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SUBSTRATE SELECTIVE INCLUSION BY A SERIES OF WATER-SOLUBLE PARACYCLOPHANES

—— HOST-GUEST RECOGNITION OF STERIC STRUCTURE AND CHARGE ——

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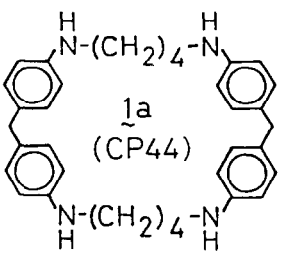
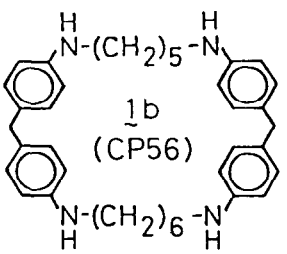
Abstract: Substrate selective complex formation was observed between a series of water-soluble paracyclophanes (1a,b,2) and organic guests in acidic aqueous solutions, and this selectivity was shown to be based upon the host-guest recognition of steric structure and charge.

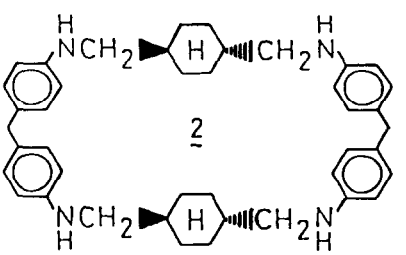
Substrate selective inclusion by host molecules such as enzymes, antibodies and receptors, which is the initial step in many important biological reactions, is one of the significant bases for the extremely high efficiencies that are widely observed in these reactions. Considering that the selectivity in substrate inclusion is mainly based upon the well-defined structure of the inclusion cavities of these biological host molecules,[1] it is worthwhile to systematically study substrate selective inclusion of organic guest molecules by artificial host compounds having an inclusion cavity of definite structure.

We have recently reported that a novel water-soluble paracyclophane, CP44,[2a,3] forms 1:1 inclusion complexes of particular geometry with organic guest molecules,[2b] and that modification of the cavity of CP44 results in a marked change of complexing ability.[2c] These results strongly suggest the formation of inclusion cavities of definite structure, which made us to expect substrate selective inclusion by this type of paracyclophanes. In this paper we describe the first systematic study[4] of substrate selective inclusion exhibited by a series of water-soluble paracyclophanes in aqueous solutions.

The hosts examined are 1a (CP44), 1b (CP56) and 2, having cavities of different size and/or hydrophobic area.[5] Complex formations between these hosts and the guests having a variety of steric structure and charge were measured quantitatively by fluorescence or qualitatively by ^{1}H NMR in acidic aqueous solutions.[3] The following results were obtained, showing interesting features exhibited by these host compounds.







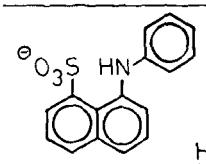
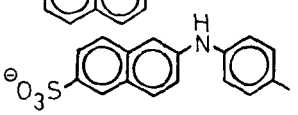
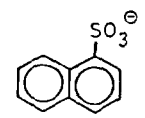
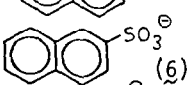
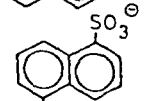
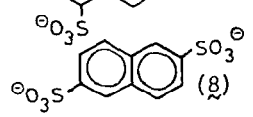
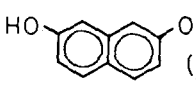
(1) As shown in Table 1 all the three hosts formed strong complexes with the anionic guests having a naphthalene ring (3 ~ 8: $K_S > 10^3\ M^{-1}$). Weaker, but relatively strong complex formation[6] was observed for the anionic guests having a benzene ring (10,11). On the contrary only weak complex formation was observed for the anionic guests having a quite different structure from the aromatic guests (12,13).[7]

(2) As for the guests having a naphthalene ring, CP44 showed selectivity for the β-substituted naphthalenes (4,6,8,9), whereas CP56 and 2 showed selectivity for the α-substituted naphthalenes (3,5,7).

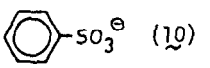
(3) Host 2 formed stronger complexes than CP56 by a factor of 10 to 17 with all the guests examined.

(4) All the three hosts formed stronger complexes with the dianion guests (7,8) than with the corresponding monoanion guests (5,6). Furthermore only weak complex formation was observed for the aromatic guests having positive charge(s) (14,15).[8]

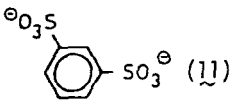
Table 1 Stability constants (K_S [M^{-1}]) of the 1:1 host-guest complexes[a]

Guest	CP44[b]	CP56[b]	2[b]
 ANS (3)	6.3 x 10^3 (0.15)[c]	4.3 x 10^4 (1.0)	5.0 x 10^5 (12)
 TNS (4)	9.6 x 10^4 (2.7)	3.5 x 10^4 (1.0)	—
 (5)	1.5 x 10^3 (0.39)	3.8 x 10^3 (1.0)	5.3 x 10^4 (14)
 (6)	1.9 x 10^4 (6.4)	2.9 x 10^3 (1.0)	3.0 x 10^4 (10)
 (7)	4.4 x 10^3 (0.041)	1.1 x 10^5 (1.0)	1.4 x 10^6 (13)
 (8)	1.8 x 10^5 (5.5)	3.3 x 10^4 (1.0)	3.2 x 10^5 (9.6)
 (9)	2.8 x 10^3 (11)	2.6 x 10^2 (1.0)	4.3 x 10^3 (17)

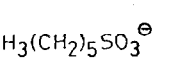
(a) Determined by the competitive inhibition method using 3 or 4 as fluorescence probe. KCl-HCl buffer (pH 1.95); 25.0 ± 0.1°C; excited at 375 nm; measured at 505 nm (3) or 495 nm (4).
(b) Protonated form under the acidic condition.
(c) The values in the parentheses are the relative stabilities of the complexes of CP44 or 2 compared with those of CP56, i.e., K_S (CP44 or 2) / K_S (CP56) for each guest.

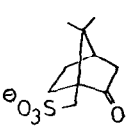
 (10)

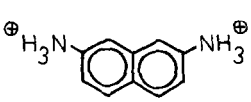
$K_S = 7.4 \times 10^2\ M^{-1}$ (CP44)

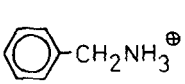
 (11)

$K_S = 9.4 \times 10^2\ M^{-1}$ (CP44)

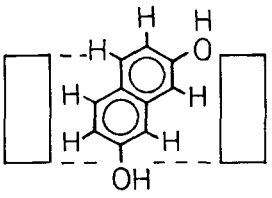
 (12)

 (13)

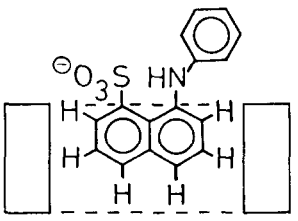
 (14)

 (15)

The previous X-ray study (CP44·4HCl-durene complex)[2a] shows the formation of an inclusion cavity having rectangularly shaped open ends (3.5 x 7.9 Å). The shorter width (3.5 Å) is very close to the thickness of an aromatic ring, and this fitness may explain the aromatic selectivity described in (1) (3 ~ 11 vs. 12,13).[9,10] In addition the previous studies on the bases of ^{1}H NMR[2b] and host modification[2c] suggest that the small cavity of CP44 includes a naphthalene ring in pseudoaxial geometry, and that the large cavities of CP56 and 2 include it in equatorial geometry (Figure 1). These may cause, from steric effects, CP44 to prefer β-substituted naphthalenes and CP56 and 2 to prefer α-substituted naphthalenes. Thus the α- and β-selectivities described in (2) may be explained. The previous study[2c] also show that the complex formation of host 2 with 3 is an order of magnitude stronger than that of CP56, and the same tendency is observed in the present study for all the guests examined as described in (3). Considering that the both hosts would have a cavity of similar size, the stronger complex formation by host 2 may be explained by the larger hydrophobic area of its cavity that brings about the better fitness with the guests.[11]



"Pseudoaxial" inclusion by CP44



"Equatorial" inclusion by CP56 or 2

Figure 1

Thus all the observations described in (1) ~ (3) are consistent with the previous studies,[2] and it is therefore reasonable to conclude that fitness of steric structure is one of the important factors for a strong complex formation by this type of paracyclophanes.[12a] On the other hand the observations in (4) clearly indicate that electrostatic interaction (with the positively charged hosts) is another important factor for a strong complex formation.[12b] Furthermore either factor alone is not sufficient as exemplified by the very weak complex formation of CP44 with 12, 13, 14 and 15; both these factors must be satisfied to form a strong complex. Thus substrate selective inclusion based upon the host-guest recognition of steric structure and charge (multiple recognition)[13] is successfully exhibited in a predictable manner by this type of paracyclophanes in aqueous solutions.

Considering in addition that the recognition of steric structure by this system is remarkably strict[14] as exemplified by the selectivity of CP44 for the β-substituted naphthalenes over the benzenes (9 vs. 10,11,12,13; 6 vs. 7,11),[15] chemical modifications of these hosts may afford an effective system for strict discrimination between the organic guests having slightly different steric and/or electronic structures.

References and Notes

1) See for example: G. E. Schulz and R. H. Schirmer, "Principles of Protein Structure", Springer-Verlag, 1979, Chapters 10 and 11.

2) (a) K. Odashima, A. Itai, Y. Iitaka and K. Koga, J. Am. Chem. Soc., 102, 2504 (1980);

(b) K. Odashima, A. Itai, Y. Iitaka, Y. Arata and K. Koga, Tetrahedron Lett., 21, 4347 (1980); (c) T. Soga, K. Odashima and K. Koga, ibid., 21, 4351 (1980).

3) This type of paracyclophanes is soluble in water as amine salts below pH 2.

4) For the studies of water-soluble paracyclophanes showing some tendency of substrate selective complex formation, see: (a) Y. Murakami, J. Sunamoto, H. Okamoto and K. Kawanami, Bull. Chem. Soc. Jpn., 48, 1537 (1975); (b) I. Tabushi, Y. Kimura and K. Yamamura, J. Am. Chem. Soc., 100, 1304 (1978).

5) The design, synthesis and characterization of these hosts are described in refs. 2a or 2c.

6) Comparable with the complexes between 3 and other water-soluble paracyclophanes. (a) I. Tabushi, Y. Kuroda and Y. Kimura, Tetrahedron Lett., 3327 (1976), $K_S = 5.5 \times 10^2 M^{-1}$; (b) I. Tabushi, H. Sasaki and Y. Kuroda, J. Am. Chem. Soc., 98, 5727 (1976), $K_S = 1.6 \times 10^3 M^{-1}$.

7) Decrease of the fluorescence intensity of 3 - CP44 (or CP56) mixture on an addition of 12 or 13 was too small (within experimental error) to determine accurate stability constant.

8) Chemical shift changes ($\Delta\delta$) of the proton signals of 14 and 15 induced by CP44 were only 0.3 ppm at most, whereas those of a neutral guest 9 were 1.90 and 1.75 ppm for H-1 and H-4, respectively.[2b] The experimental conditions were as described in ref. 2b.

9) The stronger complex formation of CP44 with the naphthalenes (3 ~ 9) than with the benzenes (10,11) may also be explained on the basis of the X-ray study[2a] since, considering from the longer width (7.9 Å) of the open ends, the cavity is somewhat too large for a benzene ring.

10) This type of selectivity is not observed in cycloamyloses which show relatively strong complexing ability ($K_S > 10^2 M^{-1}$) to the whole range of organic guests. See: M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry", Springer-Verlag, Berlin, 1978.

11) Comparing with the cavity of host 2 which have cyclohexane rings, the cavities of CP44 and CP56 may be "partly too shallow" for inclusion of an aromatic ring because of the bridging methylene chains.

12) There are some other studies of water-soluble paracyclophanes whose complexing properties may be explained on the basis of either factor. (a) References 4a and b; (b) Reference 6a.

13) Charge transfer interaction may be another important factor for the complex formation by aromatic hosts like these. But we have not obtained an evidence that strongly supports its participation. K. Odashima, T. Soga, K. Matsuo and K. Koga, unpublished results.

14) Some predictable tendencies of the recognition of steric structure are observed in other multiple recognition systems. (a) I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka and K. Yamamura, J. Am. Chem. Soc., 99, 7100 (1977); (b) Y. Matsui and A. Okimoto, Bull. Chem. Soc. Jpn., 51, 3030 (1978); (c) J. Boger, D. G. Brenner and J. R. Knowles, J. Am. Chem. Soc., 101, 7630 (1979); J. Boger and J. R. Knowles, ibid., 101, 7631 (1979); (d) B. Dietrich, M. W. Hosseini, J. M. Lehn and R. B. Sessions, ibid., 103, 1282 (1981); (e) E. Kimura, A. Sakonaka, T. Yatsunami and M. Kodama, ibid., 103, 3041 (1981).

15) In these cases the better fitness of steric structure predominates over the more favorable electrostatic interaction.

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