ORGANIC LETTERS

2002
Vol. 4, No. 22
3911−3914

A Unique Spherical Molecular Host with D_{2d} Symmetry. A Novel Intramolecular Kinetic Equilibrium in Metal Ion Complexation between Two Crown Ethers

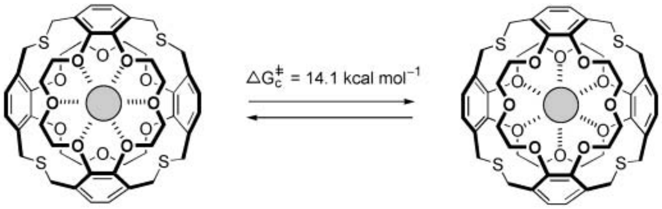
Jianwei Xu,[†,‡] Yee-Hing Lai,*,[†] and Chaobin He[‡]

Department of Chemistry, National University of Singapore, 3 Science Drive 3,
Republic of Singapore 117543, and Institute of Materials Research and Engineering,
3 Research Link, Republic of Singapore 117602

chmlaiyh@nus.edu.sg

Received August 24, 2002

ABSTRACT



A spherical host with D_{2d} symmetry consisting of a tetrathia[3.3.3.3]paracyclophane and two 18-crown-6 moieties was synthesized. Its crystal structure shows a central cavity with a diameter of 1.96 Å and a depth of 6.75 Å. A Na^+ ion could rest in the cavity center but prefers core binding to external binding in one of the crown units. An intramolecular kinetic equilibrium was reached with the Na^+ ion switching between the two crown units with an energy barrier of 14.1 ± 3 kcal/mol.

The closed-surface carcerands, which can incarcerate simple organic molecules or inorganic ions, have been extensively studied[1−4] and well documented.[5,6] Generally, a guest imprisoned by a carcerand suffers from poor communication with external species, and the confined guest cannot escape from the host unless bond breaking is involved.[6] A hemicarcerand[7] having a size-restricting portal on the surface not only holds a guest but also communicates with external ones. However, it still retains the guests firmly in its cavity. If the two cofacial, closed-surface components are crown ethers

---

[†] National University of Singapore.

[‡] Institute of Materials Research and Engineering.

(1) (a) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575. (b) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 2554.

(2) (a) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Chem. Soc. Chem. Commun.* **1990**, 1403. (b) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167. (c) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527. (d) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194.

(3) Cram, D. J. *Nature* **1992**, *356*, 29.

(4) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931.

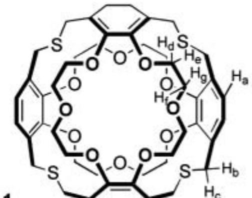
(5) Maverick, E.; Cram, D. J. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Lehn, J.-M., Eds.; Elsevier: New York, 1996; Vol. 2.

(6) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, 1994.

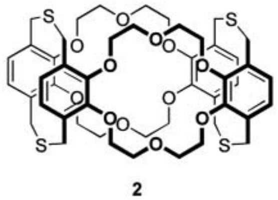
(7) (a) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717. (b) Robbins, T. A.; Knobler, C. B.; Bellew, D. R.; Cram, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 111. (c) Von dem Bussche-Hünnefeld, C.; Buehring, D.; Knobler, C. B.; Cram, D. J. *Chem. Soc. Chem. Commun.* **1995**, 1085. (d) Lutzen, A.; Hass, O.; Bruhn, T. *Tetrahedron Lett.* **2002**, *43*, 1807. (e) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95. (f) Ro, S.; Rowan, S. J.; Pease, A. R.; Cram, D. J.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 2411. (g) Warmuth, R. *J. Am. Chem. Soc.* **2001**, *123*, 6955. (h) Yoon, J.; Cram, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11796. (i) Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765. (j) Yoon, J. Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1505.

10.1021/ol026780t CCC: $22.00

and they are held by chain lengths sufficiently long to allow a window functioning as a passage for a guest, this kind of host may hold a cation firmly in its cavity and still provide the flexibility of permitting the cation to go in and out of the cavity interior. We report in this communication the model design of such a molecular host. The spherical molecular host **1** is composed of a tetrathia[3.3.3.3]-paracyclophane bridged by two 18-crown-6 units. The X-ray single-crystal determination confirms the structure of **1**, indicating that the interior cavity size is sufficiently large to accommodate a Na^+ ion. It is also demonstrated by ^1H NMR spectroscopic studies that this host can encapsulate a Na^+ ion in the interior cavity through a slow exchange between the two crown units.

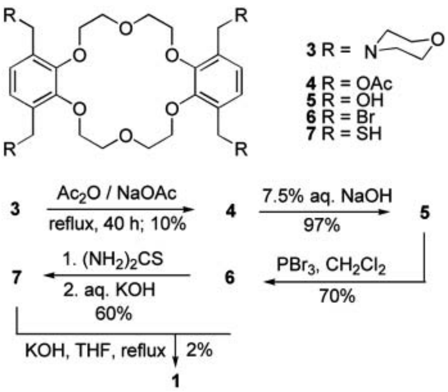


1



2

A selectively tetrasubstituted dibenzo-18-crown-6 **3** was first prepared by reacting bis(2-bromoethyl)ether with 3,6-bis(*N*-morpholinomethyl)catechol. Conversion of **3** to tetraacetate **4**[8] followed by a hydrolysis afforded tetrol **5**. Treatment of **5** with PBr_3 gave the desired tetrabromide **6**. The reaction of **6** with thiourea formed the intermediate tetrathiouronium salt, and subsequent hydrolysis of this salt yielded the tetrathiol **7**. A coupling reaction between tetrabromide **6** and tetrathiol **7** was carried out in the presence of a base under high dilution conditions.[9] A pure compound (2% yield) was isolated by column chromatography followed by preparative thin-layer chromatography. In principle, **1** and **2** could be formed from linking **6** and **7** perpendicularly and in parallel, respectively. The ^1H NMR spectrum of the isolated product shows a singlet at δ 7.07 for the aromatic protons H_a and an AB system at δ 3.44 and 3.98 ($J = 14.1$ Hz) for the bridge methylene protons H_b and H_c. Interestingly, the magnetically nonequivalent oxyethylene protons ($-OCH_dH_eCH_fH_gO-$) appear as four groups of separated signals, three of which are well-resolved, and one appears as a broad signal at δ 3.45−3.60. In its ^{13}C NMR spectrum, three signals at δ 150.54, 129.78, and 123.31, were observed for the aromatic carbon atoms, and the oxyethylene carbon atoms appeared as two singlets at δ 73.52 and 72.88. The electrospray ionization mass spectrum (ESI-MS) of the compound shows an ion at *m*/*z* 975.4 ($[M + Na]^+$) that agrees with the relative molecular mass of **1** (or **2**) combining with a Na^+ ion. The above spectral data, however, do not distinguish between the structures of **1** and **2**.



The structure of the isolated product was shown to be in agreement with **1** by an X-ray crystallographic study, and its ORTEP drawing is given in Figure 1a. The crystal was found to be associated with two water molecules occupying the packing space. The molecular structure of **1** belongs to the D_{2d} point group.[10] All aromatic rings do not significantly deviate from planarity, and the C−S bond lengths are comparable to the reported values in small dithiacyclophanes.[11] The two dibenzo-18-crown-6 units in **1** take a puckered conformation. The dihedral angles for aromatic rings are 94.0 and 127.1° for opposite and adjacent aryl rings, respectively. The space-filling drawing of **1** as shown in Figure 1b illustrates the somewhat spherical nature of this molecule with an enclosed cavity capped by the two 18-crown-6 units. The diameter[12] of each of the crown ethers was estimated to be 1.96 Å, and the depth[13] of the central molecular cavity was estimated to be 6.75 Å.

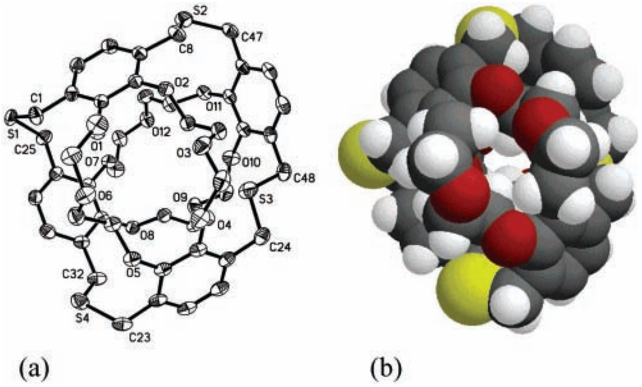


Figure 1. (a) ORTEP drawing and (b) space-filling drawing of **1**.

The ^1H NMR spectra (Figure 2) of **1** upon addition of potassium, sodium, and lithium picrate were examined in 2:1 v/v $CD_3CN/CDCl_3$. The spectra of **1** upon addition of

---

[8] A major byproduct, 1,5-bis(2-acetoxy-6-acetoxymethylphenoxy)-3-oxa-pentane, was also isolated.

[9] Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1.

[10] In addition to the C_2 and S_4 axes joining the centers of the two crown rings, there are two additional C_2' axes each joining two diagonal sulfur atoms that are perpendicular to the C_2 axis and two dihedral planes (σ_d) that lie between the C_2' axes. Thus, this molecule belongs to the D_{2d} point group.

[11] Anker, W.; Bushnell, G. W.; Mitchell, R. H. *Can. J. Chem.* **1979**, *57*, 3080.

[12] This was estimated by averaging the difference of all diagonal distances of oxygen atoms and the van der Waals diameter of an oxygen atom (2.8 Å).

[13] This was estimated by measuring the distance between the centers of the two crown rings.

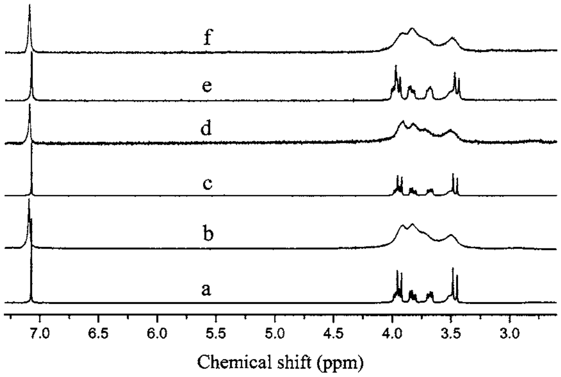


Figure 2. ^{1}H NMR (400 MHz) spectra of (a) free **1** and upon subsequent addition of (b) Na^+, (c) K^+, (d) K^+ followed by Na^+, (e) Li^+, and (f) Li^+ followed by Na^+ (1:2 v/v $CDCl_3/CD_3CN$; 300 K; [**1**] = 1.4×10^{-3} mol/dm^3; [metal picrate] = 7×10^{-3} mol/dm^3.

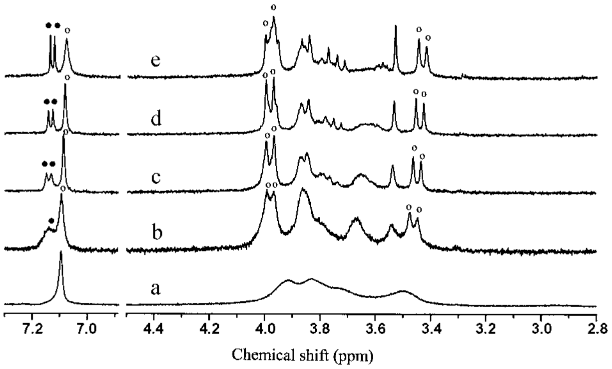


Figure 3. ^{1}H NMR (500 MHz) spectra of **1** upon addition of Na^+ ion in 1:2 v/v $CDCl_3/CD_3CN$ at (a) 300 K, (b) 273 K, (c) 263 K, (d) 253 K, and (e) 243 K ([**1**] = 1.4×10^{-3} mol/dm^3; [sodium picrate] = 7×10^{-3} mol/dm^3; (●) complexed signals, (○) uncomplexed signals).

K^+ or Li^+ ion did not suffer any significant change. The spectrum of **1** upon addition of Na^+ ion, however, exhibited severe broadening in the aliphatic region where two doublets (CH_2S) and four groups of multiplets (OCH_2) overlapped significantly and lost all distinct splitting patterns observed in the spectrum of free **1**. The ^{1}H NMR spectra of **1** upon addition of K^+ or Li^+ ion, followed by Na^+ ion, showed the same spectral characteristics as that of **1** in the presence of only Na^+ ion. Accordingly, this competitive complexation experiment indicates that host **1** has a stronger preference to binding Na^+ ion than K^+ or Li^+ ion. We believe the significant broadening in the aliphatic proton signals is due to some kind of slow exchange processes between **1** and Na^+ ion on the NMR time scale at room temperature. In some pseudorotaxane systems, broad signals in their ^{1}H NMR spectra at room temperature were also observed as a result of slow exchange rates between host and guest.[14]

To further investigate the complexation behavior of the spherical host **1** and Na^+ ion, dynamic ^{1}H NMR spectra were determined from 300 to 243 K (Figure 3). At 300 K, the aromatic protons were observed as a broad singlet at δ 7.10 that was partially resolved into two broad signals at 273 K. Further cooling to 243 K resulted in “a pair” of singlets at δ 7.12 and 7.14 and a relatively broader singlet at δ 7.07. The above observation is qualitatively consistent with two successive exchange processes between the host (**1**) and guest (Na^+). The “pair” of singlets (at 243 K) is assigned to aromatic protons of complexed host **1** and the broad singlet to those of uncomplexed **1**. This is also supported by a constant 1:1 integration ratio of one doublet at ca. δ 4.0 and the aromatic singlet at ca. δ 7.08 in the temperature range from 263 to 243 K for the uncomplexed host. However, it is impractical to differentiate the other oxyethylene proton signals due to significant overlapping. It is thus believed that the pair of singlets at δ 7.12 and 7.14 is derived from a Na^+/**1**-complexed species rather than new conformers of free **1** resulted from a change in temperature.

The singlet at δ 7.10 in the spectrum at 300 K (Figure 3a) should represent an averaged signal of the two partially resolved signals observed at 273 K (Figure 3b) corresponding to an exchange between complexed **1** and free **1**. The diameter of each crown cavity in **1** is about 1.96 Å, which is close to that of a Na^+ ion (1.90 Å) but significantly smaller than of a K^+ ion (2.66 Å). Although no X-ray crystallographic data of the **1**·Na^+ complex is available, the Na^+ ion is likely to go into the central cavity of molecule **1**, whereas the significantly larger K^+ ion may fail to do so. Due to the electrostatic repulsion of two positively charged Na^+ ions and a relatively small inner cavity size of host **1**, the formation of a 1:2 complex between **1** and Na^+ ions seems unlikely. This postulation is also supported by results derived from an ESI-MS spectroscopic study of **1** in the presence of a mixture of alkali metal (Li^+, Na^+, and K^+) picrates. The base peak was observed at m/z = 975 for the $[\mathbf{1} + Na]^+$ ion, but no 1:2 stoichiometric binding species was detected. A relatively weaker (30−35%) peak was observed at m/z 991 corresponding to the $[\mathbf{1} + K]^+$ ion, but no indication of a $[\mathbf{1} + Li]^+$ ion was detected. The former could be derived from a weak external complexation of **1** to a K^+ ion, but it is unlikely to be a centrally trapped **1**·K^+ complex as shown by the ^{1}H NMR studies discussed earlier (Figure 2). Since the **1**·Na^+ complex is in a slow exchange with the uncomplexed species, its association constant (K_{ass}) could be estimated by direct ^{1}H NMR analysis to be about 12 M^{-1} at 263 K on the basis of the integration ratio of their aromatic proton signals.

The second exchange process is likely to be an intramolecular phenomenon after the host **1** complexes to a Na^+ ion. The two well-resolved singlets at δ 7.12 and 7.14 with equal integration areas suggest that, at the low-temperature limit (243 K; Figure 3), the Na^+ ion is only complexed to

---

[14] (a) Ashton, P. R.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Schiavo, C.; Spencer, N.; Stoddart, J. F.; Tasker, P. A.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **1996**, *2*, 709. (b) Chang, T.; Heiss, A. M.; Cantrill, S. J.; Fyfr, M. C. T.; Pease, A. R.; Rowan, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Org. Lett.* **2000**, *2*, 2947.

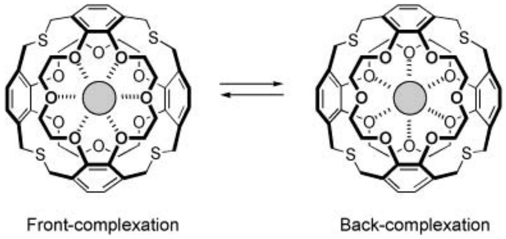


Figure 4. Intramolecular kinetic equilibrium between host **1** and guest Na^+.

one of the two crown units in **1**, resulting in magnetically nonequivalent aromatic protons between the complexed crown and the free crown. Increasing the temperature led to the collapse of the pair of singlets, which reappeared as an averaged broad signal at 273 K. This should correspond to a kinetic equilibrium, with the guest Na^+ ion exchanging complexation sites between the two intramolecular "front" and "back" crown hosts as illustrated in Figure 4. The free energy of activation ($\Delta G_c^\ddagger$) for this process could be estimated by the coalescence temperature (T_c) method. Employing the pair of noncoupled aromatic signals as a probe allowed $\Delta G_c^\ddagger$ to be estimated as 14.1 ± 0.3 kcal/mol ($T_c = 268 \pm 5$ K, $\Delta\nu = 8$ Hz) on the basis of the Eyring equation.[15]

In conclusion, the spherical molecule **1** was successfully synthesized as a model compound for our investigation. It represents one of the rare examples of a molecular structure belonging to the D_{2d} point group.[16] The host **1** shows a selective preference for complexation with a Na^+ ion in the presence of other alkali cations. The Na^+ ion is essentially trapped in the central cavity of the molecule through a novel and unique exchange between the two crown units. At higher temperatures, there exists another exchange process whereby the Na^+ ion could diffuse into the solution from the host. Thus, molecule **1** should serve as a good model of a host with preferred binding to one type of cation like the carcerands and still allow the guest to "communicate" with the external environment. In addition, the temperature factor may be used to tune the degree of complexation or diffusion of the guest to or from the host.

Acknowledgment. This work was supported by the National University of Singapore (RP-143-000-026-112). We thank Associate Professor Ang Siau Gek and Ms. Tan Geok Kheng for their assistance in the determination of the single-crystal structure.

Supporting Information Available: Crystallographic data of **1** and experimental preparations for compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026780T

---

[15] $k_c = \pi\Delta\nu/\sqrt{2}$ and $\Delta G_c^\ddagger = 2.303 \times RT_c(10.319 + \log T_c - \log k_c)$; see: Calder, I. C.; Garratt, P. J. *J. Chem. Soc. B* **1967**, 660.

[16] There were only a few reported examples of supramolecular hosts with D_{2d} symmetry; see: (a) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1018. (b) Wyler, R.; Mendoza, J. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed Engl.* **1993**, *32*, 1699.