Synthesis of Novel Water-soluble Molecular Bowls and Their Unique Complexing Behavior with 1-Anilinonaphthalene-8-sulfonate

Kei Goto, Shigehisa Akine, Tomoko Hayashi, and Renji Okazaki*
Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113

(Received December 1, 1997; CL-970904)

Novel water-soluble bowl-shaped cyclophanes **1** and **2** were synthesized. Complexation study in 25% aqueous methanol revealed that **1** and **2** form 2:1 (host/guest) complexes with 1-anilinonaphthalene-8-sulfonate (ANS). The emission wavelength of ANS encapsulated by **1** and **2** as well as the related monocyclic cyclophanes was usefully employed to demonstrate that the host/guest ratio of the complex significantly affects the micropolarity of the guest-binding site of these cyclophanes.

In the active site of enzymes, the catalytic functionality is usually embedded in the hydrophobic cavity or cleft.[1] It is well-recognized that such an apolar microenvironment around the functionality leads to the unique features of the enzymatic reactions. We have been investigating on the synthesis and application of the bowl-shaped molecules with an intracavity functionality, which we refer to as *"reaction bowls"* (Figure 1).[2] It is expected that their water-soluble derivatives will provide a novel type of hydrophobic reaction environment having the above-mentioned geometrical features of the active site of enzymes. Furthermore, their properties as a host molecule are also of interest because there have been only a few examples of water-soluble host compounds bearing a bowl-shaped structure except cyclodextrins.[3,4] Here we report the synthesis and unique complexing behavior of the water-soluble *reaction bowls* **1** and **2**. The estimation of the hydrophobicity of their guest-binding sites is also delineated.

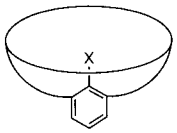
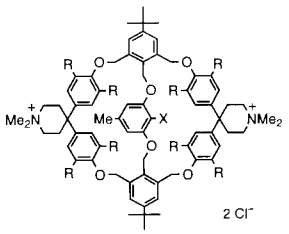


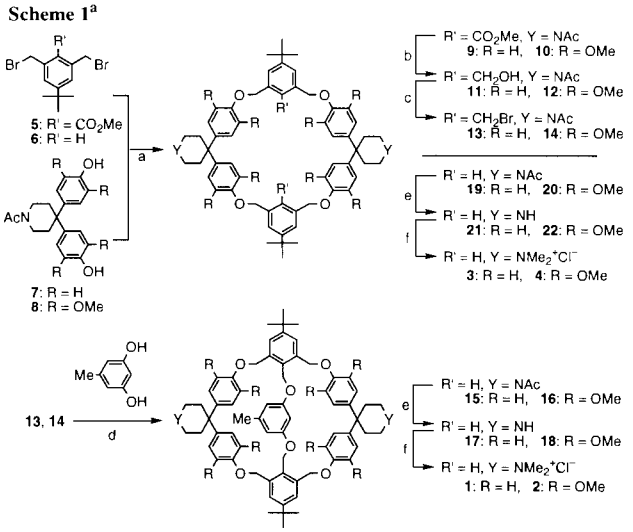
Figure 1. Schematic drawing of a *"reaction bowl"*.



1: R = H, X = H
2: R = OMe, X = H

Compounds **1** and **2** were designed as the water-soluble analogs of the bowl-shaped bimacrocyclic cyclophane we reported previously.[2b] In these molecules, the ionic centers providing water-solubility are located in the peripheral positions remote from the cavity so that the hydrophobic character of the cavity and the properties of the intracavity functionality are not perturbed by strongly hydrated charge centers.[5] Cyclophanes **1** and **2** were synthesized by the initial construction of the outer macrocycle followed by bridging with orcinol and subsequent transformation for water-solubilization (Scheme 1).[6,7] Monocyclic cyclophanes **3** and **4** were similarly prepared as the reference compounds. It was found that the octamethoxy derivatives **2** and **4** have higher critical micelle concentrations (CMCs)[8] than the unsubstituted compounds **1** and **3**.[9]

Scheme 1[a]



[a] Reagent: (a) Cs_2CO_3, DMF, r.t., **9**: 28%, **10**: 25%, **19**: 18%, **20**: 22%; (b) $LiEt_3BH$, THF, r.t., then CH_3COCl, K_2CO_3, $CHCl_3$, r.t., **11**: 79%, **12**: 70%; (c) PBr_3, 1,4-dioxane, 60 °C, **13**: 94%, **14**: 80%; (d) K_2CO_3, DMF, r.t., **15**: 85%, **16**: 56%; (e) $LiEt_3BH$, THF, r.t., **17**: 88%, **18**: 66%, **21**: 93%, **22**: 63%; (f) CH_3I, K_2CO_3, acetone, then Dowex® 1X8-400 (Cl^-), **1**: 73%, **2**: quant, **3**: 80%, **4**: 91%.

The complexing behavior of cyclophanes **1**, **2**, **3**, and **4** was investigated by using 1-anilinonaphthalene-8-sulfonate (ANS)[10] as a guest compound in 25% aqueous methanol in concentration below the CMCs. The fluorescence intensity of ANS was markedly enhanced in the presence of the host molecules, and non-linear least square analysis of the titration curves indicated the formation of 2:1 (host/guest) complexes for **1**, **2**, and **4** and a 1:1 complex for **3**. The calculated association constants are shown in Table 1, which indicates high complexing ability of these cyclophanes. The behavior of **1**, **2**, and **4** is of note because formation of a 2:1 complex between a cyclophane host and an organic substrate in aqueous solution is quite unusual. Whereas guest-encapsulation by a hydrogen-bonded dimer of self-complementary molecules in apolar solvents has been recently attracting much attention,[11] 2:1 complexation by the hydrophobic interaction has been found only in some cyclodextrin complexes.[12] The CPK model examinations indicate that the shallow bowl-shaped structure of the bicyclic cyclophanes **1** and **2** prevent full inclusion of the guest molecule, ANS, whereas their capsule-shaped dimers can readily encapsulate it. It is of interest that the octamethoxy-substituted monocyclic cyclophane **4** also forms a 2:1 complex although the unsubstituted **3** undergoes more common 1:1 complexation. These results can be explained by assuming that in the case of **4** partial inclusion of the guest molecule from one side of the cavity changes the shape of the cyclophane to the cone-like structure and the methoxyl groups on the other side prevent the guest molecule from slipping into the cavity. This situation is similar to those of

1 and **2**. On the other hand, the guest molecule can penetrate through the cavity of cyclophane **3** without methoxyl groups, resulting in 1:1 complexation.

Table 1. Association constants[a] and maximum emission wavelengths of the complexes between cyclophanes and ANS in 25% aqueous methanol at 27 °C

	compound	host/guest	K_a	wavelength
1	bicyclic (R = H, X = H)	2:1	6.4×10^9 M^{-2}	478 nm
3	monocyclic (R = H)	1:1	4.7×10^4 M^{-1}	494 nm
2	bicyclic (R = OMe, X = H)	2:1	4.5×10^7 M^{-2}	474 nm
4	monocyclic (R = OMe)	2:1	1.5×10^7 M^{-2}	474 nm
	none			517 nm

[a]Determined by fluorometric titrations.

The emission wavelength of ANS has been usefully employed to estimate the micropolarity of the binding sites of various host compounds such as water-soluble cyclophanes[10c] and cyclodextrins[10d] as well as enzymes.[13] The measurements on the complexes between ANS and cyclophanes **1**, **2**, **3**, and **4** revealed that the host/guest ratio of the complex significantly affects the hydrophobicity of the guest-binding site of these cyclophanes. Figure 2 shows the relationship between the maximum emission wavelengths in various solvents and the empirical polarity scale *Z*.[14,15] In the absence of the host molecule, the wavelength of 517 nm was observed in 25% aqueous methanol. Addition of cyclophanes **1**, **2**, **3**, and **4** caused strong blue shifts as shown in Table 1 and Figure 2(A). Particularly noteworthy is that compounds **1**, **2**, and **4**, which form a 2:1 complex with ANS, showed a remarkable blue shift of ca. 40 nm, twice as large a value as that observed for compound **3** which exhibits 1:1 complexation. The micropolarities of the binding sites of these cyclophanes are estimated to be nearly equal to 75% aqueous methanol for **3** and to methanol or ethanol for **1**, **2**, and **4**, respectively. These results suggest that in the 2:1 complexes the closed shell formed by two molecules of the cyclophane encapsulates ANS as schematically depicted in Figure 2(B), thus providing a strongly hydrophobic microenvironment for it, whereas in the 1:1 complex a larger part of the guest molecule is exposed to the polar bulk phase.

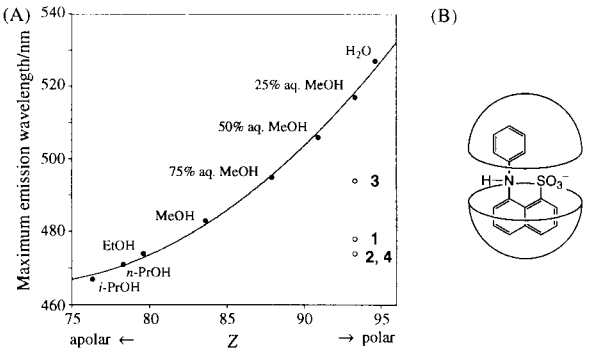


Figure 2. (A) Maximum emission wavelength of ANS in various solvents (solid circles) related to the empirical polarity scale, *Z*, and that in the presence of **1**, **2**, **3**, and **4** in 25% aqueous methanol (open circles). The excitation wavelength is 375 nm. (B) Schematic drawing of the 2:1 complex.

In summary, novel water-soluble bimacrocyclic cyclophanes were synthesized and found to make 2:1 complexation with ANS. It is probable that their shallow bowl-shaped structure, which is suitable for the formation of the capsule-shaped dimer, led to their unique complexing behavior. Further investigations on the introduction of a variety of intracavity functional groups and the estimation of the micropolarity around the functionality are currently in progress.

This work was partly supported by Grants-in-Aid for Scientific Research (No. 08454197 and 08740487) from the Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

1 D. M. Blow, *Acc. Chem. Res.*, **9**, 145 (1976).
2 a) K. Goto, N. Tokitoh, M. Goto, and R. Okazaki, *Tetrahedron Lett.*, **34**, 5605 (1993); b) K. Goto, N. Tokitoh, and R. Okazaki, *Angew. Chem., Int. Ed. Engl.*, **34**, 1124 (1995); c) K. Goto and R. Okazaki, *Liebigs Ann./Recueil*, **1997**, 2393 and references therein.
3 a) F. Diederich, "Cyclophanes," ed by J. F. Stoddart, The Royal Society of Chemistry, Cambridge (1991); b) F. Diederich, *Angew. Chem., Int. Ed. Engl.*, **27**, 362 (1988) and references therein; c) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Org. Chem.*, **50**, 4478 (1985); d) F. Vögtle, "Molecular Recognition: Receptors for Molecular Guests" in "Comprehensive Supramolecular Chemistry," ed by J.-M. Lehn, Pergamon, (1996), Vol 2.
4 Although there are a number of reports on water-soluble calixarenes which have a suitable size for organic guest inclusion (n ≥ 6), their conformations were not thoroughly studied. See ref. 3d.
5 a) F. Diederich and K. Dick, *J. Am. Chem. Soc.*, **106**, 8024 (1984); b) F. Diederich, K. Dick, and D. Griebel, *Chem. Ber.*, **118**, 3588 (1985).
6 For the synthesis of **5**, a) F. J. Urban, L. R. Chappel, A. E. Girard, B. L. Mylari, and I. J. Pimblett, *J. Med. Chem.*, **33**, 765 (1990); for **6**, b) M. Tashiro and T. Yamato, *J. Org. Chem.*, **46**, 1543 (1981); for **7**, ref. 5b; for **8**, c) D. R. Benson, R. Valentekovich, C. B. Knobler, and F. Diederich, *Tetrahedron*, **47**, 2401 (1991); and for cyclophanes related to **9** and **10**, d) K. Glow, H. Stephan, O. Heitzsch, H. Bukowsky, E. Uhlemann, R. Pollex, and E. Weber, *J. Chem. Soc., Chem. Commun.* **1994**, 1955.
7 ^{1}H NMR and HRMS data were consistent with cyclophanes **1** and **2**. Analytical data showed that these compounds were hexahydrate.
8 The critical micelle concentrations (CMCs) in 25% aqueous methanol were determined by the light scattering method as follows: **1** (1.3×10^{-5} M), **2** (3.2×10^{-4} M), **3** (1.6×10^{-5} M), and **4** (2.9×10^{-4} M).
9 S. B. Ferguson, E. M. Seward, F. Diederich, E. M. Sanford, A. Chou, P. Inocenicio-Szweda, and C. B. Knobler, *J. Org. Chem.*, **53**, 5593 (1988).
10 For examples of the use of 1,8-ANS and similar fluorescence probes as a guest molecule, see: a) I. Tabushi, H. Sasaki, and Y. Kuroda, *J. Am. Chem. Soc.*, **98**, 5727 (1976); b) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Am. Chem. Soc.*, **102**, 2504 (1980); c) Y. Murakami and J. Kikuchi, *Pure Appl. Chem.*, **60**, 549 (1988); and for cyclodextrins: d) F. Cramer, W. Saenger, and H.-C. Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967).
11 For reviews, see: a) J. Rebek, Jr., *Acta Chem. Scand.* **50**, 707 (1996); b) J. Rebek, Jr. *Chem. Soc. Rev.*, **1996**, 255.
12 a) H. Kondo, H. Nakatani, and K. Hiromi, *J. Biochem.*, **79**, 393 (1976); b) F. V. Bright and G. C. Catena, *Anal. Chem.*, **61**, 905 (1989).
13 a) L. Stryer, *J. Mol. Biol.*, **13**, 482 (1965); b) W. O. McClure and G. M. Edelman, *Biochemistry*, **5**, 1908 (1966); c) D. C. Turner and L. Brand, *Biochemistry*, **7**, 3381 (1968).
14 a) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958); b) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3261 (1958); c) E. M. Kosower, *J. Am. Chem. Soc.*, **80**, 3267 (1958).
15 We used maximum emission wavelengths of ANS measured under the same conditions as those for the measurement in the presence of the cyclophanes.