8,16,24,32-Tetramethoxy[2.2.2.2]metacyclophane-1,9,17,25-tetrayne: A Novel Ionophore Having a Preorganized but Unexpectedly Flexible Cavity

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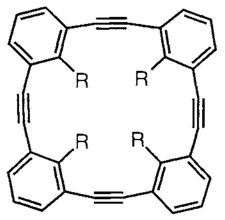
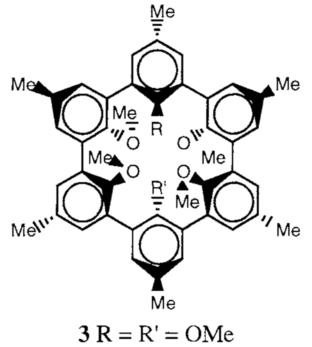
The title cyclophane has a preorganized cavity with about 1.2 Å in diameter surrounded by four oxygen atoms (X-ray analysis); however, solvent extraction experiments using alkali metal picrates revealed the unexpectedly flexible nature of the cavity that forms 1:1 complexes with various alkali metal ions with considerably large association constants.

Phenylacetylene or -diacetylene macrocycles have attracted increasing attention from both physicochemical and supramolecular points of view. Perspective of such macrocycles from the latter point seems promising because their structures are finely tunable either by modifying the ring size and shape or by introducing substituents onto the periphery or interior of their frameworks. Actually, the appropriately functionalized macrocycles have exhibited novel self-organization properties owing to π–π stacking interactions[1] and host properties toward molecular guests.[2]

As a part of our studies on strained phenylacetylene macrocycles,[3,4] we have recently reported the synthesis of moderately strained [2.$_4$]metacyclophanetetrayne **2**. Introduction of methoxy groups as substitutents inside its framework as shown as **1** would form a preorganized cavity with oxygen functionality. The tetrayne **1**, composed of four anisyl and acetylene units, can be regarded as a kind of extended spherands.[5,2c] The original spherand **3**, composed of six anisyl units, have been reported to show extremely strong binding ability toward Li$^+$ ion.[5] We here report the synthesis, structure, and host properties of **1**.



1 R = OMe
2 R = H



3 R = R' = OMe
6 R = H, R' = OMe
8 R = R' = H

The tetrayne **2** was synthesized by bromination-dehydrobromination of the corresponding metacyclophanetetraenes.[3] A similar procedure turned out to be also successful for the synthesis of **1**. The McMurry coupling (TiCl$_4$-Zn in THF) of 2,2'-dimethoxy-3,3'-diformyl-Z-stilbene **4**,[6] prepared from 2,2'-dimethoxy-Z-stilbene[7] through lithiation (*n*-BuLi-TMEDA) and formylation (DMF), afforded a mixture of cyclic dimers (26%) from which the *E,Z,E,Z*-tetraene **5** separated out as crystals in 19% yield. The structure of **5** was deduced from the spectral data and confirmed by the X-ray analysis.[6] Bromination of **5** with 6 equivalents of Br$_2$ in chloroform and subsequent dehydrobromination of the crude octabromide with 10 equivalents of *t*-BuOK in ether gave the desired tetrayne **1**[8] as a stable crystalline substance in 62% yield.

The ^{1}H and ^{13}C NMR spectra **1** are simple in agreement with the high symmetry of the molecule. The sp carbons (δ 93.17) resonate at slightly lower magnetic field than those of **2** (δ 92.20). The Raman frequency of the triple bonds (2197 cm^{-1}) is also observed at lower wave number than that of **2** (2202 cm^{-1}). These observations suggest that the strain of the bent triple bonds of **1** is slightly higher than that of **2**.

A prismatic single crystal of **1** suitable for X-ray crystallographic analysis was obtained from a benzene solution, and the molecular structure is shown in Figure 1.[9] The molecule has *Ci* symmetry in the crystal and is nonplanar unlike the almost planar **2**: while benzene rings A and C lie in the same plane formed by the four triple bonds, the other benzene rings B and D are twisted by 42° out of the plane. The methyl groups of A and D rings turn upward, and the other two downward. The triple bonds of **1** (av. 166.9°) are slightly more bent than those of **2** (av. 168.8°) in consonance with the spectral observations. The increase of strain of the molecule is probably due to steric and electronic repulsion

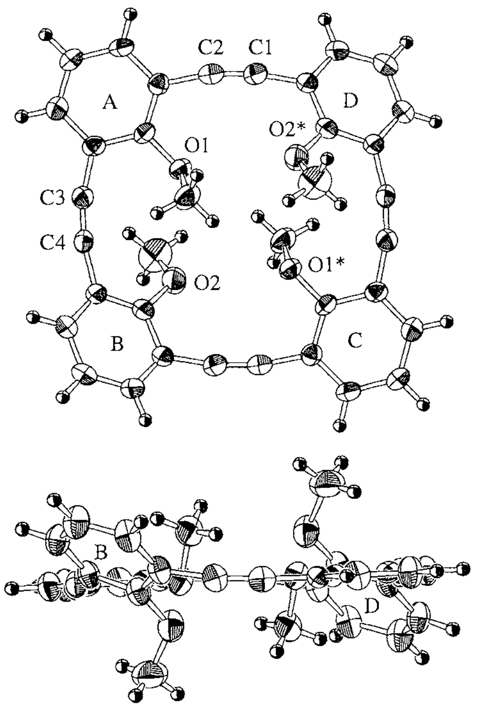


Figure 1. ORTEP drawing of **1** (50% probability): Selected bond lengths (Å): C1-C2, 1.191 (5); C3-C4, 1.182 (5). Selected distances (Å): O1···O2, 3.4; O1···O2*, 3.4: O1···O1*, 4.0; O2···O2*, 5.5.

among the methoxy groups. In this conformation, an adjacent and two sets of the opposite O-to-O distances (Figure 1) are longer than the normal van der Waals distance of 2.8 Å.

The X-ray results show that **1** has an enforced and organized cavity with 1.2 Å in diameter surrounded by four oxygen atoms of the methoxy groups. A cavity of this size would be suitable for selective encapsulation of Li^+ (diameter: 1.36 Å).[10] However, preliminary solvent extraction experiments with alkali metal picrates (PicM: M = Li^+, Na^+, K^+, Rb^+, Cs^+) indicate that **1** behaves as a good ionophore not only for Li^+ but also for other alkali metal ions except Cs^+. The plots by Shono's method show straight lines with slopes of approximately unity to suggest the formation of 1:1 complex between **1** and each metal ion in solution (Figure 2).[11,12] The values of association constants $\log K_a$ calculated from the intercepts are listed in Table 1 together with the those of **3**, a diminished spherand **6**,[13] and 18-crown-6 **7**.[14] The data reveals remarkable and unexpected features of **1** as an ionophore: (i) the log K_a values are considerably large regardless of size from Li^+ to Rb^+ (2.96 Å); (ii) this is in contrast to the high selectivity of the spherands **3** and **6**, which have similar cavity sizes, toward Li^+ and Na^+; (iii) in spite of the poorer selectivity, **1** has hundreds times selectivity for Na^+ and K^+ than for Li^+ and the $\log K_a$ value for K^+ is comparable to those of **7**.

According to the Cram's work, anisyl units are intrinsically poor ligands for metal ions. The exceptionally strong binding ability of spherand **3** has been ascribed to its enforced and preorganized cavity. The host ability of spherands decreases sharply with decrease in the number of ligating sites of the host: a bis-demethoxy spherand **8**[13], still having four methoxy groups in the cavity, exhibits poor ionophoric properties in spite of rather small structural change. Most of other ionophores[15] having four anisyl units as binding sites, such as calix[4]arene methyl ether and the nonplanar tetraene **5**, are also poor ionophores. Thus, the tetraene **1** is very different from other related hosts in the unusually high binding ability to alkali metal ions. This may be because **1** is conformationally flexible enough for embedding metal ions fairly tightly in spite of its small, well preorganized cavity in the X-ray structure.

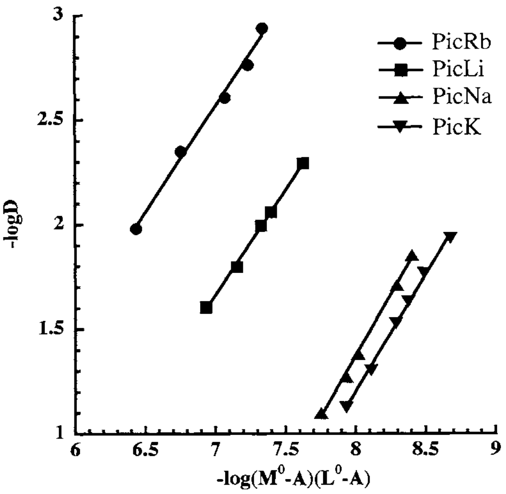


Figure 2. Plots of - logD vs. -log(M^0 - A)(L^0 - A) for **1**. M^0, L^0 : Initial concentrations of alkali metal and ligand. D : Distribution ratio. A : Picrate concentrations.

Table 1. Association constants ($\log K_a$) of **1** and related compounds with alkali metal ions

Ions / hosts	1	3	6	7
Li^+	8.23	>16.84	7.61	5.03
Na^+	10.44	14.15	4.83	6.11
K^+	10.59	–	–	>11
Rb^+	6.85	–	–	10.57

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References and Notes

1 a) J. Zhang and J. S. Moore, *J. Am. Chem. Soc.*, **114**, 9701 (1992). b) A. S. Shetty, J. Zhang, and J. S. Moore, *J. Am. Chem. Soc.*, **116**, 2655 (1994); c) J. Zhang and J. S. Moore, *J. Am. Chem. Soc.*, **118**, 1019 (1996). d) Y. Tobe, N. Utsumi, K. Kawabata, and N. Naemura, *Tetrahedron. Lett.*, **37**, 9325 (1997).

2 a) S. Höger and V. Enkelman, *Angew. Chem., Int. Ed Engl.*, **34**, 2713 (1995); D. L. Morrison, and S. Höger, *Chem. Commun.*, **1996**, 2313; c) Y. Tobe, N. Utsumi, A. Nagano, and K. Naemura, *Angew. Chem., Int. Ed. Engl.*, **37**, 1285 (1998)

3 T. Kawase, N. Ueda, H. R. Darabi, and M. Oda, *Angew. Chem. Int. Ed Engl.*, **35**, 1556 (1996).

4 T. Kawase, N. Ueda, and M. Oda, *Tetrahedron. Lett.*, **38**, 6681 (1997).

5 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, **25**, 1039 (1986), and references cited therein.

6 **4**: ^1H NMR (270 MHz, $CDCl_3$): δ 3.89 (6H, s), 6.84 (2H, s), 6.91 (2H, t, J = 7.6 Hz), 7.31 (2H, d, J = 7.6 Hz), 7.78 (2H, d, J = 7.6 Hz), 10.35 (2H, s); **5**: colorless needles, mp 318 - 320 °C; MS (FAB) m/z: 528 (M^+); ^1H NMR (400 MHz, $CDCl_3$): δ 3.29 (12H, s), 6.62 (4H, s), 6.81 (4H, s), 6.98 (4H, t, J = 7.5 Hz), 7.08 (4H, d, J = 7.5 Hz), 7.29 (4H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 60.31, 122.52, 124.97, 126.01, 128.22, 128.34, 131.32, 132.10, 156.53; Crystal Data; $C_{36}H_{32}O_4$, M = 528.65, monoclinic, space group $P2_1/a$ (#14), a = 14.608 (6), b = 12.330 (5), c = 17.299 (7) Å, β = 114.35 (3)°, V = 2838 (2)$Å^3$, Z = 4, R (Rw) = 0.054 (0.055). The details of X-ray analysis will be reported in a full paper.

7 B. K. Shankar and H. Shechter, *Tetrahedron. Lett.*, **23**, 2277 (1982).

8 **1**: colorless plates, mp >300 °C; MS (FAB) m/z: 521 (M^+ +H); ^1H NMR (400 MHz, $CDCl_3$): δ 3.96 (12H, s), 7.03 (4H, t, J = 7.8 Hz), 7.35 (8H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.93, 93.17 (sp C), 118.46, 122.89, 130.26, 166.80; UV ($CHCl_3$): λ_{max} nm (logε) 240 (4.63), 284 (4.97), 299 (5.02), 330 (4.47).

9 Crystal data for **1**: $C_{36}H_{24}O_4$, M = 520.58, monoclinic, space group $P2_1/n$ (#14), a = 12.498 (2), b = 7.891 (2), c = 14.380 (3) Å, β = 108.58(1)°, V = 1344.2 (5)$Å^3$, Z = 2, ρ_{calcd} = 1.237 gcm^{-3}, μ = 0.79 cm^{-1}, R (Rw) = 0.051 (0.053) for 1806 referections [$I > 2.0\ \sigma(I)$].

10 K. Hermansson, J. O. Thomas, and I. Olovsson, *Acta Crystallogr., Sect. B*, **B53**, 2857 (1977).

11 a) K. Kimura, T. Maeda, and T. Shono, *Talanta*, **26**, 945 (1979). b) K.E. Koenig, G. M. Lein, T. Kaneda, and D. J. Cram, *J. Am. Chem. Soc.*, **101**, 3553 (1979).

12 PicRb (y = 1.01x - 4.512, R = 0.996), PicLi (y = 1.006x - 5.382, R = 0.999), PicNa (y = 1.110x - 7.681, R = 0.998), PicK (y = 1.170x - 7.994, R = 0.999). The experiment for PicCs was difficult to be carried out because of the low binding ability for Cs^+ and the poor solubility of **1** in $CHCl_3$.

13 D. J. Cram, G. M. Lein, T. Kaneda, R. C. Helgeson, C. B. Knobler, E. Maverick, and K. N. Trueblood, *J. Am. Chem. Soc.*, **103**, 6228 (1981).

14 R. M. Izatt, K. Pawlak, J. S. Bradshow, and R. L. Bruenig, *Chem. Rev.*, **91**, 1721 (1991).

15 T. Kaneda, S. Umeda, H. Tanigawa, S. Misumi, Y. Kai, H. Horii, K. Miki, and N. Kasai, *J. Am. Chem. Soc.*, **107**, 4802 (1985); A. Ikeda and S. Shinkai, *Chem. Rev.*, **97**, 1713 (1997); Y. Okada, M. Mizutani, and J. Nishimura, *Tetrahedron Lett.*, **39**, 8467 (1998).