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DIASTEREOMERIC HOST-GUEST COMPLEX FORMATION BY AN OPTICALLY ACTIVE PARACYCLOPHANE IN WATER

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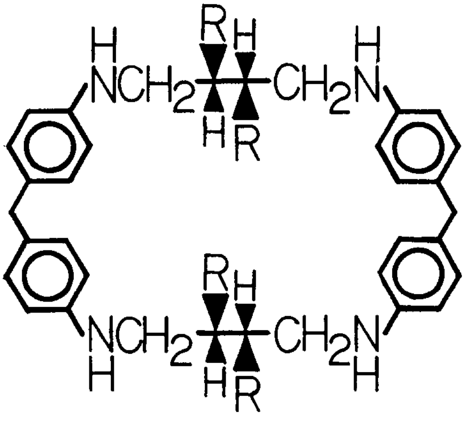
Abstract: The first synthesis of a water-soluble cyclophane possessing a chiral hydrophobic cavity, and the formation of diastereomeric inclusion complexes with chiral hydrophobic guests in water are described.

Water-soluble cyclophanes[1] constitute a promising group of artificial hosts to capture organic guests in water by hydrophobic interaction. This class of hosts would afford wide possibility of structural and functional design, since they are totally synthetic. We have recently shown by crystallographic[2a] and spectral[2b-e] studies that a series of novel, diphenylmethane-containing paracyclophanes (e.g., CP44 (**1a**)), soluble in acidic water, form *inclusion* complexes with hydrophobic guests, and that the guest inclusion occurs with *particular geometry* and *remarkable selectivity* based on host-guest recognition of steric structure and charge.[1c] These findings led us to a further study for extending this system to the recognition of chiral guests.

In this paper we report the synthesis and complexation properties of a novel paracyclophane TCP44 (**1b**),[3] in which two diphenylmethane skeletons are bridged by two chiral C_4-chains derived from L-tartaric acid; this is the first example of water-soluble cyclophane possessing a chiral hydrophobic cavity. TCP44, a simple modification of CP44, retains the two diphenylmethane skeletons, which have been proved to be essential for constructing a stable and well-defined hydrophobic cavity.[2c] In addition the chiral C_4-unit is easily prepared from L-tartaric acid, and the D_2-symmetry of the molecule will greatly facilitate analysis of the complex formation.

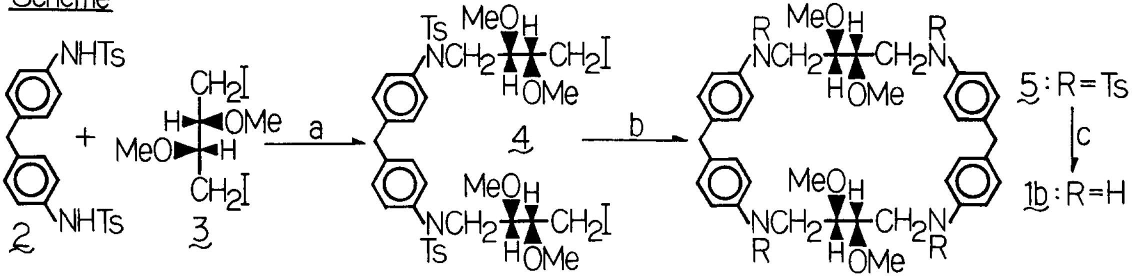


1a : R = H
1b : R = OMe

The synthesis of TCP44 was carried out as shown in the scheme. The key point of this synthesis is the "stepwise" cyclization *via* the U-shaped precursor (**4**). Thus diiodide **4**,[4a,d] $[\alpha]_D^{22.5}$ +44.7° (c = 3.60, $CHCl_3$), was synthesized in 90% yield by the reaction of **2**[5] with large excess (5.4 mol) of **3**,[4a-c] $[\alpha]_D^{22.5}$ -7.48° (c = 3.75,

$CHCl_3$),[6a] which in turn was prepared from L-tartaric acid employing well-known procedures.[6] The 1:1 cyclization between 4 and 2 in the presence of K_2CO_3 in DMF gave cyclic tetratosylate 5,[4a,d] $[\alpha]_D^{22.5}$ -51.2° (c = 2.95, $CHCl_3$), in 24% yield. On the other hand an attempt of "direct" 2:2 cyclization between 2 and 3 did not give the desired product. Detosylation of 5 in 90% H_2SO_4[7,8] smoothly gave TCP44,[4a-c] mp 175-178.5°C (from toluene), $[\alpha]_D^{22.5}$ -69.6° (c = 2.72, $CHCl_3$), in 69% yield. The cyclic structure was confirmed on the basis of the mass spectra of 5 and TCP44. TCP44 is soluble in acidic water (pH < 1.7) as an amine salt, and is sufficiently stable under the measurement conditions (*vide infra*).

Scheme



a) K_2CO_3(6.8 mol)/DMF, 80°C, 2.5 hr ; b) K_2CO_3(10 mol)/DMF, 110-115°C, 8 hr ; c) 90% H_2SO_4, rt 18 hr, then 50°C 3 hr.

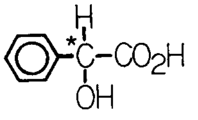
Complex formation between TCP44 and several types of chiral guests was investigated by ^1H NMR (100 MHz) in acidic D_2O (pD 1.2).[9] When inclusion complexes are formed, large upfield shift is expected to be induced on the guest proton signals, due to a strong ring current effect from the four benzene rings of the host.[1c,2a,b] The host-induced shifts[10] of the guest proton signals are represented by $\Delta\delta(\text{ppm}) = \delta(\text{Host} + \text{Guest}) - \delta(\text{Guest})$. Negative values of $\Delta\delta$ indicate upfield shifts. The following tendencies were observed as to the complexation properties of protonated TCP44 in water.

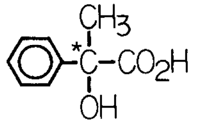
(1) Strong complex formation was observed for the noncationic[11] guests having aromatic rings (6 - 9), as indicated by large upfield shift ($\Delta\delta \sim -1.3$ ppm) of the proton signals of these guests. (See Figure 1 for a typical example.)

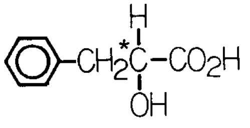
(2) In addition to the large upfield shift, the signals of (R)- and (S)-guests shifted to a different degree. This indicates the formation of diastereomeric host-guest complexes that have different stability constants and/or predominant structures.[10] Typical examples are shown for guests 6 and 7 in Figures 1 and 2, respectively, in which split of the methine (or methyl) signal is evident. Also the pattern of aromatic proton signals is different for the (R)- and (S)-enantiomers (Figure 1), suggesting that the predominant structures[10] of the diastereomeric host-guest complexes are different from each other. Similar spectral changes are observed for guests 8 and 9.

(3) As to the corresponding nonaromatic (10) or cationic (11, 12)[11] guests, the complex formation was weak ($\Delta\delta \sim -0.1$ ppm) and the split of the signals of (R)- and (S)-enantiomers was negligible. However, moderate upfield shift ($\Delta\delta \sim -0.6$ ppm) with large split of the enantiomer signals was observed for the cationic guest having a naphthalene ring (13). The split of the enantiomer signals of this guest was largest among the guests examined.

The above observations clearly show the ability of protonated TCP44 to form diastereomeric host-guest complexes, in which each of the enantiomeric guests is included with a particular geometry into the chiral hydrophobic cavity of the host. This is the first example that recognition of chirality of guest is successfully effected in water by a totally synthetic host.[12] Since this system is subject to wide structural modification, the present study will serve as a reliable basis for the application of this system to the control of asymmetric reactions in water, which is now under extensive investigation.[13,14]


6 (mandelic acid)


7 (atrolactic acid)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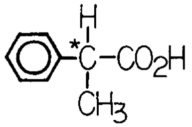
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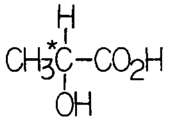
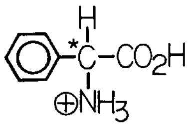
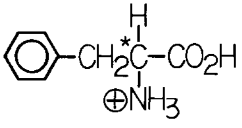

10 (lactic acid)


11 (phenylglycine)


12 (phenylalanine)

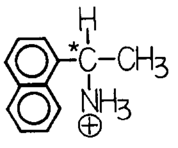

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Figure 1

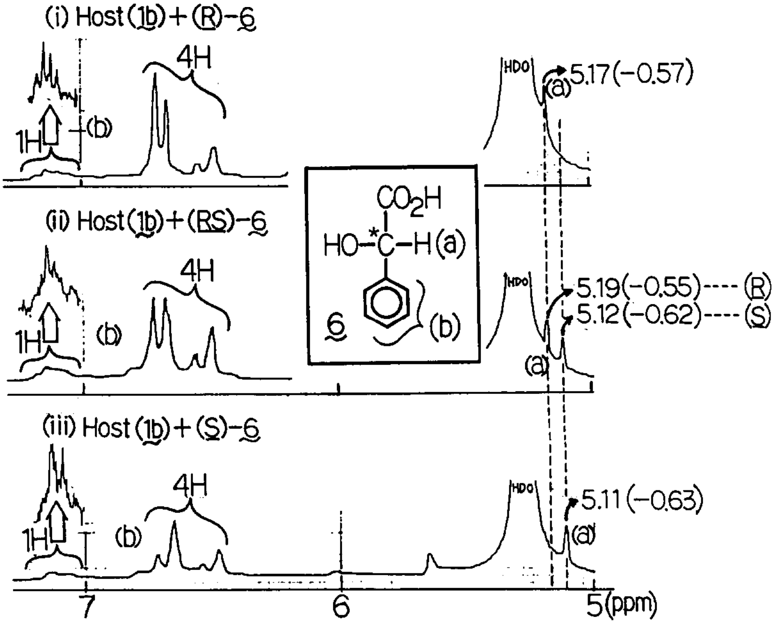

Figure 2

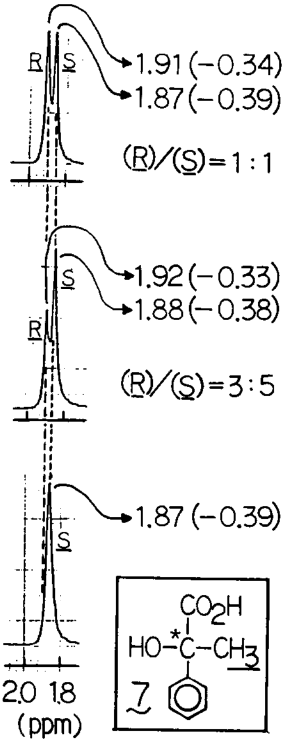

Figure 1 The formation of diastereomeric host-guest complexes between TCP44 and guest 6 in acidic D_2O (pD 1.2). [Host] = 6.0×10^{-2}M, [Guest] = 1.0×10^{-2}M. In the absence of TCP44, the signals of 6 appear as two singlets at 7.88 and 5.74 ppm.

Figure 2 The formation of diastereomeric host-guest complexes between TCP44 and guest 7 in acidic D_2O.[9] Only the methyl signals are shown.

In both of the Figures the host-induced shifts ($\Delta\delta$(ppm)) are shown in the parentheses.

References and Notes

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3) "T" of TCP44 indicates tartaric acid, from which the chirality is derived.

4) (a) Satisfactory ^{1}H NMR and IR spectra were obtained. (b) Satisfactory elemental analyses (C, H, N) were obtained. (c) Molecular ions were observed in low resolution mass spectra. (d) Molecular ions were observed in field desorption mass spectra.

5) F. E. Ray and L. Soffer, *J. Org. Chem.*, **15**, 1037-1042 (1950).

6) (a) Th. Posternak and J.-Ph. Susz, *Helv. Chim. Acta*, **39**, 2032-2040 (1956); $[\alpha]_D^{22.5}$ -7.90 ± 1.3° (c = 1.58, $CHCl_3$). (b) A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.*, **86**, 5626-5630 (1964).

7) F. E. King, R. J. S. Beer, and S. G. Waley, *J. Chem. Soc.*, 92-94 (1946).

8) Other reaction conditions (Vitride, Al-Hg, Na-Hg, Na/NH_3, Zn/AcOH, Zn/HCl) did not give satisfactory results.

9) Measured in DCl-D_2O (pD 1.2) at ambient temperature of 28 ± 2°C with TMS (neat) as an external reference. [Host] = 5.0×10^{-2}M, [Guest] = 2.5×10^{-2}M, unless otherwise stated as in Figure 1. pD was adjusted according to P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188-190 (1960).

10) Since the system is in the NMR chemical shift fast-exchange limit, the proton signals of the guest appear at the average of the chemical shift of the free guest and the chemical shift of the guest bound in each possible orientation to the host, weighed by the fractional population of the guest molecules in each environment.

11) Predominant form at pD 1.2.

12) For NMR observation of diastereomeric host-guest complex formation by cyclodextrins in water, see: D. D. MacNicol and D. S. Rycroft, *Tetrahedron Lett.*, 2173-2176 (1977). For the related studies with crown ethers and cyclic peptides in organic solvents, see for example: D. J. Cram, *et al.*, *J. Am. Chem. Soc.*, **100**, 8190-8202 (1978), *J. Org. Chem.*, **46**, 393-406 (1981); V. Madison, C. M. Deber, and E. R. Blout, *J. Am. Chem. Soc.*, **99**, 4788-4798 (1977).

13) For asymmetric reactions by cyclodextrins in aqueous system, see for example: (a) R. Breslow and A. W. Czarnik, *J. Am. Chem. Soc.*, **105**, 1390-1391 (1983); (b) R. Breslow, G. Trainor, and A. Ueno, *ibid.*, **105**, 2739-2744 (1983).

14) The authors warmly thank Sumitomo Chemical Co., Ltd. for the measurement of field desorption mass spectra.

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