STUDIES ON WATER-SOLUBLE ARTIFICIAL RECEPTORS CONTAINING CHIRAL SIDE CHAINS DERIVED FROM CARBOHYDRATES. 1. SYNTHESIS OF OPTICALLY ACTIVE CYCLOPHANE TCP44 AND ITS COMPLEXATION SELECTIVITY FOR AROMATIC GUESTS IN ACIDIC AQUEOUS SOLUTIONS†,[1]

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Abstract – The details of the synthesis and complexation properties of L-tartrate-derived cyclophane (TCP44), the first totally synthetic host with a chiral hydrophobic cavity, are described. The synthesis employs 1:1 cyclization *via* a U-shaped precursor containing chiral C_4 units derived from L-tartaric acid. TCP44, soluble in acidic water as an amine salt, displayed a complexation selectivity for hydrophobic aromatic guests. Inclusion of aromatic guests into the cavity was verified by fluorescence and ^{1}H NMR spectra. A possible structure of inclusion cavity is discussed.

INTRODUCTION

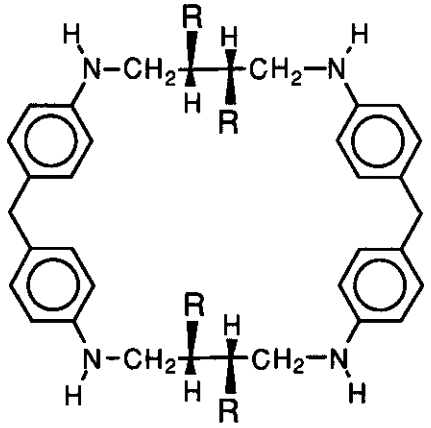
Water-soluble cyclophanes compose a class of artificial hosts with well-defined hydrophobic cavities and high design versatility.[2] Following the first direct evidence of guest inclusion by X-Ray crystallography [CP44 (**1**)·4HCl-durene complex],[3] we have reported the first optically

† Dedicated to the memory of Dr. Shun-ichi Yamada, Professor Emeritus, University of Tokyo, for his outstanding contribution to the chemistry of optically active compounds.

active cyclophane with a chiral hydrophobic cavity (TCP44, **2**),[4a] which is constructed with two diphenylmethane units bridged *via* four nitrogens by two chiral C_4 units derived from L-tartaric acid. Asymmetric hydride reduction of arylglyoxylic acids to the corresponding α-hydroxy acids by $NaBH_4$ in acidic aqueous solutions was also examined with this type of cyclophanes.[4b] Several types of cyclophanes with chiral hydrophobic cavities have been reported thereafter, showing characteristic modes of chiral recognition in aqueous solutions.[5,6] In this paper, we report the full details of the synthesis and complexation properties of the chiral host TCP44 (**2**), and discuss a possible solution structure of its inclusion cavity.

RESULTS AND DISCUSSION

Design and Synthesis. The characteristic complexation properties of CP44 (**1**) is attributable to its well-defined hydrophobic cavity constructed with diphenylmethane units. Thus, for designing a chiral hydrophobic cavity based on the CP44 system, we chose TCP44 (**2**) as the target compound, which is a simplest chiral modification of CP44 (**1**). Chiral host (**2**) has a D_2-symmetrical structure, in which two diphenylmethane units are linked by two chiral C_4 units derived from L-tartaric acid. The D_2-symmetrical nature of this host is expected to simplify spectral analyses for characterizing the structure of **2** and understanding its complexation properties.



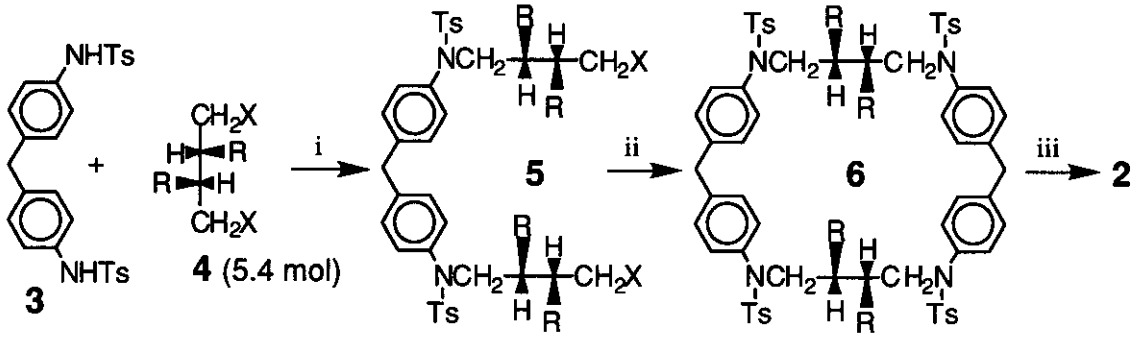
1 (CP44): R = H

2 (TCP44): R = OCH_3

The synthesis of **2** was carried out as shown in Scheme **1**. The key to this synthesis is the 1:1 cyclization between **3** and U-shaped precursor (**5a**). First, L-tartaric acid as the starting material was converted to diiodide (**4a**) *via* dimesylate (**4b**) in several steps by employing well-known procedures. The reaction of **3** with a large excess of **4a** gave the U-shaped precursor (**5a**) in 90% yield. The subsequent 1:1 cyclization to cyclic tetratosylate (**6**) was carried out with equimolar amounts of **3** and **5a** in the presence of K_2CO_3 in DMF. The yield, 31%, is acceptable but much lower than that in a similar cyclization reaction in the synthesis of the tetratosylate of **1** from **3** and an achiral (*i.e.*, nonsubstituted) U-shaped precursor (73% yield).[3b] Neither 1:1 cyclization using dimesylate (**5b**) in place of diiodide (**5a**) nor direct 2:2

cyclization between **3** and **4a~c** gave the desired cyclization product (**6**) in contrast with a satisfactory yield (24%) of 2:2 cyclization in the synthesis of the tetratosylate of **1**.[3]

For detosylation of **6**, the condition used for the tetratosylate of **1** (48% HBr-phenol at reflux)[3] was avoided because it would cause cleavage of the methoxy moieties. Therefore, various attempts for reductive cleavage (Vitride®, Al-Hg, Na-NH_3, Zn-HCl, *etc.*) were made but proved to be unsuccessful. The only successful condition turned out to be 90% H_2SO_4, which smoothly gave the desired cyclic tetraamine (**2**) in 69% yield.



a: X = I; **b**: X = OMs; **c**: X = OTs; R = OCH_3

i) K_2CO_3 (6.8 mol) / DMF; 80 °C, 2.5 h;
ii) **3** (1 mol), K_2CO_3 (10 mol) / DMF; 110 - 115 °C, 8 h;
iii) 90% H_2SO_4; rt, 18 h, then 50 °C, 3 h.

Scheme 1

The macrocyclic structure of **2** was confirmed on the basis of FABMS, which showed the molecular ion (M^+ 624) together with fragment ions such as the ones generated by elimination of methoxy group(s). The small M^+ signal observed in the FABMS of tetratosylate (**6**) (M^+ 1240) also supported the expected macrocyclic structure. The D_2-symmetrical structure of **2** and **6** was most clearly verified by ^{13}C NMR in $CDCl_3$, which showed eight and thirteen independent signals, respectively. Some of the ^{13}C signals of tetratosylate (**6**), but not of free tetraamine (**2**), accompanied small adjacent signals, which suggest the existence of a conformer in the case of **6**.

In the ^1H NMR spectrum of tetratosylate (**6**), the methoxy signal appeared at δ 2.96 ppm, approximately 0.5 ppm upfield from the position of the corresponding signals of **4a**, **4b** or **2** (*ca.* 3.5 ppm). This upfield shift can be ascribed to the anisotropic effect due to the aromatic rings of the cavity and/or the tosyl groups. The corresponding signals of the U-shaped precursor (**5a**) also showed some upfield shifts (3.27 and 3.33 ppm), probably due to a similar effect. The FABMS pattern of **6** is characteristic in that a group of small fragment ions appeared in a symmetrical manner just below the M^+ position, *i.e.*, in the region between *m/z* 1233 [$(M-8)^+$] and 1240 (M^+) (see the Experimental Section). This spectral pattern, which was not observed at all in the FABMS of **2** or **5a**, might be due to stepwise β-elimination of the hydrogens attached to the C_4 chains, leading eventually to the unsaturated macrocyclic

structure that is fully conjugated with the tosyl groups. The tendency of hydrogen elimination from **6** but not from **5a** might be due to molecular distortion of the former, arising from steric congestion in the C_4 chains.

Spectral Studies on the Formation of Host-Guest Inclusion Complexes with Hydrophobic Guests in Acidic Aqueous Solutions. TCP44 (**2**) is soluble in water below pH 1.7 as an amine salt and has sufficient chemical stability at this pH. Therefore, spectral studies were carried out in acidic aqueous solutions in a similar manner as for the achiral counterpart CP44 (**1**).[3,7,8]

1. Fluorescence Spectra in Acidic Aqueous Solutions

In the present study, 1-anilinonaphthalene-8-sulfonate (ANS; **7**), which is a representative hydrophobic probe used widely in protein and membrane researches,[9] was employed as a fluorescent guest. As shown in Figure 1, host (**2**) induced a marked emission enhancement and a blue shift in the fluorescence spectrum of **7** in acidic aqueous solution (pH 1.65), as observed for host (**1**) at pH 1.95.[3] This spectral change indicates transfer of guest (**7**) into a nonpolar environment in the presence of host (**2**), as when bound to a cavity of a protein or when dissolved in a less polar solvent.[9] The Benesi-Hildebrand plot[10,11] of the fluorescence intensity in an appropriate concentration range gave a straight line, indicating the formation of a 1:1 host-guest complex. The stability constant (K_S) for the 1:1 complex of host (**2**) and guest (**7**) at pH 1.65 was calculated to be 1.74×10^3 M^{-1}, which is comparable with the reported K_S values for the 1:1 complexes of **7** and **1** (6.3×10^3 M^{-1} at pH 1.95)[3] or other water-soluble cyclophanes.[7,12,13]

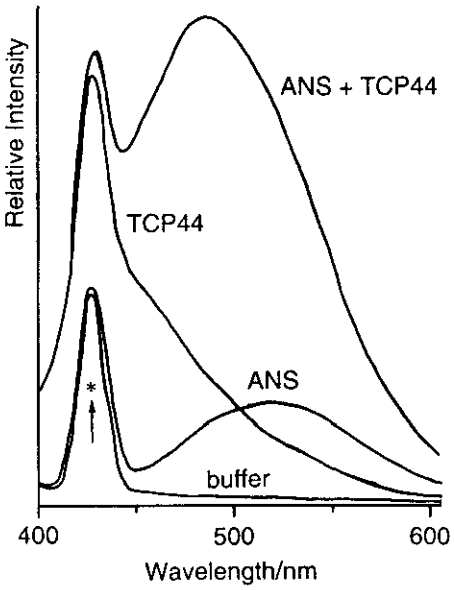
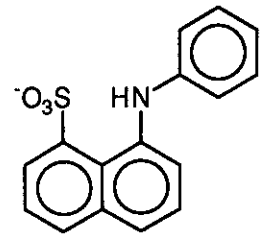


Figure 1. Fluorescence Spectra of ANS (**7**) in the Presence and Absence of TCP44 (**2**)



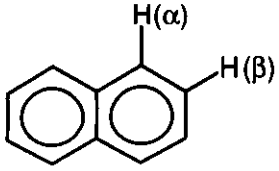
7 (1,8-ANS)

Conditions: [ANS] = 2.55×10^{-6} M, [TCP44] = 1.05×10^{-4} M; in KCl-HCl buffer (pH 1.65); 24.8 ± 0.1 °C; excited at 375 nm. These emission spectra are not corrected for the wavelength-dependent sensitivity of the photomultiplier. The asterisk indicates the Raman scattering of water.

2. ^{1}H NMR Spectra in Acidic Aqueous Solutions

2-1. Host-Induced Chemical Shift Changes of Guest Protons. Upon the formation of inclusion complexes by host (**1**) in acidic aqueous solutions, large upfield shifts were found to be induced on the guest proton signals due to a strong ring current effect of the four benzene rings of the host.[3,8] Following this example, such host-induced upfield shifts of guest proton signals have been widely observed for this and other types of cyclophane hosts.[5a-f,14-16] In many cases, the ^{1}H NMR signals of a guest in a complexation equilibrium appear in a weighed average because the formation/dissociation rates of a cyclophane complex in an aqueous solution are generally greater than the NMR chemical shift fast-exchange limit. In the present work, complexation between host (**2**) and hydrophobic guests was examined in DCl-D_2O (pD 1.2)[3,8] or DCl-D_2O/CD_3OD. The latter solvent system was used in the case that the solubility of guest alone in acidic water was poor. The host-induced chemical shift changes of the guest proton signals are represented as $\Delta\delta$ (ppm) [= δ(host + guest) – δ(guest)], and therefore negative values of $\Delta\delta$ indicate upfield shifts.

Previously, we have reported that host (**1**) exhibits a complexation selectivity for aromatic guests in acidic aqueous solutions.[13] Therefore, we first examined the complexation ability of the chiral host (**2**) with the achiral aromatic guests used in the complexation study for the achiral host (**1**). The results with some aromatic and aliphatic guests (**8**~**13**) are summarized in Table 1. In Figure 2, the ^{1}H NMR spectra of guest (**9**) in the presence and absence of host (**2**) are shown as a representative example of the spectra showing host-induced upfield shifts of guest proton signals.



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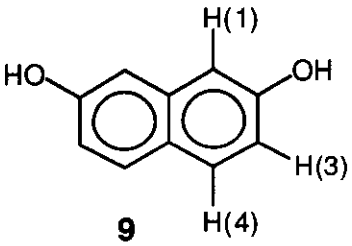

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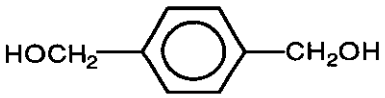

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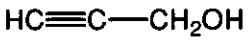

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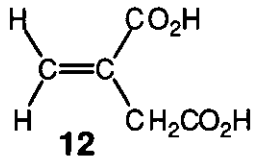

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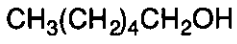

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Host (**2**) as well as host (**1**) induced large upfield shifts for the proton signals of hydrophobic *aromatic* guests (**8**~**10**), which strongly indicate the formation of an inclusion host-guest complex in each case. In contrast, the proton signals of hydrophobic *aliphatic* guests [propargyl alcohol (**11**), itaconic acid (**12**), and 1-hexanol (**13**)] showed much smaller upfield shifts ($\Delta\delta$ ~ -0.1 ppm) under similar conditions. These results clearly show that the chiral host TCP44 (**2**) displays a complexation selectivity for aromatic guests ("aromatic selectivity"), as observed with its achiral counterpart CP44 (**1**) and related hosts.[13,14c]

Table 1. Host-induced Chemical Shift Changes (Δδ) for Aromatic and Aliphatic Guests[a]

		CP44 (**1**)·nH$^+$	TCP44 (**2**)·nH$^+$		
	proton of guest	Δδ	Δδ	δ(guest)	δ(host + guest)
8[b]	ArH (α) (m)	-1.17 (2.66)[e]	-0.64 (2.40)	8.219	7.578
	ArH (β) (m)	-0.44 (1)[e]	-0.27 (1)	7.844	7.578
9[c]	ArH (1) (d, J = 2.4 Hz)	-1.90 (3.22)[f]	-1.75 (2.84)	7.499	5.746
	ArH (3) (dd, J = 2.4, 8.8 Hz)	-0.59 (1)[f]	-0.62 (1)	7.401	6.784
	ArH (4) (d, J = 8.8 Hz)	-1.75 (2.97)[f]	-1.61 (2.61)	8.154	6.541
10[c]	ArH (s)		-0.74	7.815	7.078
	CH_2 (s)		-0.34	5.048	4.711
11[d]	HC≡C (s)		-0.03	4.660	4.633
	CH_2 (s)		-0.02	3.262	3.240
12[d]	H_2C=C (Z) (br s)		-0.10	6.817	6.715
	H_2C=C (E) (br s)		-0.09	6.338	6.246
	CH_2 (s)		-0.09	3.865	3.771
13[d]	-$CH_2C\underline{H}_2OH$ (t, J = 6.8 Hz)		-0.05	4.026	3.972
	-$C\underline{H}_2CH_2OH$ (quintet, J = 6.8 Hz)		-0.07	1.971	1.899
	$CH_3(C\underline{H}_2)_3$- (br s)		-0.10	1.731	1.631
	$C\underline{H}_3(CH_2)_3$- (t, J = 6.8 Hz)		-0.07	1.297	1.227

[a] Δδ (ppm) = δ(host + guest) − δ(guest). TMS and HMDS were used as the external reference for guests (**8**)~(**10**) and (**11**)~(**13**), respectively. The values in the parentheses show the ratios of Δδ for each proton. [b] DCl-D_2O (pD 1.2)/CD_3OD (60:40); [host] = 1.0 × 10^{-2} M, [guest] = 5.0 × 10^{-3} M. [c] DCl-D_2O (pD 1.2); [host] = 5.0 × 10^{-2} M, [guest] = 2.5 × 10^{-2} M. [d] DCl-D_2O (pD 1.2); [host] = 2.5 × 10^{-2} M, [guest] = 2.5 × 10^{-2} M. [e] K. Mori, K. Odashima, and K. Koga, unpublished results. [f] Taken from ref 8.

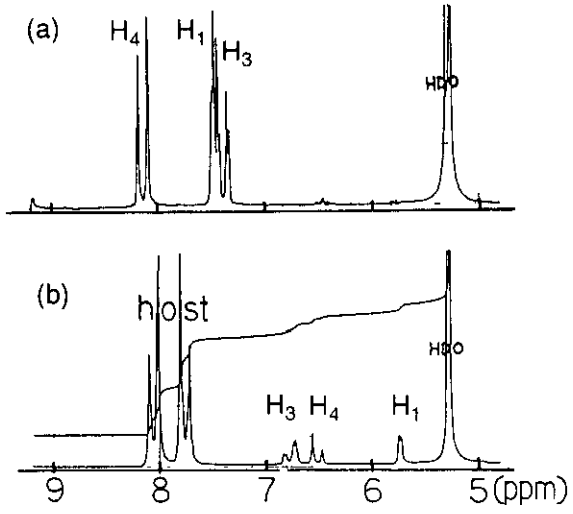


Figure 2. ^{1}H NMR spectra of (a) guest (**9**) and (b) TCP44 (**2**) + guest (**9**) in DCl-D_2O (pD 1.2) [**2**] = 5.0 x 10^{-2} M, [**9**] = 2.5 x 10^{-2} M. TMS as an external reference.

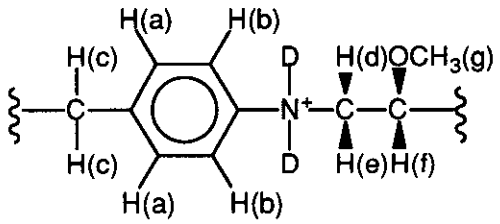
2-2. Guest-Induced Chemical Shift Changes of Host Protons. The formation of inclusion complexes between host (**2**) and aromatic guests also causes guest-induced changes in the chemical shifts of host proton signals, as observed for host (**1**) at pD 1.2.[8] The chemical shift changes in this case are represented as $\Delta\delta$(ppm) = δ(host + guest) – δ(host). The changes induced by guests (**9**) and (**10**) for each signal of host (**2**) are listed in Table 2.

Whereas the proton signals of the bridging C_4 chains appear as two sets of broad multiplets in the case of protonated **1**,[3b,8] the corresponding signals for the H(d), H(e) and H(f) of protonated **2** appear as broad ABX type signals. The large upfield shifts of these signals, as well as moderate downfield shift of the aromatic H(a) signal and negligible shifts of the H(b) and H(c) signals, are similar to the corresponding guest-induced changes for protonated **1**[8] and hence indicate the formation of inclusion complexes. The larger upfield shifts induced on the H(d), H(e) and H(f) signals by a naphthalene derivative (**9**) compared to a benzene derivative (**10**) are also consistent with the formation of inclusion complexes.

Table 2. Guest-induced Chemical Shift Changes ($\Delta\delta$) for Host (**2**)[a]

proton of host	δ(host)	guest (**9**)		guest (**10**)	
		δ(host + guest)	$\Delta\delta$	δ(host + guest)	$\Delta\delta$
H(a)	7.911 (d, J = 8.6 Hz)	8.062	+0.15	7.951	+0.04
H(b)	7.802 (d, J = 8.6 Hz)	7.776	-0.03	7.789	-0.01
H(c)	4.479 (s)	4.531	+0.05	4.485	+0.01
H(d)	4.05 (ABX type m)	3.78	-0.27	4.00	-0.05
H(e)	3.99 (ABX type m)	3.66	-0.33	3.88	-0.11
H(f)	3.74 (ABX type m)	3.38	-0.36	3.58	-0.16
H(g)	3.590 (s)	3.50	-0.09	3.602	+0.01

[a] $\Delta\delta$ (ppm) = δ(host + guest) – δ(host). TMS as an external reference. Measured in DCl-D_2O (pD 1.2). [Host] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M.



A Possible Structure of Inclusion Cavity of Protonated TCP44. Although X-Ray crystallography is not yet available for either complexed or uncomplexed TCP44 (**2**), the structure of its inclusion cavity can be deduced by first considering that of protonated CP44 (**1**) and then the structural difference between **1** and **2**.

With regard to host (**1**), the X-Ray crystallography of **1**·4HCl-durene complex has revealed the following two characteristic aspects that are essential to the formation of an inclusion cavity for an aromatic guest.[3] (i) The four benzene rings of the diphenylmethane units are

perpendicular to the mean plane of the macroring, facing one another to adopt the "face" conformation. (ii) The two C_4 bridges adopt the transplanar conformation except for the *gauche* conformation about two of the C-N bonds. As a result, a hydrophobic cavity that has rectangularly shaped open ends (~3.5 × 7.9 Å) and a depth of 6.5 Å is formed, as schematically represented in Figure 3a. Into this cavity, the guest molecule durene is fully accommodated with its aromatic ring being in a close contact with the host molecule. Since similar cavity structures are also observed for the crystalline complexes of naphthalene and CP44·4HCl or CP55·4HCl,[17] the conformation with rectangularly shaped open ends seems to be a general conformation that this type of cyclophane adopts when forming an inclusion complex with an aromatic guest. A detailed NMR study on the complexation of host (**1**) and guest (**9**) in DCl-D_2O (pD 1.2) strongly indicates that protonated **1** also adopts such a complexing conformation in aqueous solutions.[8]

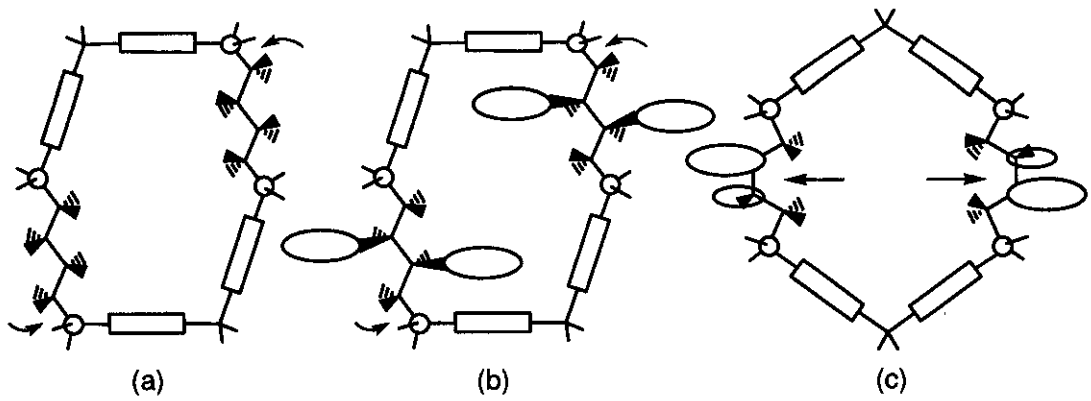


Figure 3. Possible Structures of the Inclusion Cavities of CP44·4H$^+$ and TCP44·4H$^+$
(a) C-N *gauche* conformation of CP44 (**1**)·4H$^+$ (crystal structure in the complexed state).[3,17] (b) C-N *gauche* conformation of TCP44 (**2**)·4H$^+$. (c) C-C *gauche* conformation of TCP44 (**2**)·4H$^+$. In each figure, rectangles, ellipses and circles indicate benzene rings, methoxy groups and ammonium nitrogens, respectively. Arrows exhibit the *gauche* bonds.

However, in the case of TCP44 (**2**·4H$^+$), such a rectangularly shaped conformation is unlikely as the complexing conformation because, if the cavity of **2**·4H$^+$ is drawn in a similar manner as that of **1**·4H$^+$, two of the methoxy groups must be directed inside the cavity to inhibit guest inclusion (Figure 3b). On the other hand, an alternative conformation with the C-C *gauche* geometry as shown in Figure 3c seems to be reasonable on the basis of the following reasons. First, in this conformation, all methoxy groups point away from the cavity and make a guest molecule able to be accommodated within the cavity. Second, the C-C *gauche* geometry enables the methoxy groups to point away from each other (pseudoaxial orientation relative to the macrocycle) to avoid steric congestion. The methoxy proton signal

of protonated **2** at a normal position (δ 3.59) supports the conformation shown in Figure 3c rather than 3b. In addition, the fact that the guest-induced shift of this signal is small (Table 2) suggests that the conformation in Figure 3c is the predominant one not only in the complexed state but also in the uncomplexed state.

This view is supported by preliminary PM3 calculations of the heat of formation for the two conformers; the C-C *gauche* conformer (Figure 3c) is calculated to be >10 kcal mol^{-1} favorable than the C-N *gauche* conformer (Figure 3b). This difference arises mainly from unfavorable steric interactions between the benzene rings and the adjacent methoxy substituents as well as between the vicinal methoxy substituents in **2**·$4H^+$. The open end of the resulting cavity of **2**·$4H^+$ has an extended hexagonal shape (Figure 3c) and is somewhat narrower at both sides as compared to the rectangularly shaped open ends of **1**·$4H^+$ (Figure 3a). With respect to the shorter width of the open end, the calculation indicates no substantial difference between **2**·$4H^+$ and **1**·$4H^+$.

Some ^1H NMR results of our previous and present studies indicate the "pseudoaxial" inclusion geometry for the complexes of protonated **2** and naphthalenic guests. Table 1 shows that, for naphthalenic guest (**9**), the host-induced shifts ($\Delta\delta_{H(1)}$, $\Delta\delta_{H(3)}$, $\Delta\delta_{H(4)}$) as well as their ratios ($\Delta\delta_{H(1)}/\Delta\delta_{H(3)}$, $\Delta\delta_{H(4)}/\Delta\delta_{H(3)}$) are similar for hosts (**1**) and (**2**). Since the values for host (**1**) have been shown to be consistent with the "pseudoaxial" inclusion,[8] the similar values for host (**2**) also indicate this inclusion geometry. Previously, the inclusion geometry of naphthalene (**8**) was investigated in DCl-D_2O (pD 1.2)/CD_3OD (50:50) with CP44 (**1**) and its higher homologues (CP55~CP88 with C_5~C_8 bridges). The $\Delta\delta_{H(\alpha)}/\Delta\delta_{H(\beta)}$ values decreased with increasing size of the cavity; actually, the $\Delta\delta_{H(\alpha)}/\Delta\delta_{H(\beta)}$ value decreased from 2.66 (CP44) to 1.07 (CP55), 0.68 (CP66), 0.64 (CP77) and 0.75 (CP88).[18] These observations can be most reasonably interpreted by a change in the predominant inclusion geometry of **8** from the "pseudoaxial" to the "equatorial" type. In fact, a change in the inclusion geometry from the "pseudoaxial" to the "equatorial" has been directly shown for the CP44·$4H^+$-**8** and CP55·$4H^+$-**8** complexes, respectively, by X-Ray crystallography.[17] The similar $\Delta\delta_{H(\alpha)}/\Delta\delta_{H(\beta)}$ values for hosts (**1**) and (**2**) observed in acidic aqueous solutions (2.66 and 2.40, respectively; Table 1) indicate that the inclusion geometry of the complex of protonated **2** and guest (**8**) is also "pseudoaxial" despite a difference in the structures of the inclusion cavities of **1** and **2**.

CONCLUSION

Novel water-soluble cyclophane TCP44 (**2**), having a well-defined chiral hydrophobic cavity, was synthesized by employing as the key step 1:1 cyclization *via* a U-shaped precursor. The formation of inclusion complexes by host (**2**) in acidic aqueous solutions was confirmed by fluorescence and ^1H NMR spectral studies. A complexation selectivity for aromatic guests ("aromatic selectivity"), as observed for the corresponding achiral host CP44 (**1**), was also exhibited by host (**2**). The solution structure of the inclusion cavity of protonated **2** was

deduced to be an extended hexagonal structure, which is different from the rectangular structure of the inclusion cavity of protonated **1**. It seems that, despite this difference, the inclusion geometry for naphthalenic guests is fundamentally the same for protonated **1** and **2** ("pseudoaxial" inclusion). Detailed ^{1}H NMR spectral studies for TCP44 (**2**) with *chiral* aromatic guests will be reported separately in conjunction with asymmetric recognition by the chiral hydrophobic cavity in aqueous solutions.

EXPERIMENTAL SECTION

General. All melting points are uncorrected. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Nuclear magnetic resonance (NMR) spectral measurements were carried out on a JEOL JNM-FX100 (^{1}H, 100 MHz) and JNM-GX200 (^{1}H, 270 MHz; ^{13}C, 67.5 MHz) Fourier transform NMR spectrometers. Chemical shifts are reported in δ values in ppm downfield from tetramethylsilane (TMS) as an internal/external reference or hexamethyldisiloxane (HMDS) as an external reference. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Conformer peaks (if any) are indicated by an asterisk. Infrared (IR) spectra were measured on a JASCO IRA-1 and DS-701G diffraction grating infrared spectrophotometers. Mass spectra (MS; EI and FAB modes) were taken with a JEOL JMS DX-303 mass spectrometer. *m*-Nitrobenzyl alcohol (MNBA) was used as a matrix in the FABMS measurements. Fluorescence measurements were conducted with a Hitachi MFP-4 fluorescence spectrophotometer. pH (pD) was measured with a Toyo digital pH/mV meter Model PT-3D and Orion Research Model SA 210 equipped with a glass electrode, using standard buffer solutions of pH 4.0 and 6.8.

4,4'-Bis(*p*-toluenesulfonamido)diphenylmethane (**3**)[19] was prepared according to the literature [colorless needles, mp 187-188 °C (EtOH); lit.,[19b] mp 186-187.5 °C (aq EtOH)]. Commercially available guests were purchased in their purest grades.

(*S*,*S*)-2,3-Dimethoxy-1,4-butanediol Dimethanesulfonate (4b). To a stirred, ice-cooled solution of (*S*,*S*)-(+)-2,3-dimethoxy-1,4-butanediol[20] (15.6 g, 0.104 mol; prepared according to ref 20c) in dry pyridine (45 mL) was added a solution of methanesulfonyl chloride (53.3 g, 0.466 mol) in dry pyridine (45 mL) over a period of 20 min. The mixture was stirred at 0 °C for 75 min, then poured onto crushed ice (*ca.* 300 g). After extraction with AcOEt (300 mL), the aqueous layer was saturated with NaCl, and further extracted with AcOEt (250 mL × 2). The combined organic extracts were successively washed with satd aq $CuSO_4$ (100 mL × 5) and satd aq NaCl (100 mL × 3), then dried over anhyd $MgSO_4$. Filtration and evaporation gave (*S*,*S*)-(-)-**4b** as a pale brown solid (29.2 g, 92%; mp 51.5-54 °C). An analytical sample was obtained by recrystallization from AcOEt-hexane as colorless needles: mp 53.8-54.5 °C; $[\alpha]_D^{25}$ -1.48 °, $[\alpha]_{365}^{25}$ -6.36° (*c* = 3.68, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.05 (6 H, s, $SO_2C\underline{H}_3$), 3.50 (6 H, s, $OC\underline{H}_3$), 3.64-3.70 (2 H, m, MeO-C<u>H</u>), 4.29 (2 H, dd, *J* = 10.7, 4.9 Hz, one of $C\underline{H}_2OMs$), 4.42 (2 H, dd, *J* = 10.7, 3.9 Hz, one of $C\underline{H}_2OMs$). ^{13}C

NMR (67.5 MHz, $CDCl_3$) δ 37.4/37.3* ($SO_2\underline{C}H_3$), 59.3 ($O\underline{C}H_3$), 68.9/67.5* ($\underline{C}H_2OMs$), 77.8 (MeO-$\underline{C}$H). IR (KBr) ν 2830, 1343, 1172 cm^{-1}. EIMS *m/z* (relative intensity) 306 (M^+, 11), 274 (5), 238 (6), 230 (2), 212 (9), 198 (17), 180 (36), 166 (12), 154 (96), 116 (36), 102 (100). *Anal.* Calcd for $C_8H_{18}O_8S_2$: C, 31.37; H, 5.92. Found: C, 31.40; H, 5.82.

The corresponding ditosylate [(*S,S*)-**4c**][20] was also prepared from (*S,S*)-(+)-2,3-dimethoxy-1,4-butanediol according to ref 20b.

(*R,R*)-1,4-Diiodo-2,3-dimethoxybutane (4a). To a stirred solution of (*S,S*)-(-)-**4b** (64.2 g, 0.210 mol) in methyl ethyl ketone (900 mL) was added anhyd NaI (90.0 g, 0.600 mol) in small portions at *ca.* 60 °C over a period of 5 min, and the mixture was stirred at reflux. After 3.5 h, a further amount of anhyd NaI (10.0 g, 0.067 mol) was added, and the stirring was continued at reflux for an additional 1 h. After cooled to rt, the reaction mixture was diluted with CH_2Cl_2 (600 mL), stirred for 30 min, filtered and then evaporated. The residue was dissolved in a mixture of Et_2O (600 mL) and H_2O (100 mL), and the organic layer was successively washed with 5% aq $Na_2S_2O_3$ and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and evaporation gave (*R,R*)-(-)-**4a** as a pale orange oil (76.0 g, 98%), which was sufficiently pure for use in the next step. An analytical sample was obtained by distillation on a Kugelrohr as a pale orange oil: $bp_{0.4\text{-}1.2}$ 125-150 °C (lit.,[20a] $bp_{0.045}$ 64-70 °C); $[\alpha]_D^{25}$ -7.48° (*c* = 3.75, $CHCl_3$) [lit.,[20a] $[\alpha]_D^{18}$ -7.90 ± 1.3° (*c* = 1.58, $CHCl_3$)]. ^1H NMR (270 MHz, $CDCl_3$) δ 3.32 (4 H, d, *J* = 5.4 Hz, $C\underline{H}_2I$), 3.50 (6 H, s, $OC\underline{H}_3$), 3.69 (2 H, t, *J* = 5.4 Hz, MeO-C$\underline{H}$) (consistent with the data reported in ref 20d). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 2.8 ($\underline{C}H_2I$), 59.0 ($O\underline{C}H_3$), 80.8 (MeO-$\underline{C}$H). IR (neat) ν 2820, 1186, 1110, 1082 cm^{-1}. FABMS *m/z* (relative intensity) 371 [$(M+1)^+$, 7], 339 (11), 311 (3), 289 (6), 259 (6), 243 (5), 228 (6), 185 (21), 167 (16), 107 (26), 91(40), 77 (48), 69 (60), 55 (100). *Anal.* Calcd for $C_6H_{12}O_2I_2$: C, 19.48; H, 3.27. Found: C, 19.26; H, 3.08. Positive by the Beilstein test.

(2*S*,2'*S*,3*R*,3'*R*)-4,4'-Bis[*N*-(4-iodo-2,3-dimethoxybutyl)-*N*-(*p*-toluenesulfonyl)-amino]diphenylmethane (5a). To a stirred solution of **3** (0.552 g, 1.09 mmol) and (*R,R*)-(-)-**4a** (2.19 g, 5.91 mmol) in dry DMF (25 mL) was added powdered anhyd K_2CO_3 (1.024 g, 7.41 mmol), and the mixture was stirred at 80 °C for 2.5 h. After cooled to rt, the reaction mixture was poured onto a mixture of satd aq NaCl (30 mL) and AcOEt (30 mL). After addition of water to dissolve insoluble inorganic materials, the organic layer was separated, and the aqueous layer was further extracted with AcOEt (50 mL × 2). The combined organic extracts were successively washed with 5% $Na_2S_2O_3$ (30 mL) and satd aq NaCl (30 mL × 2), then dried over anhyd $MgSO_4$. Filtration and evaporation gave a pale yellow viscous oil containing mainly **4a** and **5a**. This mixture was separated by column chromatography (silica gel) to give unreacted **4a** (1.281 g, 93% of theoretical recovery; elution with C_6H_6) and **5a** [972 mg, 90%; elution with C_6H_6-AcOEt (3:1)]. The U-shaped precursor [(2*S*,2'*S*,3*R*,3'*R*)-(+)-**5a**] was obtained as a colorless caramel: $[\alpha]_D^{22.5}$ +46.7° (*c* = 3.91, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 2.42 (6 H, s, Ar-$C\underline{H}_3$), 3.27 and 3.33 (each 6 H, two s, $OC\underline{H}_3$), 3.46-3.89 (12 H, m, $NC\underline{H}_2$, $C\underline{H}_2I$, MeO-C$\underline{H}$), 3.96 (2 H, s, $ArC\underline{H}_2Ar$), 7.02 and 7.11 [each 4 H, two d, *J* = 8.3 Hz,

NAr$\underline{H}_{meta}$ and NAr$\underline{H}_{ortho}$], 7.25 [4 H, d, J = 8.3 Hz, SAr$\underline{H}_{meta}$], 7.47 [4 H, d, J = 8.3 Hz, SAr$\underline{H}_{ortho}$]. ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 1.8 ($\underline{C}H_2I$), 21.0 (Ar-$\underline{C}H_3$), 40.3 (Ar$\underline{C}H_2$Ar), 49.0 (N$\underline{C}H_2$), 57.8, 58.6 (O$\underline{C}H_3$), 77.9, 79.6 (MeO-$\underline{C}$H), 127.2, 127.8, 128.1, 128.9, 134.2, 137.6, 139.9, 143.1 (aromatic $\underline{C}$). IR (KBr) ν 2830, 1597, 1503, 1348, 1161, 1087, 810 cm^{-1}. FABMS *m/z* (relative intensity) 990 (M^+, 34), 836 (27), 761 (24), 708 (21), 645 (10), 576 (12), 531 (7), 502 (15), 461 (20), 413 (25), 353 (29), 289 (32), 223 (62), 178 (41), 154 (base peak; MNBA). Positive by the Beilstein test. This sample was immediately used for the next step *without further purification.*

(*S*,*S*,*S*,*S*)-3,4,22,23-Tetramethoxy-1,6,20,25-tetrakis(*p*-toluenesulfonyl)-1,6,-20,25-tetraaza[6.1.6.1]paracyclophane (6). To a solution of **3** (241 mg, 0.475 mmol) *and* (2*S*,2'*S*,3*R*,3'*R*)-(+)-**5a** (463 mg, 0.468 mmol) in dry DMF (50 mL) was added powdered anhyd K_2CO_3 (0.65 g, 4.7 mmol), and the mixture was stirred successively at (i) 90 °C for 7 h, (ii) 105 °C for 1.5 h, and (iii) 120 °C for 8 h. After cooled to rt, the reaction mixture was poured onto a mixture of satd aq NaCl (50 mL) and AcOEt (70 mL). After addition of water to dissolve insoluble inorganic materials, the organic layer was separated, and the aqueous layer was further extracted with AcOEt (70 mL × 2). The combined organic extracts were washed with satd aq NaCl (30 mL × 3), then dried over anhyd $MgSO_4$. Filtration and evaporation gave crude **6** as a red viscous oil (663 mg). Purification by column chromatography [silica gel, C_6H_6-AcOEt (5:1)] afforded (*S*,*S*,*S*,*S*)-(-)-**6** (pure by TLC and NMR) as a colorless caramel (182 mg, 31%): $[\alpha]_D^{22.5}$ -59.9° (*c* = 2.22, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.38 (12 H, s, Ar$\underline{CH}_3$), 2.97 (12 H, s, O$\underline{CH}_3$), 3.98 (4 H, s, Ar$\underline{CH}_2$Ar), 3.31-3.51 (4 H, m, MeO-C$\underline{H}$), 3.66-3.81 (8 H, m, $\underline{CH}_2$), 6.77 and 7.00 [each 8 H, two d, J = 8.5 Hz, NAr$\underline{H}_{meta}$ and NAr$\underline{H}_{ortho}$], 7.27 [8 H, d, J = 8.5 Hz, SAr$\underline{H}_{meta}$], 7.47 (8 H, d, J = 8.5 Hz, SAr$\underline{H}_{ortho}$]. ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.4 (Ar-$\underline{C}H_3$), 40.6 (Ar$\underline{C}H_2$Ar), 47.9/49.0* (N$\underline{C}H_2$), 57.8/58.2* (O$\underline{C}H_3$), 82.8 (*MeO*-$\underline{C}$H), 127.7/127.1*, 128.6/128.5*, 129.4, 129.6/129.5*, 134.7/134.6*, 138.2, 140.5, 143.5 (aromatic $\underline{C}$). IR ($CHCl_3$) ν 2830, 1600, 1505, 1351, 1163, 1090, 812 cm^{-1}. FABMS *m/z* (relative intensity) 1240 (M^+, 1), 1239 (2), 1238 (3), 1237 (4), 1236 (6), 1235 (3), 1234 (2), 1233 (1), 1185 (3), 1085 (14), 997 (5), 930 (6), 899 (3), 884 (6), 841 (3), 776 (3), 706 (2), 519 (4), 154 (base peak; MNBA). This sample was immediately used for the next step without further *purification.*

(*S*,*S*,*S*,*S*)-3,4,22,23-Tetramethoxy-1,6,20,25-tetraaza[6.1.6.1]paracyclophane (TCP44; 2). A solution of (*S*,*S*,*S*,*S*)-(-)-**6** (1.92 g, 1.55 mmol) in 90% H_2SO_4 (20 mL) was stirred at rt for 18 h, then at 50 °C for 3 h. After cooled to rt, the reaction mixture was poured onto crushed ice (100 g), and the resulting aqueous solution was made alkaline (pH 11) by addition of 5*N* NaOH at 0 °C with stirring. After extraction with AcOEt (100 mL), the aqueous layer was saturated with NaCl, and then further extracted with AcOEt (100 mL × 2). The combined organic extracts were washed with satd aq NaCl (50 mL × 3), then dried over anhyd $MgSO_4$. Filtration and evaporation gave crude **2** as a pale-brown solid (0.93 g). Purification by column chromatography [silica gel, C_6H_6-AcOEt-CH_2Cl_2 (3:4:3)] afforded

(*S*,*S*,*S*,*S*)-(-)-**2** (pure by TLC and NMR) as a colorless solid (0.46 g, 69%): mp 175-178 °C. Recrystallization from toluene gave an analytical sample as slightly yellow needles: mp 175-178.5 °C; $[\alpha]_D^{22.5}$ -69.6° (*c* = 2.72, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$) δ 3.10-3.30 (8 H, dd type m, NCH_2), 3.50 (12 H, s, OCH_3), 3.60 (4 H, br s, MeO-CH), 3.75 (4 H, s, $ArCH_2Ar$), 4.01 (4 H, br s, NH), 6.46 (8 H, d, *J* = 8.3 Hz, $NArH_{ortho}$), 6.91 (8 H, d, *J* = 8.3 Hz, $NArH_{meta}$). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 39.9 ($ArCH_2Ar$), 43.2 (NCH_2), 58.4 (OCH_3), 81.0 (MeO-CH), 113.3, 129.5 (aromatic C_{ortho} and C_{meta}), 131.3 (aromatic C_{para}), 146.0 (aromatic C_{ipso}). IR (KBr) ν 3360, 1611, 1512, 1312, 1246, 1084, 805 cm^{-1}. FABMS *m/z* (relative intensity) 625 [$(M + 1)^+$, 32], 624 (M^+, 52), 581 (91), 537 (91), 518 (50), 455 (48), 417 (53), 392 (42), 369 (52), 342 (25), 327 (60), 287 (82), 268 (74), 250 (61), 240 (51), 203 (58), 192 (100), 176 (17), 154 (base peak; MNBA). *Anal.* Calcd for $C_{38}H_{48}N_4O_4$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.09; H, 7.77; N, 8.72. An analytical sample of (*S*,*S*,*S*,*S*)-(-)-**2** was used in the following complexation studies.

Measurement of Fluorescence Spectra. Purification of 1,8-ANS (**7**) and determination of K_s (by the Benesi and Hildebrand plot[10,11]) were carried out in a similar manner as those described in our previous paper.[3b]

Measurement of ^1H NMR Spectra. In general, an appropriate amount of guest was dissolved in a DCl-D_2O solution (pD 1.2) of TCP44 (**2**). For a guest with poor solubility in water, a CD_3OD solution of the guest was mixed with the DCl-D_2O solution of the host. pD was adjusted according to Glasoe and Long[21] on the basis of the equation: pD = pH meter reading + 0.40. ^1H NMR spectra were measured at 100 MHz (spectral width, 1000 Hz; data point, 8 K; TMS as an external reference; 28 ± 2 °C) for guests (**8**)~(**10**) and at 270 MHz (spectral width, 4000 Hz; data point, 8 K; HMDS as an external reference; 27 ± 1 °C) for guests (**11**)~(**13**). In the present work, the chemical shift of external HMDS was set at 1.10 ppm [DCl-D_2O (pD 1.2)] downfield of TMS as an external reference.

PM3 Calculations. The PM3 calculations of tetraprotonated host conformers were made using the MOPAC-PM3 program (ver. 6.0)[22] contained in the CAChe scientific software (SONY Techtronics) on Power Macintosh 8100/80AV. Since bond angles and bond lengths from the X-Ray crystallographic data of the inclusion complex of CP44·4HCl and durene[3] are not significantly deviated from ordinary values, calculations were done without any specific assumptions. The local minima in the heat of formation of two tetraprotonated TCP44 conformers (Figures 3b and 3c) are 781 and 766 kcal mol^{-1}, respectively.[23]

ACKNOWLEDGMENT

This work was partly supported by the Grants for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan to I. T. (Grant No. 93-06857168). The support from the Sumitomo Foundation (Osaka, Japan) to I. T. is also acknowledged.

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23. The details will be published elsewhere.

Received, 6th June, 1997