

A new cavitand ionophore bearing two rigid crown ether groups

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Abstract—A new cavitand (**1**) bearing two rigid crown ether groups has been synthesized from tetrahydroxycavitand (**2**). The binding properties of this cavitand towards alkali metal ions as well as ammonium ion were also examined.
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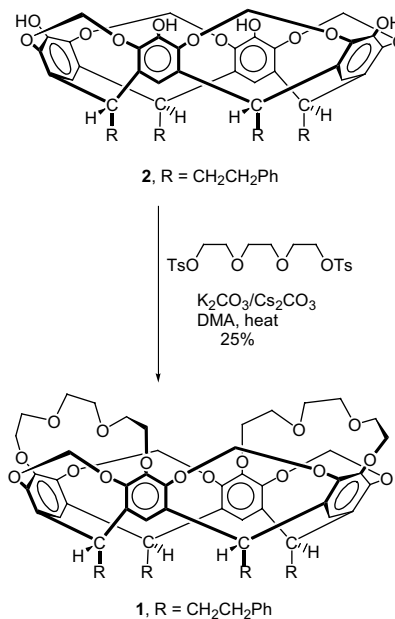
In the last two decades, an amazing number of different synthetic receptors for binding and recognition of various guests have been designed and prepared in the field of supramolecular chemistry.¹ In this regard, cavitands are certainly one of the most important classes of host molecules. Cavitands are synthetic host compounds with open-ended enforced cavities large enough to accommodate organic guest molecules and ions.² Recently, various cavitand derivatives have been synthesized as host compounds for metal ion recognition,³ anion recognition⁴ and organic guests.⁵

For the most related example, Hamada et al. reported the syntheses and binding properties of mono- and bis-aza-15-crown-5 modified cavitands via regioselective mono and bis-chloromethylation of cavitands.^{3c}

However, as far as we are aware, there has not been any attempt to introduce the crown ether ligand directly to the cavitand moiety. The rigidity of the crown ether ring in our novel cavitand **1** provides a unique conformation, which was confirmed by MMFF force field calculations. Herein, we report the synthesis of bis(crown ether) modi-

fied cavitand and binding properties of this compound towards cations (Scheme 1).

Tetrahydroxycavitand **2** has been better known as an intermediate for the syntheses of carcerands or hemicarcerands.⁶ Our synthesis began with this



Scheme 1. Synthesis of compound **1**.

Keywords: Cavitand; Ionophore; Complexation; Resorcinarene; Recognition; Metal ions.

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tetrahydroxycavitand **2**, which was prepared using published procedures.^{7,8} However, it is worth mentioning the recent publication by Kaifer and co-worker in which the yield of tetrabromocavitand, the precursor of tetrahydroxycavitand, was improved from 52% to 94%.⁸ Treatment of this tetrahydroxycavitand with tri(ethylene glycol)di-*p*-tosylate in the presence of K_2CO_3 and Cs_2CO_3 led bis(crown ether)cavitand **1**⁹ in a 25% yield after the column chromatography using 5% acetone– $CHCl_3$ as an eluent. We could not observe any formation of hemicarcerand under this reaction condition.

Even though there are examples that crown or azacrown ethers were introduced, as far as we know, there has not been any attempt to introduce the crown ether ligand directly to the cavitand moiety. This novel crown ether type ligand consists of six oxygens and should represent a rigid binding pocket. To obtain the most stable conformation of this system, a Monte Carlo conformation search was carried out using MMFF force field.¹⁰ For computational simplification, the four $CH_2CH_2C_6H_5$ groups were replaced with CH_3 groups to provide **1-Me**. The lowest energy conformation has C_2 symmetry, and three oxygen atoms in each crown ether type ring moiety are pre-organized to bind a metal cation. Figure 1 shows the MMFF optimized structure of **1-Me**. The most interesting feature of this structure would be the conformation of three different kinds of oxygens. Since the OCH_2O linker is bent inward in the calculated structure, the lone pair electrons of those oxygens are facing outward. So, those oxygens cannot participate in the metal binding easily. The other two sets of oxygens can make a binding pocket for metal ions, however, the phenolic oxygens ($ArOCH_2CH_2$) suffers the steric congestion from methylene group (OCH_2O) and too

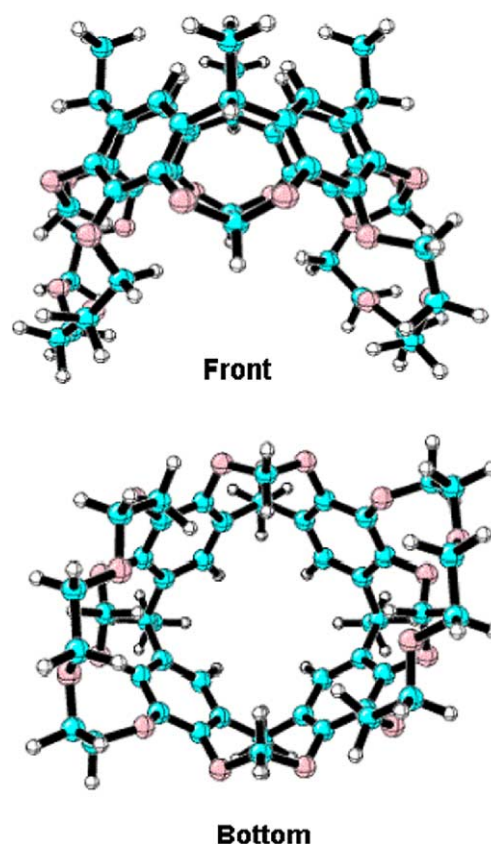


Figure 1. Optimized structure of **1-Me** using MMFF force field.¹⁴

much rigidity. So ‘ $ArOCH_2CH_2OCH_2CH_2OCH_2CH_2OAr$ ’ ligand in host **1** should form a quite different binding site than similar ligand as an open chain.

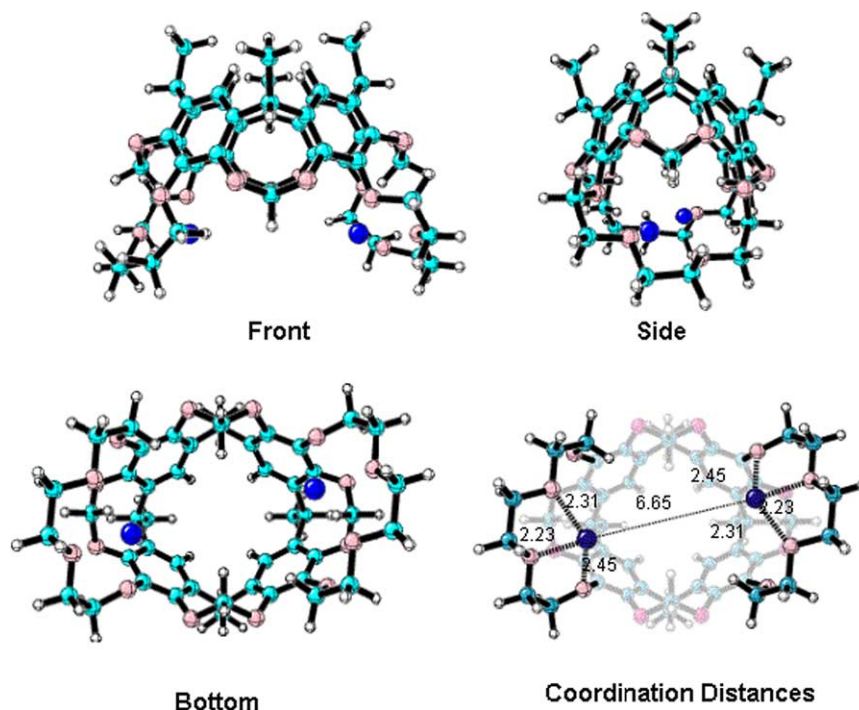


Figure 2. Optimized structure of **1-Me@2Na⁺** complex using MMFF force field. Distances are in angstrom.¹⁴

Table 1. The percent extraction of alkali metal and ammonium picrates by cavitand **1** with at 25 °C^a

	Na ⁺	K ⁺	Rb ⁺	Cs ⁺	NH ₄ ⁺
Host 1	42.4	15.1	11.1	24.6	25.4

^a The values are average values from aqueous phase of three trials (errors < 15%).

Table 2. Competitive transport of metal ions by bulk liquid membrane using cavitand **1** (%)

	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
Host 1	0	17.5	2.12	0.38	0

Figure 2 explains the MMFF optimized structure of **1**-Me coordinating two Na⁺ ions. The coordination distances (2.2–2.5 Å) are within ideal range for Na⁺ ion. A couple of solvent molecules may fill the space between the Na⁺ ions to relieve the electrostatic repulsion of two positive charges.

In the electrospray ionization (ESI) mass spectrum, a peak at *m/z* 1519.1, which corresponds to [1+2Na⁺+picrate]⁺ was clearly observed (see Supporting information).

The binding properties of this cavitand towards the alkali metal ions as well as ammonium ions were examined using extraction experiments (Table 1).¹¹ The extraction experiments display that host **1** binds more tightly with sodium picrate over the other cationic guests. All the experiments were repeated three times. The selectivity for Na⁺ is about 2.8 times that for K⁺. This can be productively compared with the selectivity (Na⁺/K⁺) observed in 12-crown-4 (1.3), 15-crown-5 (0.94) or benzo-15-crown-5 (1.03).¹²

Competitive transports of metal ions with host **1** were performed using the U-tube method. (Table 2).¹³ The concentrations of metal ions were determined using ICP atomic emission spectrometer. The cavitand **1** showed a moderate selectivity for Na⁺ over the other metal ions examined.

In conclusion, a novel cavitand bearing two rigid crown ether groups has been prepared. The conformations of this cavitand and the complex were examined via MMFF force field calculations. The computational results indicated the newly created host molecule possesses two rigid binding sites that can selectively accommodate Na⁺ ions. The binding affinities towards alkali metal ions as well as ammonium ion were studied by extraction experiments. This host with immobilized and rigid binding sites displays a large selectivity for Na⁺ over K⁺.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.063. Experimental Sections including ESI mass spectrum are available.

References and notes

1. *Comprehensive Supramolecular Chemistry*; (a) Vötle, F., Ed.; Pergamon: Oxford, 1996; Vol. 2; (b) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspective*; Wiley: Weinheim, 1995.
2. (a) Cram, D. J. *Science* **1983**, 219, 1177; (b) Cram, D. J.; Cram, M. J. *Container Molecules and Their Guests*. In *Monographs in Supramolecular Chemistry*; Stoddard, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1994; (c) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, 52, 2663; (d) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, 99, 931; (e) Sherman, J. *Chem. Commun.* **2003**, 1617.
3. (a) Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, 62, 7148; (b) Yoon, J.; Paek, K. *Tetrahedron Lett.* **1998**, 39, 3161; (c) Hamada, F.; Ito, S.; Narita, M.; Nashirozawa, N. *Tetrahedron Lett.* **1999**, 40, 1527; (d) Pellet-Rostaining, S.; Nicod, L.; Chitry, F.; Lemaire, M. *Tetrahedron Lett.* **1999**, 40, 8793; (e) Paek, K.; Yoon, J.; Suh, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 916; (f) Moon, B.-S.; Kim, S. K.; Kand, B.-G.; Lee, J.-H.; Yoon, J.; Lee, K. D. *Bull. Korean Chem. Soc.* **2003**, 24, 133.
4. (a) Boerrigter, H.; Grave, L.; Nissink, J. W. M.; Chriss-toffels, L. A. J.; van der Maas, J. H.; Verboom, W.; de Jong, F.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, 63, 4174; (b) Dumazet, I.; Beer, P. D. *Tetrahedron Lett.* **1999**, 40, 785; (c) Ahn, D.-R.; Kim, T. W.; Hong, J.-I. *Tetrahedron Lett.* **1999**, 40, 6045; (d) Lim, C. W.; Hong, J.-I. *Tetrahedron Lett.* **2000**, 41, 3113; (e) Lücking, U.; Rudkevich, D. M.; Rebek, J., Jr. *Tetrahedron Lett.* **2000**, 41, 9547; (f) Oshovsky, G. V.; Verboom, W.; Fokkens, R. H.; Reinhoudt, D. N. *Chem. Eur. J.* **2004**, 10, 2739.
5. (a) Ahn, D.-R.; Kim, T. W.; Hong, J.-I. *Tetrahedron Lett.* **1999**, 40, 6045; (b) Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Org. Chem.* **1999**, 64, 4555; (c) Resio, A. R.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, 122, 4573; (d) Ihm, C.; In, Y.; Park, Y.; Paek, K. *Org. Lett.* **2004**, 6, 369.
6. Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, 34, 95.
7. (a) Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, 111, 4527; (b) Sherman, J. C.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, 113, 2194.
8. Román, E.; Peinador, C.; Mendoza, S.; Kaifer, A. E. *J. Org. Chem.* **1999**, 64, 2577.
9. *Cavitand (1)*. Into a 500 mL three-neck round bottom flask equipped with a magnetic stirrer and blanketed with argon were placed K₂CO₃ and Cs₂CO₃ (696 mg, 95:5) and 240 mL of degassed DMA. The reaction mixture was heated to 60 °C. To this reaction mixture, tetrahydroxycavitand **1** (500 mg, 0.491 mmol) and tri(ethylene glycol)di-*p*-tosylate (660 mg, 1.5 mmol) in 127 mL of degassed DMA was added dropwise for 9 h via additional funnel. After stirring for 24 h at 60 °C, additional tri(ethylene glycol)di-*p*-tosylate (330 mg, 0.75 mmol) was added. Two more portions of tri(ethylene glycol)di-*p*-tosylate (330 mg, 0.75 mmol) were added after each 24 h stirring. The reaction mixture was stirred at 80 °C for 24 h and 100 °C for additional 24 h. The solvent was rotary evaporated and the residue was dissolved in 200 mL of CHCl₃ and filtered through a 1 cm

pad of Celite. The solvent was rotary evaporated again to ~50 mL volume and poured into 300 mL of methanol. The precipitate that formed was filtered and chromatographed with 5% acetone in CHCl_3 to give 153 mg (25%) of **2**: mp 285 °C dec. ^1H NMR (CDCl_3 , 200 MHz): δ 2.47–2.67 (m, 16H), 3.78 (s, 12H), 4.44 (d, $J = 7.0$ Hz, 4H), 4.58 (s, 8H), 4.81 (t, $J = 7.6$ Hz, 4H), 5.77 (d, $J = 7.0$ Hz, 4H), 6.85 (s, 4H), 7.20 (m, 20H); ^{13}C NMR (CDCl_3 , 50 MHz): δ 32.4, 34.5, 37.0, 51.9, 69.9, 114.1, 126.0, 128.3, 138.6, 141.5, 144.0, 147.5, 169.5; MS (FAB, NBA) $m/z = 1245$ ($\text{M} + \text{H}^+$). Anal. Calcd for $\text{C}_{76}\text{H}_{76}\text{O}_{16} \cdot 3\text{H}_2\text{O}$: C, 70.25; H, 6.36. Found: C, 70.45; H, 6.00.

10. Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

11. (a) Bartsch, R. A.; Eley, M. D.; Marchand, A. P.; Shukla, R.; Kumar, K. A.; Reddy, G. M. *Tetrahedron* **1996**, *52*, 8979; (b) Marchand, A. P.; Chong, H.-S.; Takhi, M.; Power, T. D. *Tetrahedron* **2000**, *56*, 3121; (c) Arnaud-Neu, F.; Asfari, Z.; Souley, B.; Vicens, J. *New J. Chem.* **1996**, *20*, 453.
12. Gokel, G. In *Crown Ethers & Cryptands*; Stoddard, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1991; pp 79.
13. Maruyama, K.; Tsukube, H.; Araki, T. *J. Am. Chem. Soc.* **1982**, *104*, 5197.
14. Figures prepared with Houk/mol, version 2.6.3; Nakamura, K.; Houk, K. N. NAIST: UCLA, 2004.