particular diol is highly (up to 97:3) trans-selective at the initial stage but ends up with a moderate (80:20) cis-selectivity, when carried out under competitive conditions using a 1:1 mixture of the cis and trans isomers.

In the starting single crystals of adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6), the two ester molecules (antiparallel with each other) are incorporated in each cavity via hydrogen bonding (O-H···O-H···O=C) between a pair of hydrogen-bonded OH groups (O-H···O-H) of compound **1** and the guest carbonyl group. The two benzene molecules, on the other hand, are crystallographically not equivalent. One is incorporated in the

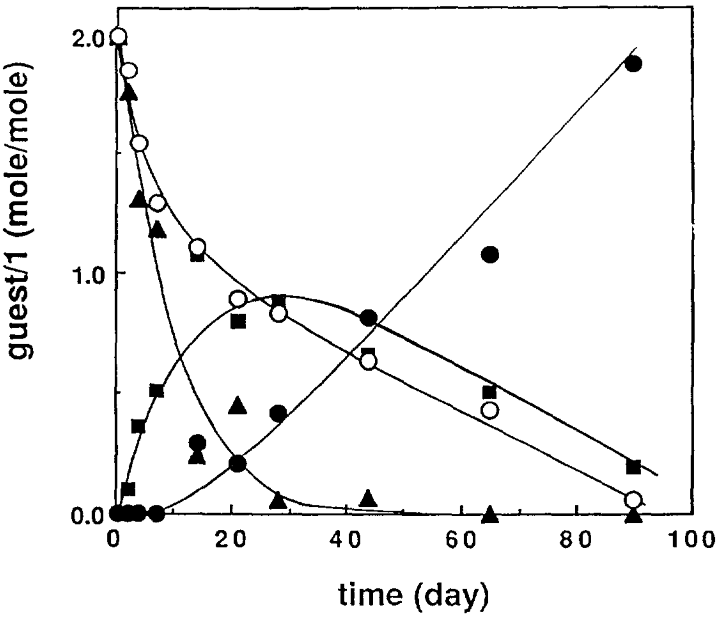

Fig. 2. Time-courses of the uptake of choline (●) and acetylcholine (■) and the loss of ethyl acetate (▲) and benzene (○) in the solid-state guest-exchange for single crystals of adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6) dipped in an aqueous solution of choline (1.5 M) and acetylcholine (1.5 M) at room temperature.

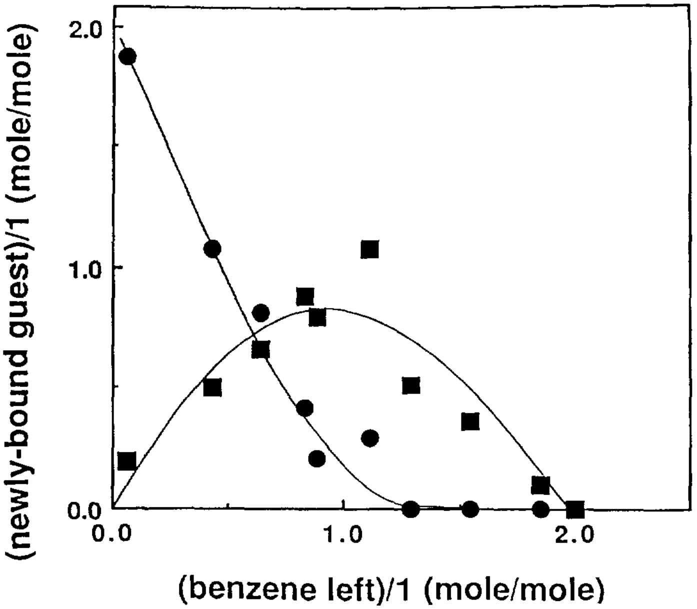

Fig. 3. Correlations between the amounts of choline (●) or acetylcholine (■) incorporated and that of benzene left in the solid-state guest-exchange for single crystals of adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6) dipped in an aqueous solution of choline (1.5 M) and acetylcholine (1.5 M) at room temperature.

cavity, while the other is located in the space between the sheets (Figures 1b and 1c). It is interesting to consider the above-mentioned benzene-dependencies of the selectivities in light of different locations of the two benzene molecules.

Guest-Binding to Apohost. Heating in vacuo of adduct **1**·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6) resulted in a complete loss of included guest molecules. The resulting *apohost* **1** is polycrystalline as judged by its powder-pattern X-ray diffractions (Figure 4b) and there is little evidence for the presence of crystal lattices for the starting adduct (Figure 4a). When dipped in water, the apohost became hydrated with ~16 molecules of water, as confirmed by both ^{1}H NMR spectroscopy and thermal gravimetry. The powder-pattern diffractions of the hydrated host (Figure 4c) are much simpler and more intense than those of apohost (Figure 4b). This may reflect an enhanced single-crystallinity of the hydrated host as compared with the apohost.

The guest-binding to apohost **1** was found to be much faster than the guest-exchange for adduct **1**·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6).[6] A typical time-course is shown in Figure 5 for the binding of *trans*-1,2-cyclohexanediol. Such guests as mentioned above as well as ketones (acetone and 3-pentanone) were bound in this manner and gave 1:2 adducts **1**·2(guest). The stereoselectivity between stereoisomers of 1,4-cyclohexanediol was not dependent on the extent of guest-binding and was moderately (80:20) cis-selective. This is in accord with the above-described stereoselectivity in the guest-exchange using adduct **1**·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6) after benzene has been completely lost.

Thermal gravimetry indicated that adducts **1**·2(butyl acetate) and **1**·2(3-pentanone) contained at most ~5 and ~3 molecules of water, respectively; the water contents of the adducts are thus much smaller than that of the hydrated host. More detailed characterization of adduct **1**·2(butyl acetate) as a representative case was made in reference to the authentic water-free single-crystals of this adduct obtained by recrystallizing compound **1** from butyl acetate. (1) Both adducts showed identical IR spectra having a $\nu_{C=O}$ for bound guest at 1703 cm^{-1}, as compared with $\nu_{C=O}$ = 1743 cm^{-1} for free guest as a neat liquid ($\Delta\nu_{C=O}$ = 40 cm^{-1}).[7] (2) Both adducts exhibited essentially the same powder-pattern X-ray diffractions, as shown in Figures 4d and 4e. These results indicate that the two adducts obtained under different conditions, either hydrous or anhydrous, have essentially the same structures. In particular, the adduct obtained by the present guest-binding from an aqueous solution must have a high degree of single-crystallinity as well as host-guest hydrogen-bonding.[8]

The results presented above are interpreted as indicating that the hydrogen-bonded network involved is strong enough to survive the guest-free[9] or the aqueous conditions. Moreover, the guest-free cavities in the apohost can even be stabilized by incorporating ~16 molecules of water. They may cooperate with the OH groups of the host to form a hydrogen-bonded water pool.[10,11] This may have relevance to the similar hydration-stabilization of the proteins. The binding of two guest molecules in the cavity is actually a water-guest exchange. In addition to the hydrophobic and van der Waals interactions, host-guest hydrogen-bonding must at least partially be responsible for the present complexation under aqueous conditions.

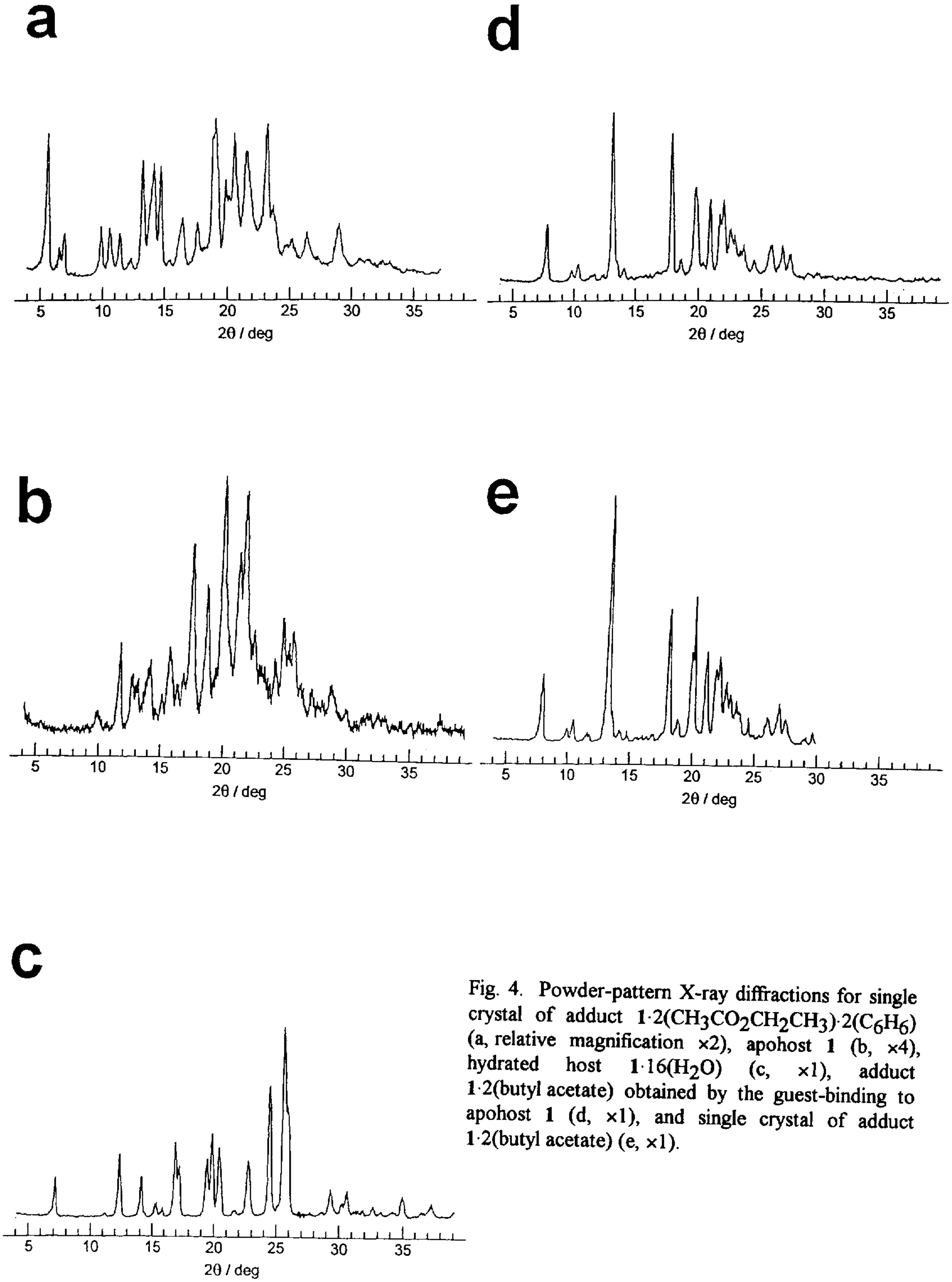

Fig. 4. Powder-pattern X-ray diffractions for single crystal of adduct 1·2($CH_3CO_2CH_2CH_3$)·2(C_6H_6) (a, relative magnification ×2), apohost **1** (b, ×4), hydrated host **1**·16(H_2O) (c, ×1), adduct **1**·2(butyl acetate) obtained by the guest-binding to apohost **1** (d, ×1), and single crystal of adduct **1**·2(butyl acetate) (e, ×1).

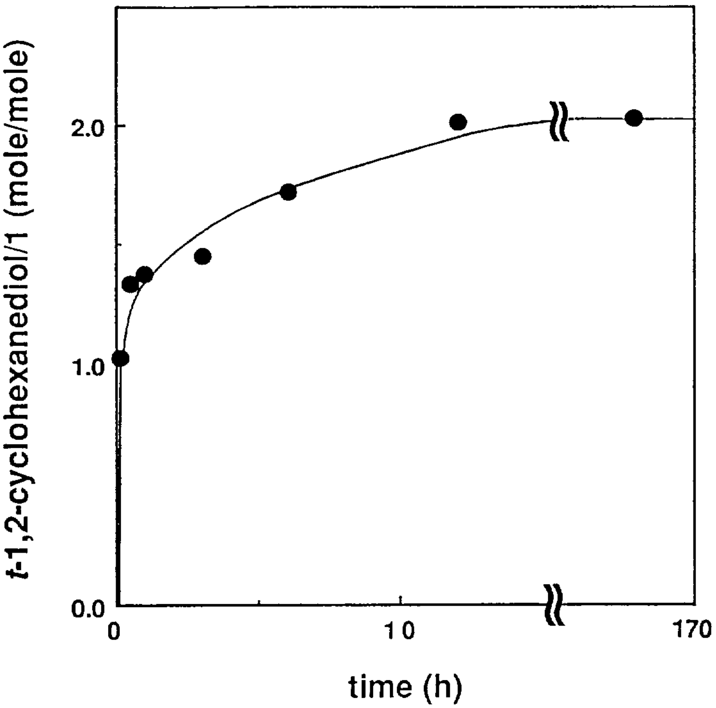

Fig. 5. Time-course of the solid-state guest-binding to apohost **1** dipped in an aqueous solution of *trans*-1,2-cyclohexanediol as a guest (1.0 M) at room temperature.

Supramolecular Cavities in Porous Molecular Crystals As Novel Hosts. The substrate-binding sites of enzymes are three-dimensional and are maintained by intramolecular *interactions* involving multiple hydrogen bonding. The enzyme-substrate complexation in most cases is promoted by a cooperation of polar and apolar interactions. None of these characteristic aspects can be mimicked readily by using synthetic models. Water-soluble cyclophanes have been occupying a central position of synthetic hosts working in aqueous media.[12] They usually afford a cylintrical binding site, which is far from three-dimensional and is constructed by covalent bonds. In addition, the major driving force of host-guest complexation is apolar interactions. In fact, the use of hydrogen bonding for the construction of supramolecular structures in aqueous media is one of the big challenges of molecular recognition and related areas.[13]

In these respects, the supramolecular cavities in molecular crystals of host **1** bear a number of at least formal similarities to the binding sites of enzymes. They are three-dimensional and maintained by hydrogen bonds. The present work further demonstrates that the supramolecular cavities survive in an aqueous environment and are capable of either undergoing hydration (in the absence of any guest) or stoichiometric guest-binding, which seems to be promoted by a cooperation of hydrogen bonding and hydrophobic/van-der-Waals interactions.[14]

Furthermore, the size and shape of the cavities are predictable or even designable on the basis of expected hydrogen bonding interactions. Catalytic functionalities may also be introduced. These characteristic aspects suggest a potential use of this type of porous organic crystalline solids as a new class of enzyme-mimetic receptors, catalysts, and adsorbents, i.e., as an organic counterpart of a variety of inorganic porous materials such as zeolite.[15]

EXPERIMENTAL SECTION.

Materials. Compound **1**[4] (ca. 1 g) was dissolved in ethyl acetate (30 mL). Benzene (30 mL) was added slowly with careful stirring to avoid precipitation of **1** on the wall of the flask. The resulting solution was kept in an atmosphere of benzene vapor in a sealed container. Single crystals of adduct $1\cdot 2(CH_3CO_2CH_2CH_3)\cdot 2(C_6H_6)$ of an approximate size of 2 x 1 x 1 mm^3 separated in a couple of days. Compound **1** was dissolved in refluxing butyl acetate. The resulting solution was allowed to cool down at a rate of 1 °C/min. Single crystals of adduct **1**·2(butyl acetate) separated at temperatures < 70 °C. Single crystals of adduct $1\cdot 2(CH_3CO_2CH_2CH_3)\cdot 2(C_6H_6)$ were heated in vacuo at 80 °C for 3 h, 150 °C for 8 h, and finally at 170 °C for 1 h to give pieces of apohost **1**. Although they became no longer transparent but turbid, they appeared to retain the shape and size of the original single crystals.

Instruments. The ^{1}H NMR spectra were taken for DMSO-d_6 solutions on a JEOL-GX 270 or a JEOL EX 400 spectrometer. IR spectra were obtained for KBr disks (host-guest adducts) or neat liquids (free guests) with a JASCO IR-810 spectrophotometer. Thermal gravimetry was carried out using a SEIKO TG/DTA-20 apparatus with a SSC/580 thermal controller.

Guest Exchange and Guest Binding. Into an aqueous solution of an appropriate guest was added 30-50 pieces of the single crystals of adduct $1\cdot 2(CH_3CO_2CH_2CH_3)\cdot 2(C_6H_6)$. The single crystals were of a similar size (approximately 2 x 1 x 1 mm^3). The guest concentrations were 1 or 1.5 M for such highly hydrophilic guests as cyclohexanediol, choline and acetylcholine, and acetone. Those of cyclohexanol, ethyl acetate, propyl acetate, butyl acetate, and 3-pentanone were 0.17, 0.30, 0.10, 0.04, and 0.30 M, respectively. The volume of the aqueous guest solution was so chosen as to allow a 20-fold excess of a guest over the host. The mixture was left at room temperature without stirring. Several pieces of the crystals were picked up at appropriate time intervals. They were quickly washed with a small amount of water and wiped with a filter paper. They were combined and dissolved in DMSO-d_6 for the ^{1}H NMR analysis for the amounts of pre-bound and newly-bound guest molecules. The yield in terms of weight of the recovered crystals was ~100% in every case. The solid-state guest-binding to micro-crystals (approximate size, 2 x 1 x 1 mm^3) of apohost **1** was carried out similarly.

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5. Our recent results (Aoyama, Y.; Endo, K.; Kobayashi, K.; Masuda, H. *Supramolecular Chemistry*, in press) indicate that host **1** forms 1:2 host-guest adducts with a variety of guests such as esters, ketones, and alcohols. The X-ray structures of the ester adducts are similar to that of adduct $1 \cdot 2(CH_3CO_2CH_2CH_3) \cdot 2(C_6H_6)$. Two ester molecules are included in each cavity via hydrogen bonding; they are parallel with respect to the anthracene moieties at the roof and floor of the cavity (refer to Figure 1b) and are antiparallel with respect to each other. The $\nu_{C=O}$ value for the ester undergoes a significant shift to lower wavenumber upon binding.
6. For the crystalline-phase guest-addition, -removal, and -exchange in the cholic acid intercalation crystals, see: Miyata, M.; Shibakami, M.; Chirachanchai, S.; Takemoto, K.; Kasai, N.; Miki, K. *Nature*, **1990**, *343*, 446.
7. Ethyl acetate and propyl acetate exhibited similar $\Delta\nu_{C=O}$. The $\Delta\nu_{C=O}$ values for ketone guests are 17 and 23 cm^{-1} for acetone and 3-pentanone, respectively.
8. The shift in $\nu_{C=O}$ could not be due to interaction of the bound guest with coincluded water molecules, since the water-induced shift in $\nu_{C=O}$ would be smaller than observed. For example, the $\nu_{C=O}$ values of acetone in water and as a neat liquid are 1705 and 1715 cm^{-1}, respectively; the $\Delta\nu_{C=O}$ value of 10 cm^{-1} can not account for the $\Delta\nu_{C=O} = 17$ cm^{-1} observed.[7]
9. Cavities in inclusion lattices often collapse in the absence of guest molecules. In some cases, however, such cavities are retained in their absence. See: (a) MacNicol, D. D.; McKendrick, J. J.; Wilson, D. R. *Chem. Soc. Rev.*, **1978**, *7*, 65. (b) Ung, A. T.; Bishop, R.; Craig, D. C.; Dance, I. G.; Scudder, M. L. *J. Chem. Soc., Chem. Commun.*, **1991**, 1012. (c) Bishop, R.; Craig, D. C.; Dance, I. G.; Scudder, M. L.; Ung, A. T. *Mol. Cryst. Liq. Cryst.*, **1992**, *211*, 141.
10. In reference to Figure 1a, the anthracene-anthracene distance along an anthracene column is ~ 14 Å.

The column-to-column distance for two neighboring anthracene columns and the sheet-to-sheet distance are ~10 Å and ~7 Å, respectively.[4] The size of the supramolecular cavity is enough to incorporate a cluster of ~16 water molecules.

11. For the extraction of a water pool into unimolecular polyhydroxy cores in apolar organic media, see: K. Kobayashi, F. Ikeuchi, S. Inaba, Y. Aoyama, *J. Am. Chem. Soc.*, **1992**, *114*, 1107.
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