STUDIES ON WATER-SOLUBLE ARTIFICIAL RECEPTORS CONTAINING CHIRAL SIDE CHAINS DERIVED FROM CARBOHYDRATES. 2.[1] FORMATION OF DIASTEREOMERIC INCLUSION COMPLEXES BETWEEN OPTICALLY ACTIVE CYCLOPHANE TCP44 AND CHIRAL AROMATIC GUESTS IN ACIDIC AQUEOUS SOLUTIONS[2]

Ichiro Takahashi,*,[a] Yuuko Aoyagi,[a] Itsumi Nakamura,[a] Akinao Kitagawa,[a] Kazutsugu Matsumoto,[a] Hidehiko Kitajima,[a] Kimio Isa,[b] Kazunori Odashima,*,[c] and Kenji Koga*,[c,d]

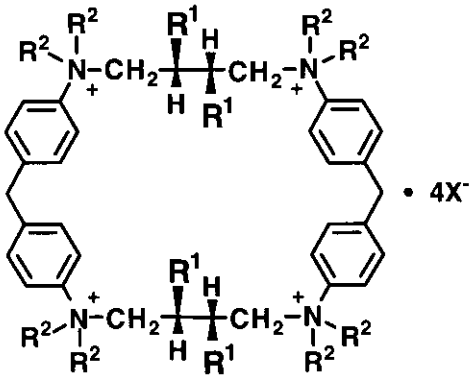
[a] Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Fukui University, Bunkyo, Fukui-Shi 910-8507, Japan [b] Department of Science Education, Faculty of Education, Fukui University, Bunkyo, Fukui-Shi 910-8507, Japan [c] Graduate School of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-Ku, Tokyo 113-0033, Japan [d] Present address: Research and Education Center for Materials Science, Nara Institute of Science and Technology (NAIST), Takayama-Cho, Ikoma-Shi, Nara 630-0101, Japan

Abstract – Systematic ^{1}H NMR investigations on the formation of diastereomeric complexes of optically active cyclophane host TCP44 and chiral aromatic guests in acidic aqueous or mixed aqueous/ methanolic solutions are described. Inclusion of chiral aromatic guests into the cavity led to enantiomeric splitting of the guest proton signals, particularly those of the protons near the chiral center. The chiral recognition was quantitatively evaluated for 1-hydroxy-arylacetic acids and 1-arylethanols on the basis of the stability constants and complexation shifts of 1:1 complexes, determined by ^{1}H NMR titration experiments. A possible mode of chiral recognition is discussed.

INTRODUCTION

Water-soluble paracyclophane TCP44 (**1**) was reported as the first totally synthetic, optically active host with a chiral hydrophobic cavity for inclusion of organic guests in aqueous solutions.[2] The chiral hydrophobic cavity is constructed with two diphenylmethane units bridged *via* four nitrogens by two chiral C_4 units derived from L-tartaric acid. The formation of

diastereomeric inclusion complexes[2] as well as asymmetric hydride reduction of arylglyoxylic acids to the corresponding 1-hydroxy acids[3] was investigated using this host. The details of the complexation properties of this host were examined by fluorescence and ^{1}H NMR spectroscopic methods, using *achiral* hydrophobic guests for initial investigations.[1] A selectivity for aromatic guests ("aromatic selectivity") was clearly observed for host (**1**) in acidic aqueous solutions, as in the case of the corresponding achiral tetraamine host CP44 (**2a**)[4a] and quaternary ammonium host QCP44 (**2b**).[4b] On the basis of the guest-induced changes in the ^{1}H NMR chemical shifts of host (**1**) in acidic aqueous solutions as well as PM3 calculations of representative conformers of tetraprotonated **1**, the inclusion cavity of protonated **1** was deduced to have an extended hexagonal structure, which is different from the rectangular structure of the inclusion cavity of protonated **2a**.[5] Despite this difference, the inclusion geometry for naphthalene guests seems to be fundamentally the same for protonated **1** and **2a** ("pseudoaxial" inclusion).[1] In this paper, we wish to report detailed ^{1}H NMR studies on the complexation of TCP44 (**1**) and a variety of *chiral* hydrophobic guests in acidic aqueous or mixed aqueous/methanolic solutions, leading to the formation of diastereomeric inclusion complexes. A possible mode of chiral recognition will be discussed.



1 (TCP44)·4HX: $R^1 = OCH_3$, $R^2 = H$
2a (CP44)·4HX: $R^1 = R^2 = H$
2b (QCP44): $R^1 = H$, $R^2 = CH_3$

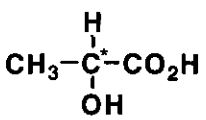
RESULTS AND DISCUSSION

In the case of cyclophane hosts, ^{1}H NMR is a most useful spectroscopic tool because, upon complexation, large upfield shifts are induced on the guest proton signals due to a strong ring current effect of the aromatic ring(s) of the host.[5,6] In many cases, time-averaged signals reflecting the weighed average of the signals of complexed and uncomplexed guest appear 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 case of complexation between *optically active* cyclophanes and *chiral* guests, the formation of diastereomeric host-guest complexes can, in principle, be manifested as *enantiomeric splitting* of the guest signals, which is due to the difference in the stability and/or the predominant geometry of the diastereomeric complexes formed.[7] Following the first report on TCP44 (**1**),[2] such examples have been reported for several types of cyclophane hosts in aqueous or mixed aqueous/organic solutions.[8,9] In the present study, complexation between

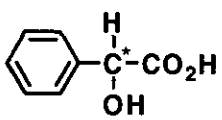
TCP44 (**1**) and chiral hydrophobic guests was examined in detail by ^{1}H NMR in DCl-D_2O (pD 1.2) or DCl-D_2O/CD_3OD. The latter condition was used whenever the solubility of guest alone in acidic water was poor. The ^{1}H NMR measurements were carried out first at fixed concentrations for host and guest to observe enantiomeric splitting of guest signals, and then at varying concentrations to determine the stability constants and complexation shifts for each diastereomeric complex. The host-induced changes in the chemical shifts of guest proton signals, represented as $\Delta\delta$ (ppm) [= δ(host + guest) – δ(guest)], were used as an indication of the formation of inclusion complexes.

1. Qualitative Analysis of Chiral Recognition by ^{1}H NMR Experiments under Fixed Concentrations

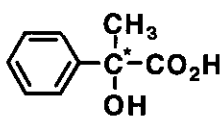
The shifts of the ^{1}H NMR signals of chiral aliphatic guest (**3**) in the presence of host (**1**) in an acidic aqueous solution were negligible ($\Delta\delta$ ~ -0.04 ppm), as in the case of achiral aliphatic guests such as propargyl alcohol, itaconic acid and 1-hexanol.[1] Therefore, chiral *aromatic* guests with hydrophilic group(s) (**4**~**19**) were examined. For each guest, the predominant



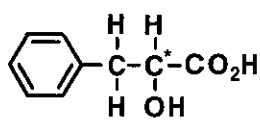
3 (lactic acid)



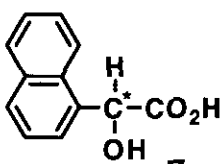
4 (mandelic acid)



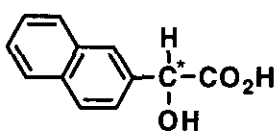
5 (atrolactic acid)



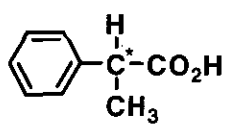
6



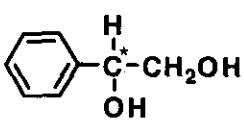
7



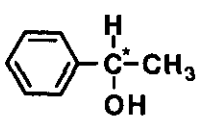
8



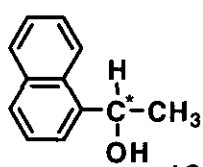
9



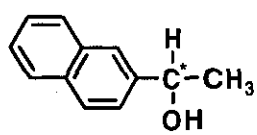
10



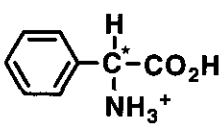
11



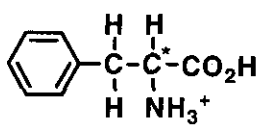
12



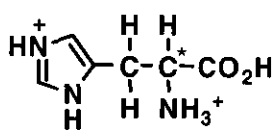
13



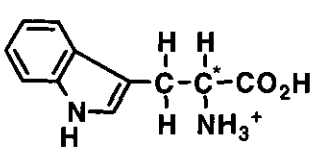
14 (phenylglycine)



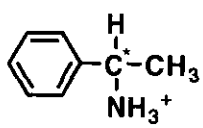
15 (phenylalanine)



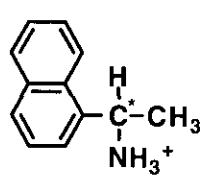
16 (histidine)



17 (tryptophan)



18



19

Table 1. Host-Induced Changes in the Chemical Shifts [Δδ (ppm)] for Aromatic Proton Signals of Chiral Guests Having a Benzene or Small Aromatic Ring[a]

guest	$\Delta\delta(ArH_{ortho})$	$\Delta\delta(ArH_{meta})$	$\Delta\delta(ArH_{para})$	condition[b]
(*R*)-**4** (mandelic acid)		(*ca.* -1.1)[c]	-0.7	A1
(*R*)-**4** (mandelic acid)		(*ca.* -1.3)[c]	-0.7	A2
(*S*)-**5** (atrolactic acid)		(< -0.8)[c,d]	< -0.5[d]	A1
(*R*)-**6**		(*ca.* -1.0)[c]	-0.7	A1
(*S*)-**9**	-1.35	-1.114	-0.696	A1
(*R*)-**10**		(< -0.4)[c,d]		A1
(*RS*)-**11**		(< -0.5)[c,d]		A1
(*R*)-**14** (phenylglycine)		(-0.09)[c]		A1
(*R*)-**15** (phenylalanine)		(-0.12)[c]		A1
(*R*)-**16** (histidine)	~ 0 (H-5)		~ 0 (H-2)	A1
(*R*)-**18**		(-0.07)[c]		A1

[a] Δδ (ppm) = δ(host + guest) − δ(guest). Negative values indicate upfield shifts. The measurements with chiral guests were made using either a single enantiomer or a racemate, as noted for each guest. [b] Condition A1: [host] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M in DCl-D_2O (pD 1.2). Condition A2: [host] = 6.0×10^{-2} M, [guest] = 1.0×10^{-2} M in DCl-D_2O (pD 1.2). [c] The signals of ArH_{ortho} and ArH_{meta} (**4**~**6**) or ArH_{ortho}, ArH_{meta} and ArH_{para} (**10**, **11**, **14**, **15**, **18**) overlapped. [d] Described as minimum upfield shift.

forms in an acidic solution are shown. The δ and/or Δδ values for aromatic and aliphatic protons of chiral aromatic guests are listed in Tables 1~3. The δ and Δδ values for all assignable signals, including those that are not listed in the tables, are described in the *Experimental Section*. The following tendencies were observed as to the complexation properties of protonated TCP44 (**1**·nH^+) in acidic aqueous or mixed aqueous/methanolic solutions.

(i) The formation of stable inclusion complexes was observed for all of the noncationic aromatic guests examined (**4**~**13**), as indicated by the large upfield shifts induced by the host on the aromatic proton signals of these guests (Tables 1 and 2). Under the experimental conditions, host-induced upfield shifts of larger than 0.4 ppm were observed for the guests having a benzene ring (**4**~**6**, **9**~**11**; Table 1). In the case of the guests having a naphthalene ring (**7**, **8**, **12**, **13**), only the δ values for each guest in the presence and absence of the host are listed (Table 2) because accurate Δδ values could not be determined due to overlap of the signals. However, it is still clearly indicated from Table 2 that the host-induced upfield shifts for these guests are even larger than those for the guests having a benzene ring. In the case of the naphthalene guests, their poor solubility in water forced the measurements to be

Table 2. Chemical Shifts [δ (ppm)] of Aromatic Proton Signals of Chiral Guests Having a Naphthalene or Large Aromatic Ring[a]

	δ(guest)	δ(host + guest)	condition[b]
(*RS*)-**7**	7.9~8.1 (4H, br m, H-2, 3, 6, 7) 8.3~8.5 (2H, br m, H-4, 5) 8.5~8.7 (1H, br m, H-8)	7.1~7.4 (br m) + 7.57 (br s) + 7.62 (br s) (*ca.* 5H in total)	B1
(*RS*)-**8**	7.9~8.1 (3H, m, H-3, 6, 7) 8.3~8.5 (4H, m, H-1, 4, 5, 8)	6.6 (1H, br), 6.8~7.2 (2H, br) 7.2~7.5 (4H, two br)	B1
(*RS*)-**12**	7.9~8.1 (4H, *m*, H-2, 3, 6, 7) 8.2~8.4 (2H, m, H-4, 5) 8.5~8.7 (1H, m, H-8)	7.1~7.6 (5~6H, *m*)	B1
(*RS*)-**13**	7.9~8.1 (3H, m, H-3, 6, 7) 8.2~8.4 (4H, m, H-1, 4, 5, 8)	6.8~7.6 (*ca.* 7H, m)	B1
(*R*)-**17** (tryptophan)	7.5~7.8 (2H, m, H-4, 7) 7.758 (1H, s, H-2) 7.8~8.2 (2H, m, H-5, 6)	7.1~7.4 (3H, br m) + 7.56 (1H, br d) (ArH-4~7) 7.666 (1H, s, H-2, Δδ = -0.092)	A1
(*R*)-**19**	7.9~8.2 (4H, m, H-2, 3, 6, 7) 8.3~8.6 (3H, m, H-4, 5, 8)	7.5~7.7 (1~2H, m)[c]	A1

[a] Δδ (ppm) = δ(host + guest) − δ(guest). Negative values indicate upfield shifts. The measurements with chiral guests were made using either a single enantiomer or a racemate, as noted for each guest. [b] Condition A1: [host] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M in DCl-D_2O (pD 1.2). Condition B1: [host] = 1.0×10^{-2} M, [guest] = 0.50×10^{-2} M in DCl-D_2O (pD 1.2)/CD_3OD (9:1 v/v). [c] Major part of the ArH signals of the guest (corresponding to 5~6H) overlapped with the aromatic proton signals of the host.

carried out at low concentrations of host and guest in a solvent system containing 10% v/v CD_3OD. Considering that these conditions are unfavorable for complexation by hydrophobic interactions, the larger upfield shifts observed for the naphthalene guests compared to those for the benzene guests indicate a remarkable hydrophobic effect of a naphthalene ring.

(ii) In addition to the large upfield shifts of aromatic proton signals, a number of cases were found where the signals of (*R*)- and (*S*)-guests shifted to a different degree. Such an enantiomeric splitting was observed particularly for the signals of aliphatic protons near the chiral centers of the aromatic guests (Table 3). In some cases, not only the degree of upfield shift but also the pattern of the aromatic proton signals was different for the (*R*)- and (*S*)-enantiomers of guests [*e.g.*, guests (**4**) and (**5**) in Figures 1 and 2, respectively]. These observations suggest the formation of diastereomeric host-guest complexes that have different predominant structures. Such differences in the spectrum pattern were also found for guests (**6**), (**8**), (**9**) and (**10**). Assignments of the signals of (*R*)- and (*S*)-enantiomers were made on the basis of unequal integration of the enantiomeric signals of the samples that are *partially optically active*, as shown for example in Figure 3.

Table 3. Host-Induced Changes in the Chemical Shifts [Δδ (ppm)] for Aliphatic Proton Signals of (*R*)- and (*S*)-Enantiomers of Chiral Guests[a]

guest	proton	Δδ(*R*) (ppm)	Δδ(*S*) (ppm)	condition[b]	Δδ(*S*)/Δδ(*R*)
(*R*)- or (*S*)-**4**	C<u>H</u>COOH (s)	-0.509	-0.559	A1	1.10 (*S*)[c]
(*RS*)-**5**	C<u>H</u>$_3$CCOOH (s)	-0.339	-0.382	A1	1.13 (*S*)
(*R*)- or (*S*)-**6**	CH$_2$C<u>H</u>COOH (dd)	-0.340	-0.352	A1	1.04 (*S*)
	C<u>H</u>$_2$CHCOOH (1) (dd)	-0.438	-0.467		1.07 (*S*)
	C<u>H</u>$_2$CHCOOH (2) (dd)	-0.441	-0.437		~1
(*RS*)-**7**	C<u>H</u>COOH (s)	-0.324	-0.404	B1	1.25 (*S*)
(*RS*)-**8**	C<u>H</u>COOH (s)	-0.336	-0.402	B1	1.20 (*S*)
(*RS*)-**9**[d]	C<u>H</u>$_3$CHCOOH (d)	-0.401	-0.435	A1	1.08 (*S*)
(*R*)- or (*S*)-**10**	CH$_2$C<u>H</u>OH (t)	-0.241	-0.264	A1	1.10 (*S*)
	C<u>H</u>$_2$CHOH (d)	-0.204	-0.220		1.08 (*S*)
(*RS*)-**12**	CH$_3$C<u>H</u>OH (q)[e]	-0.352	-0.291	B1	0.83 (*R*)
	C<u>H</u>$_3$CHOH (d)[e]	-0.148	-0.104		0.70 (*R*)
(*R*)- or (*S*)-**17**[d]	C<u>H</u>COOH (t)	-0.11	-0.09	A1	0.8 (*R*)
(*R*)- or (*S*)-**19**	CH$_3$C<u>H</u>NH$_3^+$ (q)[e]	-0.200	-0.139	A1	0.70 (*R*)
	C<u>H</u>$_3$CHNH$_3^+$ (d)[e]	-0.080	-0.052		0.65 (*R*)

[a] Δδ (ppm) = δ(host + guest) − δ(guest). Negative values indicate upfield shifts. The measurements with chiral guests were made using either single enantiomers or a racemate, as noted for each guest. [b] Condition A1: [host] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M in DCl-D_2O (pD 1.2). Condition B1: [host] = 1.0×10^{-2} M, [guest] = 0.50×10^{-2} M in DCl-D_2O (pD 1.2)/CD_3OD (9:1 v/v). [c] The enantiomer with a larger upfield shift (more negative Δδ value) is shown in the parenthesis. [d] The Δδ value for the signal of C<u>H</u>COOH (**9**) or C<u>H</u>$_2$CHCOOH (**17**) could not be obtained due to overlap with the signals of the host. [e] The corresponding signals of guest (**11**) or (**18**) did not show enantiomeric splitting under the same conditions.

(iii) The host-induced changes in the chemical shifts of the aliphatic protons at or adjacent to the chiral centers are listed in Table 3. With regard to the carboxylic acid guests (**4**~**9**), enantiomeric signal splitting was observed for all of the protons attached at the α or β position with respect to the aromatic ring. For all of the 1-hydroxy acids (**4**~**8**) and related guests (**9**, **10**), the (*S*)-enantiomers showed larger upfield shifts than the corresponding (*R*)-enantiomers [Δδ(*S*)/Δδ(*R*) = ~1.25].

(iv) Naphthalene guests generally showed greater differences in the Δδ(*S*) and Δδ(*R*) values than the corresponding benzene derivatives (**7**, **8** vs **4**; **12** vs **11**; **19** vs **18**). This may reflect better steric fit of a naphthalene ring, compared with a benzene ring, to the hydrophobic cavity of protonated TCP44 (**1**), as observed for the corresponding achiral host CP44 (**2a**).[4a]

(v) The formation of inclusion complexes with chiral cationic guests having a benzene or small aromatic ring was very weak, as indicated by very small or negligible $\Delta\delta$ values [$\Delta\delta$ ~ -0.1 ppm for **14**, **15**, and **18**; $\Delta\delta$ ~ 0 for **16** (dicationic)]. Enantiomeric splitting of the guest proton signals was also negligible. Weak complexation due to unfavorable electrostatic interactions between the cationic guests and the host that is positively charged by multiple protonation was also observed for the corresponding achiral host CP44 (**2a**).[4a] However, it should be pointed out that moderate upfield shifts ($\Delta\delta$ ~ -0.2 ppm) were observed for guests (**17**) and (**19**), indicating the formation of moderately stable inclusion complexes with the guests having large aromatic rings for effective hydrophobic interactions. The enantiomeric splitting of the signals of **19** was largest among the chiral guests examined in this study.

As described earlier, enantiomeric signal splitting induced by TCP44 (**1**) in acidic aqueous or mixed aqueous/methanolic solutions indicate the formation of diastereomeric host-guest inclusion complexes that have different predominant structures and/or stabilities. Such enantiomeric signal splitting has also been observed for some other types of cyclophane hosts in aqueous or mixed aqueous/organic solutions.[8] In order to estimate the contribution of the geometrical and stability factors, it is necessary to carry out a quantitative analysis by ^{1}H NMR titration experiments.

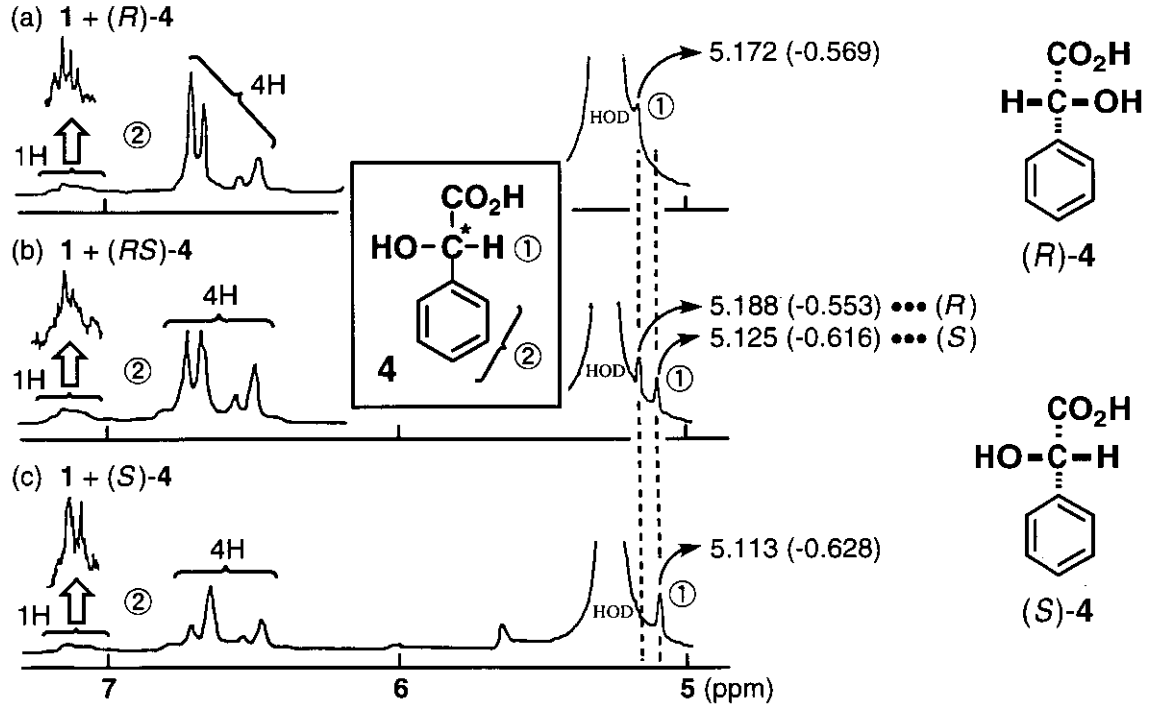


Figure 1. ^{1}H NMR signals of mandelic acid (**4**) in the presence of TCP44 (**1**) in DCl-D_2O (pD 1.2) (condition A2), showing the formation of diastereomeric complexes. TMS as an external reference. Chemical shifts (δ) are shown with the $\Delta\delta$ values in parentheses.

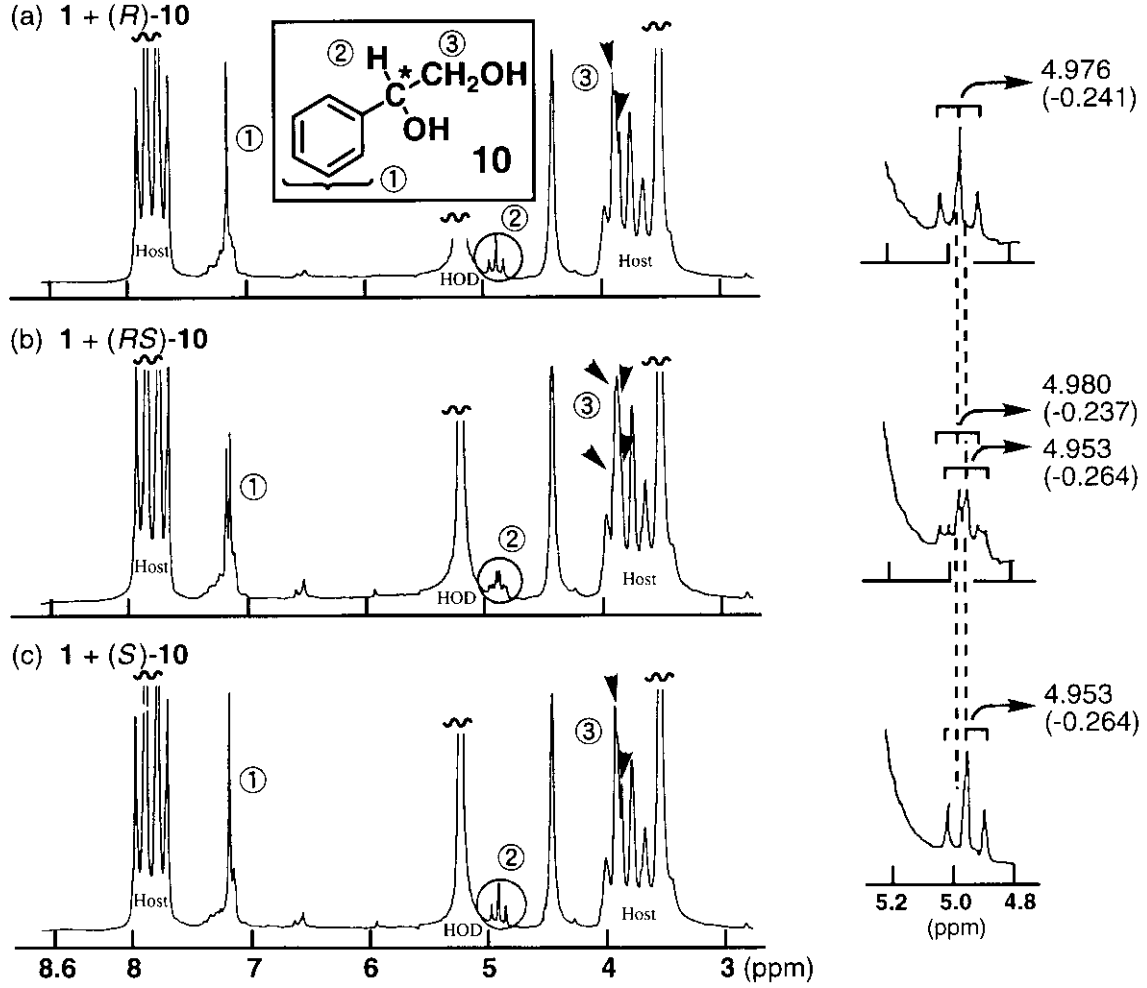


Figure 2. ^{1}H NMR signals of phenylethane-1,2-diol (**10**) in the presence of TCP44 (**1**) in DCl-D_2O (pD 1.2) (condition A1), showing the formation of diastereomeric complexes. TMS as an external reference. Chemical shifts (δ) are shown with the Δδ values in parentheses.

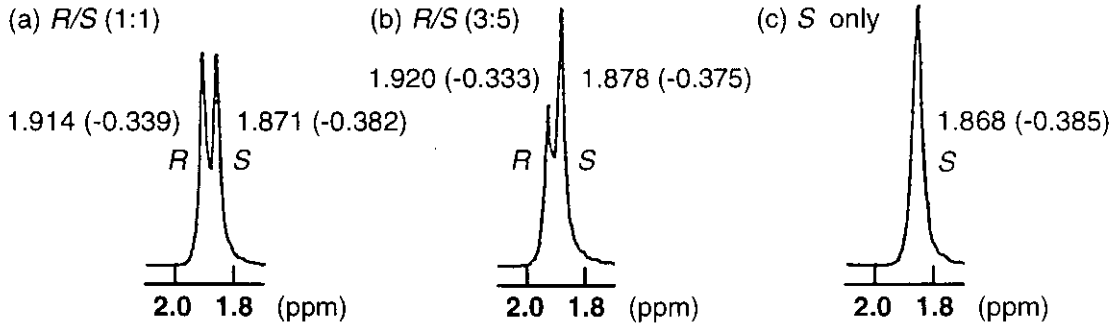


Figure 3. ^{1}H NMR signals of the methyl group of atrolactic acid (**5**) of various *R/S* ratio in the presence of TCP44 (**1**) in DCl-D_2O (pD 1.2) (condition A1), showing the formation of diastereomeric complexes. TMS as an external reference. Chemical shifts (δ) are shown with the Δδ values in parentheses.

2. Quantitative Analysis of Chiral Recognition by ^{1}H NMR Titration Experiments

Quantitative investigations to determine the parameters concerning host-guest complexation were carried out for the complexes of TCP44 (**1**) and chiral 1-hydroxy-arylacetic acids (**4**, **7**, **8**; mandelic acid type) or 1-arylethanols (**11**~**13**; 1-phenethyl alcohol type). Complexation shift ($\Delta\delta_{comp}$; maximum change of δ value in the presence of the host), stability constant (K_S), and complexation energy ($\Delta G°$) were determined by ^{1}H NMR titration experiments (Table 4). A mixed solvent system, DCl-D_2O (pD 1.0)/CD_3OD (9:1 v/v), was used because all of the guests were soluble in this medium. In all combinations of host and guest, the $\Delta\delta$ data obtained were consistent with the formation of 1:1 complexes. The following tendencies were observed as to the complexation selectivities of protonated TCP44 (**1**·nH$^+$) for enantiomeric guests in acidic aqueous/methanolic solutions.

(i) The results in Table 4 show that TCP44 (**1**) forms stronger complexes with the guests having a naphthalene ring (**7**, **8**, **12**, **13**) than those having a benzene ring (**4**, **11**) in an acidic D_2O-CD_3OD medium. These observations are reasonable because stronger hydrophobic interactions are expected for the former guests, as observed for protonated **2a**.[4,10] Moreover, an α/β-selectivity, manifested as stronger complexation of the β-substituted naphthalenes compared to the corresponding α-substituted ones (**8** vs **7**; **13** vs **12**), was observed. As discussed in our previous paper,[1] protonated **1** prefers the "pseudoaxial" inclusion geometry for naphthalene guests, similarly as the corresponding achiral host (**2a**·nH$^+$).[5] It is reasonable to consider that the preference of this geometry leads to stronger complexation of the β-substituted naphthalene guests than the corresponding α-substituted ones by steric reasons (Figure 4).[4]

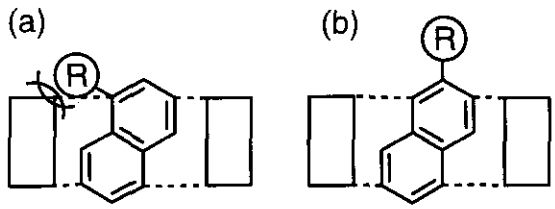


Figure 4. Plausible inclusion geometries for α- and β-substituted naphthalene guests in the cavity of protonated **1**, assuming the "pseudoaxial" inclusion of the naphthalene ring.

(ii) Complexation with 1-hydroxy-arylacetic acids was stronger than the corresponding 1-arylethanols (**4** vs **11**; **8** vs **13**). This indicates some contribution of electrostatic interactions of the carboxylic acid guests with protonated **1** *via* the COOH group of the former.

(iii) Appreciable enantiomeric discrimination in the stability of complex was observed for the guests having a naphthalene ring, as indicated by the K_S ($\Delta G°$) values in Table 4. The (*S*)-enantiomers of 1-hydroxy-naphthylacetic acids (**7**, **8**) and the (*R*)-enantiomers of 1-naphthylethanols (**12**, **13**) were found to be more favorable for complexation by protonated **1**. These results are parallel to the host-induced upfield shifts in the sense that larger $\Delta\delta$ values were observed for the preferred enantiomers of guests, as seen in both fixed

Table 4. Complexation Parameters Obtained by ^{1}H NMR Titration Experiments[a]

guest	proton	$\Delta\delta_{comp}$ (ppm)		K_s (M^{-1})		$\Delta G°$ (kcal mol^{-1})		configuration of preferred enantiomer
		(*R*)	(*S*)	(*R*)	(*S*)	(*R*)	(*S*)	
4	C<u>H</u>COOH	-0.807	-0.895	34.5	35.7	-2.11	-2.13	*S*
		(1.11)[c]		(1.03)[d]	[1.01][e]	(-0.02)[f]		
	C<u>H</u>COOH[b]	-0.833	-0.827	45.2	63.0	-2.27	-2.47	*S*
		(0.99)		(1.39)	[1.11]	(-0.20)		
7	C<u>H</u>COOH	-0.652	-0.736	112	137	-2.81	-2.93	*S*
		(1.13)		(1.22)	[1.09]	(-0.12)		
8	C<u>H</u>COOH	-0.408	-0.477	404	449	-3.58	-3.64	*S*
		(1.17)		(1.11)	[1.03]	(-0.06)		
11	$CH_3C\underline{H}OH$	-0.691[g]		18.0		-1.72		
	$CH_3C\underline{H}OH$[b]	-0.579[g]		27.8		-1.98		
	$C\underline{H}_3CHOH$	-0.440[g]						
	$C\underline{H}_3CHOH$[b]	-0.363[g]						
12	$CH_3C\underline{H}OH$	-0.734	-0.719	90.5	70.5	-2.69	-2.54	*R*
		(0.98)		(0.78)	[0.88]	(+0.15)		
	$C\underline{H}_3CHOH$	-0.324	-0.274					
		(0.85)						
13[h]	$C\underline{H}_3CHOH$	-0.181	-0.169	134	123	-2.92	-2.87	*R*
		(0.93)		(0.92)	[0.96]	(+0.05)		

[a] ^{1}H NMR measurements were carried out at 300 K in DCl-D_2O (pD 1.0)/CD_3OD (9:1 v/v) unless noted otherwise. HMDS as an external reference. [b] The results obtained in DCl-D_2O (pD 1.2). [c] $\Delta\delta_{comp}(S)/\Delta\delta_{comp}(R)$. [d] $K_s(S)/K_s(R)$. [e] $F(S)/F(R)$; $F = c_{HG}/C_G$; c_{HG} = concentration of complexed guest, C_G = total concentration of complexed and uncomplexed guest. Calculated from the $K_s(S)$ and $K_s(R)$ values by applying the concentrations of [host] = 5.0×10^{-2} M and [guest] = 2.5×10^{-2} M for guest (**4**) and [host] = 1.0×10^{-2} M and [guest] = 5.0×10^{-3} M for all other guests. [f] $\Delta G°(S) - \Delta G°(R)$ (kcal mol^{-1}). [g] No enantiomeric signal splitting. [h] The C<u>H</u>COOH signal was not observable due to overlap with the HOD signal.

concentration and titration experiments ($\Delta\delta$ values in Table 3 and $\Delta\delta_{comp}$ values in Table 4). On the other hand, enantiomeric discrimination in terms of K_s was not observed for benzene derivatives (**4**, **11**) in the acidic D_2O-CD_3OD medium, though moderate discrimination was observed for **4** in the acidic D_2O medium.

(iv) In the acidic D_2O/CD_3OD medium, the greatest enantiomeric discrimination in the stability of complex was observed for guest (**12**) with a free energy difference of 0.15 kcal mol^{-1} (Table 4). Somewhat greater difference of 0.20 kcal mol^{-1} was observed for guest (**4**)

in the acidic D_2O medium. Interestingly, a greater enantiomeric discrimination [$|\Delta G°(S) - \Delta G°(R)|$] was observed for more weakly complexing α-substituted naphthalenes (**7**, **12**) than for the corresponding β-substituted ones (**8**, **13**). The enantiomeric differences in complexation energy for host (**1**) are comparable to the most of such values reported for other types of cyclophanes in aqueous or mixed aqueous/organic solutions.[8a-d]

(v) Since the enantiomeric differences in the stability of complex is only as high as 1.4-fold [$K_s(S)/K_s(R)$ = 0.78~1.39], the differences in the complexation percentage for (*R*)- and (*S*)-enantiomers, calculated at the concentrations of host and guest in fixed concentration experiments (Table 3), are small [$F(S)/F(R)$ = 0.94~1.11]. By comparing the $F(S)/F(R)$ and $\Delta\delta_{comp}(S)/\Delta\delta_{comp}(R)$ values in Table 4, the enantiomeric splitting shown in Table 3 can be mainly attributed to the enantiomeric difference in complexation shift ($\Delta\delta_{comp}$) in the case of guests (**4**) (in D_2O-CD_3OD medium) and (**8**), and that in the stability of complex (K_s) in the case of guest (**4**) (in D_2O medium). For other guests, both of these parameters are involved in the enantiomeric splitting.

The quantitative analysis of enantiomer recognition by TCP44 (**1**) in acidic media shows that not only the stability factor (K_s) but also the geometrical factor ($\Delta\delta_{comp}$) contribute to the enantiomeric splitting of guest proton signals. A possible mode of chiral recognition will be discussed in the following section.

3. A Possible Mode of Chiral Recognition by TCP44 in Acidic Aqueous Medium

In our preceding paper,[1] the predominant complexing conformer of tetraprotonated TCP44 (**1**·$4H^+$) was deduced, on the basis of the ^1H NMR results and PM3 calculations, as the C-C *gauche* type conformer (Figure 5a, left; hexagonal cavity) rather than the C-N *gauche* type one (Figure 5a, right; rectangular cavity). Assuming the hexagonal cavity structure as depicted in Figure 5a (right), the axially oriented methoxy groups would make three open spaces, L (large), M (medium) and S (small), into which the three substituents attached to the chiral center of the complexed aromatic guest can be accommodated according to their bulkiness (Figure 5b). A similar model was proposed for chiral discrimination of protonated 1-phenethylamine guests by chiral crown ethers.[11]

On the basis of this model, the stronger complexation with the (*S*)-enantiomers of 1-hydroxy-naphthylacetic acids (**7**, **8**) may be interpreted as follows: Upon the formation of a host-guest complex with inclusion of the naphthalene ring of the guest, the three substituents attached to the chiral center, *i.e.*, COOH, OH, and H, will be accommodated into the three open spaces. Considering the size of these groups, a more stable complex will be formed for the (*S*)-enantiomer that allows the COOH, OH, and H substituents occupy the spaces L, M, and S, respectively. This geometry is also favorable in the sense that the COOH and OH groups are directed to the cationic centers (protonated nitrogens) of the host for hydrogen bonding

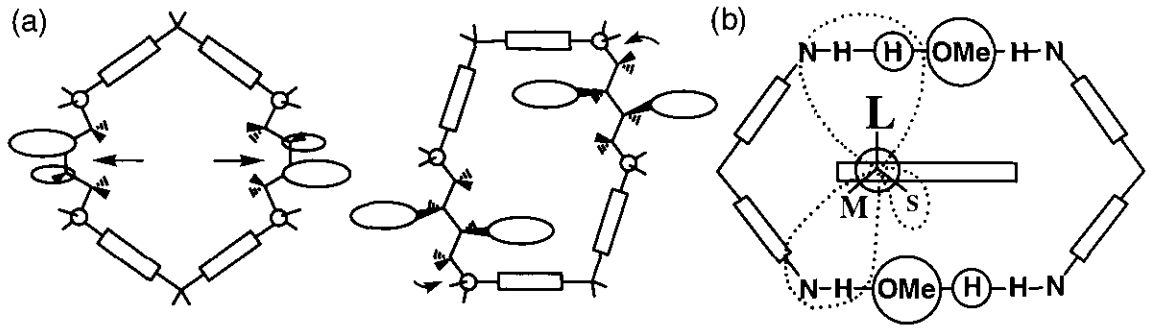


Figure 5. (a) Possible structures of the inclusion cavities of tetraprotonated TCP44 (**1**·4H$^+$). Hexagonal cavity with the C-C *gauche* conformation (left) and rectangular cavity with the C-N *gauche* conformation (right). In each figure, rectangles, ellipses and circles indicate benzene rings, methoxy groups and ammonium (protonated amine) nitrogens, respectively. Arrows exhibit the *gauche* bonds. (b) A possible model of chiral recognition by protonated TCP44 (**1**) in acidic media. Three open spaces, L (large), M (medium) and S (small), of the chiral cavity can accommodate the three substituents attached to the chiral center of the complexed aromatic guest.

interactions.

The same interpretation based on the relative bulkiness of the substituents can be applied to the stronger complexation with the (*S*)-enantiomer of the corresponding phenyl derivative (**4**) and also with the (*R*)-enantiomers of 1-naphthylethanols (**12**, **13**).

CONCLUSION

Chiral recognition properties of TCP44 (**1**) in acidic aqueous media were investigated in detail by ^{1}H NMR experiments, using *chiral aromatic guests*. The formation of diastereomeric inclusion complexes was confirmed by host-induced enantiomeric splitting of the upfield-shifted signals of chiral guests. In addition, enantiomeric discrimination was quantitatively evaluated by determining the complexation shifts ($\Delta\delta_{comp}$) and stability constants (K_S) for 1:1 complexes with each enantiomer of guests by ^{1}H NMR titration experiments. Enantiomeric splitting of the signals of chiral guests by this and other types[8] of cyclophanes may afford a new type of ^{1}H NMR shift reagents applicable to aqueous systems.[12] However, as for other chiral cyclophane hosts,[8a-d] the enantiomeric discrimination by protonated TCP44 (**1**·*n*H$^+$) in terms of the stability of complex is still small ($|\Delta G°(S) - \Delta G°(R)| \sim 0.20$ kcal mol^{-1}), indicating that achieving a high enantiomeric discrimination based mainly on nonpolar interactions in aqueous or aqueous/organic media is still difficult. This situation contrasts excellent enantiomeric discrimination by cyclophane hosts in nonpolar organic media, based on directed multiple hydrogen bonding interactions (maximum $|\Delta G°(S) - \Delta G°(R)|$ of > 3.5 kcal mol^{-1}).[13] The design and synthesis of cyclophane hosts for high enantiomeric discrimination in aqueous systems still remain as a challenging problem, which involves molecular recognition based on nonpolar interactions.

EXPERIMENTAL SECTION

General. ^{1}H NMR measurements were carried out with a JEOL JNM-PS100 NMR spectrometer (100 MHz) and a JEOL JNM-GX200 Fourier transform NMR spectrometer (270 MHz). Chemical shifts are reported as δ values in ppm downfield from tetramethylsilane (TMS) or hexamethyldisiloxane (HMDS) as an external reference. The following abbreviations are used: singlet (s), singlet with shoulders (s*), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). The pH (pD) measurements were made 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.

Materials. The details of the synthesis of TCP44 (**1**) are described in our preceding paper.[1] Commercially available guests were purchased in their extra pure grades. Other guests were prepared according to well-known procedures, as reported separately.[14] The purities of the guests were checked by mp, TLC, ^{1}H NMR, and $[\alpha]_D$ values.

Complexation Studies by ^{1}H NMR Spectra. Preparation of Samples. In general, an appropriate amount of guest was dissolved in a DCl-D_2O solution (pD 1.0) of TCP44 (**1**). For the guests with poor solubility in DCl-D_2O, a CD_3OD solution of the guest was mixed with the aqueous solution of host described above in 1:9 ratio (v/v). pD was adjusted according to Glasoe and Long on the basis of the equation: pD = pH meter reading + 0.40.[15]

Measurement of ^{1}H NMR Spectra. The ^{1}H NMR measurements were conducted at either 100 or 270 MHz with 8 K data point. The probe temperature was 28 ± 2 °C (100 MHz) or 27 ± 1 °C (270 MHz). For 100 MHz, TMS was used as an external reference, based on which the signals of HOD and CD_3OD appeared at 5.275 ± 0.015 ppm and 3.690 ± 0.015 ppm, respectively. For 270 MHz, HMDS was used as an external reference, the chemical shift of which was set at 1.00 ppm [DCl-D_2O (pD 1.0)] or 1.04 ppm [DCl-D_2O (pD 1.0)/CD_3OD (9:1 v/v)] downfield of external TMS. The signals of HOD and CD_3OD appeared at 5.245 ± 0.015 ppm and 3.715 ± 0.015 ppm, respectively.

All measurements were conducted at 100 MHz unless noted otherwise. The host-induced changes in the chemical shifts of guest proton signals are represented as Δδ (ppm) = δ(host + guest) − δ(guest). The compositions of the sample solutions are as follows. Condition A1: [**1**] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M in DCl-D_2O (pD 1.2). Condition A2: [**1**] = 6.0×10^{-2} M, [guest] = 1.0×10^{-2} M in DCl-D_2O (pD 1.2). Condition A3: [**1**] = 1.0×10^{-2} M, [guest] = 0.5×10^{-2} M in DCl-D_2O (pD 1.2). Condition B1: [**1**] = 1.0×10^{-2} M, [guest] = 0.5×10^{-2} M in DCl-D_2O (pD 1.2)/CD_3OD (9:1 v/v). Condition B2: [**1**] = 5.0×10^{-2} M, [guest] = 2.5×10^{-2} M in DCl-D_2O (pD 1.0)/CD_3OD (9:1 v/v).

The δ and Δδ values for all assignable signals, including those listed in Tables 1~3, are described hereafter for each guest. In some cases, observation and/or assignment of guest proton signals was difficult due to overlap of the signals. In such cases, the δ and/or Δδ values are not shown or, where applicable, shown as minimum upfield shift (for example, Δδ

< -0.5). The signals of guests that are not observable in the presence of the host because of overlap with the signals of the host or HOD are indicated with superscript †.

Lactic Acid (3). *Condition A1.* For (*RS*)-**3**: δ 1.839 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$), 4.809 (1H, q, *J* = 7.0 Hz, C<u>H</u>COOH). For (*RS*)-**3** + **1**: δ 1.805 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$, Δδ = -0.034), 4.773 (1H, q, *J* = 7.0 Hz, C<u>H</u>COOH, Δδ = -0.036).

Mandelic Acid (4). *Condition A1.* For (*R*)-**4**: δ 5.733 (1H, s, C<u>H</u>COOH), 7.881 (5H, s, ArH). For (*R*)-**4** + **1**: δ 5.224 [1H, s, C<u>H</u>COOH, Δδ(*R*) = -0.509], 6.7~6.9 [4H, m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*R*) ~ -1.1], 7.2 [1H, m, ArH$_{para}$, Δδ(*R*) = -0.7]. For (*S*)-**4** + **1**: δ 5.174 [1H, s, C<u>H</u>COOH, Δδ(*S*) = -0.559], 6.6~7.0 [4H, m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*S*) ~ -1.0], 7.2 [1H, br m, ArH$_{para}$, Δδ(*S*) = -0.7]. *Condition A2.* For (*R*)-**4**: δ 5.741 (1H, s, C<u>H</u>COOH), 7.884 (5H, s, ArH). For (*R*)-**4** + **1**: δ 5.172 [1H, s, C<u>H</u>COOH, Δδ(*R*) = -0.569], 6.5~6.7 [4H in total, m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*R*) ~ -1.3], 7.1 [1H, m, ArH$_{para}$, Δδ(*R*) = -0.7]. For (*S*)-**4** + **1**: δ 5.113 [1H, s, C<u>H</u>COOH, Δδ(*S*) = -0.628], 6.5~6.8 [4H in total, m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*S*) ~ -1.3], 7.1 [1H, br m, ArH$_{para}$, Δδ(*S*) = -0.7]. For (*RS*)-**4** + **1**: δ 5.125 and 5.188 (equal area) [1H in total, two s, C<u>H</u>COOH, Δδ(*S*) = -0.616, Δδ(*R*) = -0.553].

Atrolactic Acid (5). *Condition A1.* For (*RS*)-**5** and (*S*)-**5**: δ 2.253 (3H, s, C<u>H</u>$_3$), 7.8~8.1 (5H, m, ArH). For (*RS*)-**5** + **1**: δ 1.871 and 1.914 [1.5H + 1.5H, two s, C<u>H</u>$_3$, Δδ(*S*) = -0.382, Δδ(*R*) = -0.339], 6.7~7.1 (4H, m, ArH$_{ortho}$ and ArH$_{meta}$), 7.26 (1H, br t, *J* = 6 Hz, ArH$_{para}$, Δδ < -0.5). For **5** (*R*/*S* 3:5) + **1**: δ 1.878 (larger) and 1.920 (smaller) [3H in total, two s, C<u>H</u>$_3$, Δδ(*S*) = -0.375, Δδ(*R*) = -0.333]. For **5** (*R*/*S* 1:3) + **1**: δ 1.878 and 1.921 (shoulder) [3H in total, two s, C<u>H</u>$_3$, Δδ(*S*) = -0.375, Δδ(*R*) = -0.332]. For (*S*)-**5** + **1**: δ 1.868 [1H, s, C<u>H</u>$_3$, Δδ(*S*) = -0.385], 6.7~7.1 (4H, br m, ArH$_{ortho}$ and ArH$_{meta}$), 7.28 (1H, br t, *J* = 6 Hz, ArH$_{para}$, Δδ < -0.5).

2-Hydroxy-3-phenylpropanoic Acid (6). *Condition A1.* For (*R*)-**6**: δ 3.423 [1H, dd, *J* = 7.5, 14.1 Hz, C<u>H</u>$_2$(1)], 3.586 [1H, dd, *J* = 5.0, 14.1 Hz, C<u>H</u>$_2$(2)], 4.972 (1H, dd, *J* = 5.0, 7.5 Hz, C<u>H</u>COOH), 7.76 (5H, s*, ArH). For (*R*)-**6** + **1**: δ 2.985 [1H, dd,[a] C<u>H</u>$_2$(1), Δδ(*R*) = -0.438], 3.145 [1H, dd,[a] C<u>H</u>$_2$(2), Δδ(*R*) = -0.441], 4.632 [1H, dd, *J* = 5.4, 7.7 Hz, C<u>H</u>COOH, Δδ(*R*) = -0.340], 6.6~7.0 [4H, br m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*R*) ~ -1.0], 7.1 [1H, br, ArH$_{para}$, Δδ(*R*) ~ -0.7]. For (*S*)-**6** + **1**: δ 2.956 [1H, dd, *J* = 7.8, 14.2 Hz, C<u>H</u>$_2$(1), Δδ(*S*) = -0.467], 3.149 [1H, dd, *J* = 4.8, 14.2 Hz, C<u>H</u>$_2$(2), Δδ(*S*) = -0.437], 4.620 [1H, dd, *J* = 4.8, 7.8 Hz, C<u>H</u>COOH, Δδ(*S*) = -0.352], 6.7~7.0 [4H, m, ArH$_{ortho}$ and ArH$_{meta}$, Δδ(*S*) ~ -0.9], 7.2 [1H, m, ArH$_{para}$, Δδ(*S*) ~ -0.6].

[a] Coupling constants could not be estimated directly due to some broadening of the signals.

2-Hydroxy-(1-naphthyl)acetic Acid (7). *Condition B1.* For (*RS*)-**7**: δ 6.344 (1H, s, C<u>H</u>COOH), 7.9~8.1 (4H, br m, ArH-2, 3, 6, 7), 8.3~8.5 (2H, br m, ArH-4, 5), 8.5~8.7 (1H, br m, ArH-8). For (*RS*)-**7** + **1**: δ 5.940 and 6.020 [0.5H + 0.5H, two s, C<u>H</u>COOH, Δδ(*S*) = -0.404, Δδ(*R*) = -0.324], 7.1~7.4, 7.57 and 7.62 (*ca.* 5H in total, br m, br s and br s, part of ArH). For **7** (*R*/*S* 55:45) + **1**: δ 5.964 (smaller) and 6.045 (larger) [1H in total, two s, C<u>H</u>COOH, Δδ(*S*) = -0.380, Δδ(*R*) = -0.299], 7.1~7.5, 7.59 and 7.64 (*ca.* 5H in total, br m, br s and br s, part of ArH).

2-Hydroxy-(2-naphthyl)acetic Acid (8). *Condition B1.* For (*RS*)-**8**: δ 5.883 (1H, s, CHCOOH), 7.9~8.1 (3H, m, ArH-3, 6, 7), 8.3~8.5 (4H, m, ArH-1, 4, 5, 8). For (*RS*)-**8** + **1**: δ 5.481 and 5.547 (equal area) [1H in total, two s, CHCOOH, Δδ(*S*) = -0.402, Δδ(*R*) = -0.336], 6.6, 6.8~7.2 and 7.2~7.5 (1H + 2H + 4H, br, br and two br, ArH). For **8** (*R/S* 18:82) + **1**: δ 5.498 (larger) and 5.563 (smaller) [1H in total, two s, CHCOOH, Δδ(*S*) = -0.385, Δδ(*R*) = -0.320], 6.6, 6.9~7.1 and 7.3~7.5 (1H + 3H + 3H, br, br m and br m).

2-Phenylpropanoic Acid (9). *Condition A1.* For (*RS*)-**9**: δ 1.881 (3H, d, *J* = 7.2 Hz, CH_3), 4.278† (1H, q, *J* = 7.2 Hz, CHCOOH), 7.80 (5H, s*, ArH). For (*RS*)-**9** + **1**: δ 1.446 and 1.480 [1.5H + 1.5H, two d, *J* = 7.1 Hz, CH_3, Δδ(*S*) = -0.435, Δδ(*R*) = -0.401], 6.451 and 6.502 [2H in total, two d, *J* = 7.1 Hz, ArH_{ortho}, Δδ(*S*) = -1.35, Δδ(*R*) = -1.30], 6.689 [2H, t, *J* = 7.1 Hz, ArH_{meta}, Δδ(*R*) = Δδ(*S*) = -1.114], 7.107 [1H, t, *J* = 7.1 Hz, ArH_{para}, Δδ(*R*) = Δδ(*S*) = -0.696]. *Condition A3.* For **9** (*R/S* 3:1) + **1**: δ 1.623 (smaller) and 1.650 (larger) [3H in total, two d, *J* = 7.3 Hz, CH_3], 6.9~7.6 (*ca.* 5H, br m, ArH).

Phenylethane-1,2-diol (10). *Condition A1.* For (*S*)-**10**: δ 4.163 (2H, d, *J* = 6.0 Hz, CH_2), 5.217 (1H, t, *J* = 6.0 Hz, CHOH), 7.838 (5H, s, ArH). For (*R*)-**10** + **1**: δ 3.959 [2H, d, *J* = 6.0 Hz, CH_2, Δδ(*R*) = -0.204], 4.976 [1H, t, *J* = 6.0 Hz, CHOH, Δδ(*R*) = -0.241], 7.1~7.5 [5H, m, ArH, Δδ(*R*) < -0.4]. For (*S*)-**10** + **1**: δ 3.943 [1H, d, *J* = 6.1 Hz, CH_2, Δδ(*S*) = -0.220], 4.953 [1H, t, *J* = 6.1 Hz, CHOH, Δδ(*S*) = -0.264], 7.1~7.5 [5H, m, ArH, Δδ(*S*) < -0.4]. For (*RS*)-**10** + **1**: δ 3.942[a] and 3.962[a] [*ca.* 2H in total, two d, *J* = 6.0 Hz, CH_2, Δδ(*S*) = -0.221, Δδ(*R*) = -0.201], 4.953 and 4.980 [0.5H + 0.5H, two t, *J* = 6.0 Hz, CHCOOH, Δδ(*S*) = -0.264, Δδ(*R*) = -0.237]. [a] Appeared as shoulders of the signals of the host.

1-Phenethyl Alcohol (11). *Condition A1.* For (*RS*)-**11**: δ 1.887 (3H, d, *J* = 6.6 Hz, CH_3), 5.331 (1H, q, *J* = 6.6 Hz, CHOH), 7.83 (5H, s*, ArH). For (*RS*)-**11** +**1**: δ 1.707 [3H, d, *J* = 6.7 Hz, CH_3, Δδ(*R*) = Δδ(*S*) = -0.180], 5.029 [1H, q, *J* = 6.7 Hz, CHOH, Δδ(*R*) = Δδ(*S*) = -0.302], 7.0~7.4 (5H, br m, ArH, Δδ < -0.5).

1-(1-Naphthyl)ethanol (12). *Condition B1.* For (*RS*)-**12**: δ 2.027 (3H, d, *J* = 6.5 Hz, CH_3), 6.136 (1H, q, *J* = 6.5 Hz, CHOH), 7.9~8.1 (4H, m, ArH-2, 3, 6, 7), 8.2~8.4 (2H, m, ArH-4, 5), 8.5~8.7 (1H, m, ArH-8). For (*RS*)-**12** + **1**: δ 1.879 and 1.923 [1.5H + 1.5H, two d, *J* = 6.1 Hz, CH_3, Δδ(*R*) = -0.148, Δδ(*S*) = -0.104], 5.784 and 5.845 (equal area) [1H in total, two q, *J* = 6.1 Hz, CHOH, Δδ(*R*) = -0.352, Δδ(*S*) = -0.291], 7.1~7.6 (5~6H, m, part of ArH). *Condition B2.* For **12** (*R/S* 2:1) + **1** (270 MHz): δ 1.773 (larger) and 1.825 (smaller) (3H in total, two d, *J* = 6.3 Hz, CH_3), 5.572 (larger) and 5.622 (smaller) (1H in total, two q, *J* = 6.3 Hz, CHOH).

1-(2-Naphthyl)ethanol (13). *Condition B1.* For (*RS*)-**13**: δ 1.947 (3H, d, *J* = 6.5 Hz, CH_3), 5.472† (1H, q, *J* = 6.5 Hz, CHOH), 7.9~8.1 (3H, m, ArH-3, 6, 7), 8.2~8.4 (4H, m, ArH-1, 4, 5, 8). For (*RS*)-**13** + **1**: δ 1.852 [3H, br d, *J* = 6.4 Hz, CH_3, Δδ(*R*) = Δδ(*S*) = -0.095], 6.8~7.6 (*ca.* 7H, m, ArH). *Condition B2.* For **13** (*R/S* 1:1) + **1** (270 MHz): δ 1.803 and 1.816 (equal area) [3H in total, two d, *J* = 6.3 Hz, CH_3]. For **13** (*R/S* 3:1) + **1** (270 MHz): δ 1.829 (larger) and 1.838 (smaller) [3H in total, two d, *J* = 6.3 Hz, CH_3].

Phenylglycine (14). *Condition A1.* For (*R*)-**14**: δ 5.633 (1H, s, CHCOOH), 7.95 (5H, s*, ArH). For (*R*)-**14** + **1**: δ 5.621 [1H, s, CHCOOH, Δδ(*R*) = -0.012], 7.86[a] [5H, (s), ArH, Δδ(*R*) = -0.09]. For (*S*)-**14** + **1**: δ 5.609 [1H, s, CHCOOH, Δδ(*S*) = -0.024], 7.86[a] [5H, (s), ArH, Δδ(*S*) = -0.09]. [a] The only observable line. The other lines overlapped with the aromatic proton signals of the host.

Phenylalanine (15). *Condition A1.* For (*R*)-**15**: δ 3.662[†] [1H, dd, *J* = 7.5, 14.5 Hz, CH_2(1)], 3.792[†] [1H, dd, *J* = 5.8, 14.5 Hz, CH_2(2)], 4.801 (1H, dd, *J* = 5.8, 7.5 Hz, CHCOOH), 7.80 (5H, br s*, ArH). For (*R*)-**15** + **1**: δ 4.764 [1H, dd, *J* = 6.2, 7.1 Hz, CHCOOH, Δδ(*R*) = -0.037], 7.68 [5H, br s*, ArH, Δδ(*R*) = -0.12]. For (*S*)-**15** + **1**: δ 4.771 [1H, dd, *J* = 6.2, 7.4 Hz, CHCOOH, Δδ(*S*) = -0.030], 7.69 [5H, br s*, ArH, Δδ(*S*) = -0.11].

Histidine (16). *Condition A1.* For (*S*)-**16**: δ 3.890[†] (2H, d, *J* = 6.7 Hz, CH_2), 4.843 (1H, t, *J* = 6.7 Hz, CHCOOH), 7.885 (1H, d, *J* = 1.3 Hz, ArH-5), 9.133 (1H, d, *J* = 1.3 Hz, ArH-2). For (*R*)-**16** + **1**: δ 4.846 [1H, t, *J* = 6.6 Hz, CHCOOH, Δδ(*R*) ~ 0], 7.9[a] [1H, ArH-5, Δδ(*R*) ~ 0], 9.135 [1H, d, *J* = 1.3 Hz, ArH-2, Δδ(*R*) ~ 0]. For (*S*)-**16** + **1**: δ 4.846 [1H, t, *J* = 6.6 Hz, CHCOOH, Δδ(*S*) ~ 0], 7.9[a] [1H, ArH-5, Δδ(*S*) ~ 0], 9.131 [1H, d, *J* = 1.2 Hz, ArH-2, Δδ(*S*) ~ 0]. [a] Overlapped with one of the aromatic proton signals of the host.

Tryptophan (17). *Condition A1.* For (*R*)-**17**: δ 3.92[†] (2H, m, CH_2), 4.828 (1H, dd, *J* = 5.8, 6.8 Hz, CHCOOH), 7.5~7.8 (2H, m, ArH-4, 7), 7.758 (1H, s, ArH-2), 7.8~8.2 (2H, m, ArH-5, 6). For (*R*)-**17** + **1**: δ 4.722 [1H, t, *J* = 6.5 Hz, CHCOOH, Δδ(*R*) = = -0.11], 7.1~7.4 and 7.56 (3H + 1H, br m and br d, ArH-4~7), 7.666 [1H, s, ArH-2, Δδ(*R*) = -0.092]. For (*S*)-**17** + **1**: δ 4.738 [1H, t, *J* = 6.4 Hz, CHCOOH, Δδ(*S*) = -0.09], 7.1~7.4 and 7.59 (3H + 1H, m and br d, ArH-4~7), 7.676 [1H, s, ArH-2, Δδ(*S*) = -0.082].

1-Phenethylamine (18). *Condition A1.* For (*R*)-**18**: δ 2.064 (3H, d, *J* = 6.9 Hz, CH_3), 4.962 (1H, q, *J* = 6.9 Hz, $CHNH_3^+$), 7.896 (5H, s, ArH). For (*R*)-**18** + **1**: δ 2.053 [3H, d, *J* = 7.0 Hz, CH_3, Δδ(*R*) = -0.011], 4.949 [1H, q, *J* = 7.0 Hz, $CHNH_3^+$, Δδ(*R*) = -0.013], 7.83[a] [5H, ArH, Δδ(*R*) = -0.07]. For (*S*)-**18** + **1**: δ 2.056 [3H, d, *J* = 7.0 Hz, CH_3, Δδ(*S*) ~ -0.01], 4.953 [1H, q, *J* = 7.0 Hz, $CHNH_3^+$, Δδ(*S*) ~ -0.01], 7.84[a] [5H, ArH, Δδ(*S*) = -0.06]. [a] Overlapped with one of the aromatic proton signals of the host.

1-(1-Naphthyl)ethylamine (19). *Condition A1.* For (*R*)-**19**: δ 2.189 (3H, d, *J* = 6.8 Hz, CH_3), 5.864 (1H, q, *J* = 6.8 Hz, $CHNH_3^+$), 7.9~8.2 (4H, m, ArH-2, 3, 6, 7), 8.3~8.6 (3H, m, ArH-4, 5, 8). For (*R*)-**19** + **1**: δ 2.109 [3H, d, *J* = 6.7 Hz, CH_3, Δδ(*R*) = -0.080], 5.664 [1H, q, *J* = 6.7 Hz, $CHNH_3^+$, Δδ(*R*) = -0.200], 7.5~7.7[a] (1~2H, m, part of ArH). For (*S*)-**19** + **1**: δ 2.137 [3H, d, *J* = 6.6 Hz, CH_3, Δδ(*S*) = -0.052], 5.725 [1H, q, *J* = 6.6 Hz, $CHNH_3^+$, Δδ(*S*) = -0.139], 8.1~8.3[a] (1~2H, m, part of ArH). [a] Major part of the ArH signals of the guest (corresponding to 5~6H) overlapped with the aromatic proton signals of the host (δ 7.7~8.1, dd).

^{1}H NMR Titration Experiments and Calculation of Stability Constants. In general, *ca.* 5.0×10^{-2} M solution of host (**1**) in DCl-D_2O (pD 1.0) was mixed with *ca.* 2.5×10^{-1} M solution of a single enantiomer or a racemate of guest in CD_3OD in a ratio of 9:1 (v/v). This mixture was successively diluted with DCl/D_2O (pD 1.0)-CD_3OD (9:1) to give a series of

sample solutions for titration experiments under a constant concentration ratio of the host and guest.[16] The corresponding solutions containing only guest were also prepared. The use of a D_2O-CD_3OD mixed solvent prevented precipitation of naphthalene guests at high concentrations. In the case of using a single enantiomer [*e.g.*, guest (**4**)] or a racemate with enantiomeric signal splitting [*e.g.*, guest (**7**)], the titration data were simulated by the program "COMPLEX2 MULTIFIT"[17] based on our linear approximation method to directly give the $\Delta\delta_{comp}$ and K_s values for each enantiomer. In the case of using a racemic guest with no enantiomeric signal splitting, the *three* component system [host, (*R*)-guest, and (*S*)-guest] can be treated as the corresponding *two* component system [host, (*R*)- plus (*S*)-guest].

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.

REFERENCES

1. Part 1 of this series: I. Takahashi, Y. Hirano, H. Arakawa, H. Kitajima, M. Hatanaka, K. Isa, K. Odashima, and K. Koga, *Heterocycles*, 1997, **46**, 589.
2. A part of this work was published as a communication: I. Takahashi, K. Odashima, and K. Koga, *Tetrahedron Lett.*, 1984, **25**, 973.
3. I. Takahashi, K. Odashima, and K. Koga, *Chem. Pharm. Bull.*, 1985, **33**, 3571.
4. (a) K. Odashima, T. Soga, and K. Koga, *Tetrahedron Lett.*, 1981, **22**, 5311. (b) K. Odashima, H. Kawakami, A. Miwa, I. Sasaki, and K. Koga, *Chem. Pharm. Bull.*, 1989, **37**, 257.
5. (a) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Am. Chem. Soc.*, 1980, **102**, 2504; *idem*, *J. Org. Chem.*, 1985, **50**, 4478. (b) K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 4347.
6. See the literatures cited in the following monographs and reviews: (a) F. Diederich, *Cyclophanes*, Monographs in Supramolecular Chemistry 2, The Royal Society of Chemistry, Cambridge, U. K., 1991. (b) F. Vögtle, *Cyclophane Chemistry: Synthesis, Structures, and Reactions*, John Wiley and Sons, Chichester, U. K., 1993. (c) Y. Murakami, J. Kikuchi, Y. Hisaeda, and O. Hayashida, *Chem. Rev.*, 1996, **96**, 721. (d) K. Odashima and K. Koga, in *Molecular Recognition: Receptors for Molecular Guests*, ed. by F. Vögtle, Comprehensive Supramolecular Chemistry 2, Elsevier Science, Oxford, U. K., 1996, Chapter 5 (pp. 143-194).
7. In contrast to enantiomeric splitting of guest signals, the fast complexation equilibrium results in the absence of splitting of host proton signals upon complexation with chiral guests though, in principle, the host-guest complex becomes dissymmetrical even when the host itself has a symmetrical nature as in the case of **1** (D_2-symmetrical).

8. For examples, see: (a) M. A. Petti, T. J. Shepodd, R. E. Barrans, Jr., and D. A. Dougherty, *J. Am. Chem. Soc.*, 1988, **110**, 6825. (b) P. P. Castro, T. M. Georgiadis, and F. Diederich, *J. Org. Chem.*, 1989, **54**, 5835. (c) T. M. Georgiadis, M. M. Georgiadis, and F. Diederich, *J. Org. Chem.*, 1991, **56**, 3362. (d) T. H. Webb, H. Suh, and C. S. Wilcox, *J. Am. Chem. Soc.*, 1991, **113**, 8554. (e) J. M. Coterón, C. Vicent, C. Bosso, and S. Penadés, *J. Am. Chem. Soc.*, 1993, **115**, 10066.
9. For a review, see: T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev.*, 1993, 383.
10. Strong hydrophobic interactions leading to the formation of stable inclusion complexes with naphthalene guests are also manifested as a marked solubilization effect of protonated **1** for these guests. For example, the maximum solubility of guest (**12**) to DCl-D_2O (pD 1.0)/CD_3OD (9:1 v/v) increased from *ca.* 0.50×10^{-2} M to *ca.* 2.5×10^{-2} M by addition of TCP44 (**1**) to a concentration of *ca.* 5.0×10^{-2} M.
11. E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *J. Am. Chem. Soc.*, 1973, **95**, 2692; E. P. Kyba, J. M. Timko, L. J. Kaplan, F. de Jong, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 4555.
12. I. Takahashi, K. Odashima, K. Koga, and H. Kitajima, *Chem. Express*, 1992, **7**, 653. See also: G. Uccello-Barretta, F. Balzano, A. M. Caporusso, and P. Salvadori, *J. Org. Chem.*, 1994, **59**, 836; G. Uccello-Barretta, F. Balzano, A. M. Caporusso, A. Iodice, and P. Salvadori, *J. Org. Chem.*, 1995, **60**, 2227; G. Uccello-Barretta, F. Balzano, R. Menicagli, and P. Salvadori, *J. Org. Chem.*, 1996, **61**, 363.
13. J.-I. Hong, S. K. Namgoong, A. Bernardi, and W. C. Still, *J. Am. Chem. Soc.*, 1991, **113**, 5111; S. S. Yoon and W. C. Still, *J. Am. Chem. Soc.*, 1993, **115**, 823; S. S. Yoon and W. C. Still, *Tetrahedron Lett.*, 1994, **35**, 2117.
14. I. Takahashi, Y. Aoyagi, I. Nakamura, A. Kitagawa, and K. Matsumoto, *Mem. Fac. Eng., Fukui Univ.*, 1997, **45**, 319.
15. P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188.
16. The ^1H NMR titration experiments were made under a constant concentration ratio of host and guest because of the following reasons: (i) Convergence of simulation is mathematically proven by our *linear approximation method.*[17] (ii) Measurement errors can be minimized because the sample solutions are prepared by systematic dilution of the original, high-concentration solutions. (iii) Relative S/N ratio of the host and guest signals is kept constant. The detailed discussions and comparison with other titration conditions with regard to the concentrations of host and guest are given in ref 17c.
17. (a) I. Takahashi, A. Nomura, and H. Kitajima, *Mem. Fac. Eng., Fukui Univ.*, 1992, **40**, 7. (b) I. Takahashi, A. Nomura, and H. Kitajima, *Chem. Express*, 1993, **8**, 593. (c) I. Takahashi and H. Kitajima, *Mem. Fac. Eng., Fukui Univ.*, 1994, **42**, 143.

Received, 1st February, 1999