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A New Cryptand: Synthesis and Complexation with Paraquat

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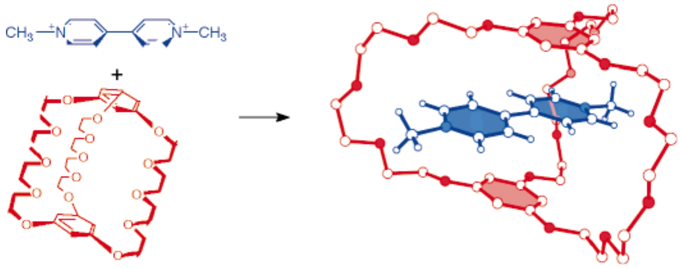
ABSTRACT



Inspired by folded, nonpseudorotaxane complexes of bis(*m*-phenylene)-32-crown-10 systems, we synthesized a new bicyclic crown ether containing two 1,3,5-phenylene units linked by three tetra(ethyleneoxy) units. The new cryptand forms a "pseudorotaxane-like" inclusion complex with *N*,*N*′-dimethyl-4,4′-bipyridinium bis(hexafluorophosphate) with association constant $K_a = 6.1 \times 10^4$ M^{-1}, 100-fold greater than that of an analogous simple crown ether.

Crown ethers were first reported in 1967,[1] nearly simultaneously[2] with the first rotaxanes (compounds consisting of cyclic molecules threaded by linear molecules with no covalent bonds between them, Figure 1). Not long thereafter, bicyclic compounds with cavities capable of inclusion of ions and small molecules were reported.[3] Such cryptands, defined as "bicyclic ligands",[4] have been demonstrated to be valuable hosts for a variety of guests; indeed, association constants can be 10^3−10^4 times higher than those of the analogous macrocycles,[4−6] attributable to the preorganization of their structures.[7]

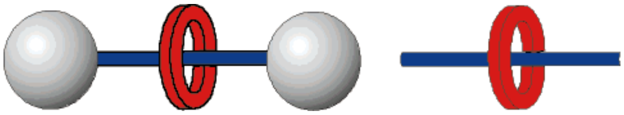


Figure 1. Schematic representations of a rotaxane (left) and a pseudorotaxane (right). Cyclic molecular unit in red, linear molecular unit in blue, and blocking group in gray.

Crown ethers have played a significant role in the emerging field of supramolecular chemistry. Interestingly, one of the most significant advances in the field resulted

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[1] (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017. Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021.

[2] Schill, G.; Zöllenkopf, H. *Nachr. Chem. Technol.* **1967**, *79*, 149. Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723. Schill, G.; Zöllenkopf, H. *Ann. Chem.* **1969**, *721*, 53.

[3] Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428. 2429; 2431. Dietrich, B.; Lehn, J.-M.; Sauvage, J.-P. *Tetrahedron Lett.* **1969**, 2885.

[4] Dietrich, B. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Series Eds.; Pergamon Press: New York, 1996; Vol. 1, Gokel, G., Vol. Ed., Chapter 4, pp 153−211.

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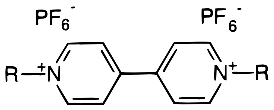
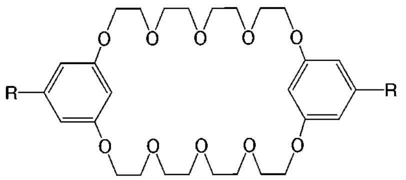
from the quest for effective hosts for complexation of “paraquats”, *N*,*N*′-dialkyl-4,4′-bipyridinium salts (**1**), by Stoddart et al. in the early 1980s.[8,9a] It was discovered that bisarylene crown ethers in the size range of 32−34 atoms, in particular, form pseudorotaxanes (mechanically threaded structures without bulky end groups to provide thermodynamic stability against dethreading, Figure 1) with paraquats with association constants on the order of 10^2−10^3 M^{-1},[8,9] and from this genesis, a variety of pseudorotaxanes, rotaxanes (Figure 1), catenanes, and polyrotaxanes have been synthesized.[10]



1

a. R = CH_3
b. R = CH_2CH_2OH

During the characterization of bis(1,3-phenylene)-32-crown-10 systems (**2**), folded, “exo” complexes have been observed by X-ray crystallography. For example, we recently reported[11] a “cradled barbell” crystal structure and not the expected pseudorotaxane structure from the parent system **2a**[9a,12] with *N*,*N*′-dibenzyl(*m*-xylylene)diammonium bis(hexafluorophosphate), although the parent macrocycle is not folded in its crystal.[9a] Examination of the complexation of the diol **2b**[13] with paraquat **1a** led to the isolation of crystals of the complex **1a**:**2b**, which, as shown in Figure 2, also proved to be of the same folded, exo type and not the expected pseudorotaxane structure, even though its FAB mass spectrum displays a peak (*m*/*z* 927.3) corresponding to (**1a**:**2b**-PF_6)$^+$ and in its crystal structure **2b** itself does not exhibit this folded structure. Note that in complex **1a**:**2b** the electron rich aromatic rings of the host are nicely aligned vertically with and parallel to the electron poor aromatic rings of the guest species; the bipyridinium twist angle is 11.4° from coplanar and the crown aromatic rings are tilted 6.9° with repect to each other. The centroid−centroid distance of the aromatic rings of the crown ether is 7.39 Å. There are three H-bonds of two of the acidic α-protons of the paraquat unit with the ether oxygen atoms of the host. Uniquely, the counterion, PF_6^-, also participates in stabilization of the complex through H-bonds to two of the protons of the paraquat guest unit; though this effect has been observed in dialkylammonium ion−crown ether complexes,[15] to our knowledge it has not been previously seen in paraquat-based pseudorotaxanes.



2

a. R = H
b. R = CH_2OH
c. R = $OCH_2C_6H_5$
d. R = OH

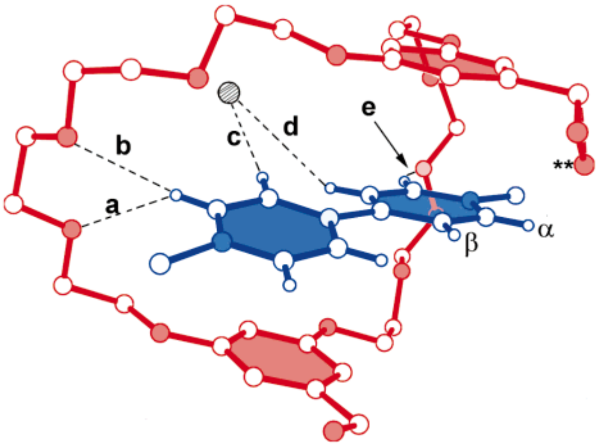


Figure 2. Solid-state structure of **1a**:**2b** as determined by X-ray crystallography[14a,b] [disordered solvent molecules (water and acetone, which share a site) and counterions omitted for clarity, except for a fluorine atom of one PF_6, represented by the gray circle)]. Both positions of the disordered oxygen atom of the hydroxymethyl group, denoted by **, are shown treated as half-populated. H-bond distances in Å: **a** = 2.44, **b** = 2.83, **c** = 2.34, **d** = 2.42, **e** = 2.72. H-bond angles (C−H- -O, C−H- -F, or O−H- -O) in degrees: **a** = 144, **b** = 130, **c** = 168, **d** = 144, **e** = 156.

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(7) The concept of preorganization can logically be traced to the “lock and key” idea of Fischer (*Chem. Ber.* **1894**, *27*, 2985). The enhanced effectiveness of macrocyclic hosts (coronands) over linear analogues (podands) (ref 1), the macrocyclic effect, suggested further improvements with cryptands. Further development included significant contributions from Cram (Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, UK, 1994) and Lehn (ref 6). For a very instructive review of these concepts, see: Inoue, Y.; Wada, T. *Adv. Supramol. Chem.* **1997**, *4*, 55.

(8) Stoddart, F. *Chem. Br.* **1991,** 714.

(9) (a) Allwood, B. L.; Spencer, N.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1058. (b) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, *119*, 302. (c) Asakawa, M.; Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Gillard, R. E.; Kocian, O.; Raymo, F. M.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1997**, *62*, 26 and references therein.

(10) Reviews: Mahan, E.; Gibson, H. W., In *Cyclic Polymers*, 2nd ed.; Semlyen, A. J., Ed.; Thomson Science and Professional: London, UK, in press. Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 9, ASAP web posting June 11, 1999. Harada, A. *Acta Polym.* **1998**, *49,* 3. Gibson, H. W. In *Large Ring Molecules*; Semlyen, J. A., Ed.; John Wiley & Sons: New York, 1996; Chapter 6, pp 191−262. Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, 1155.

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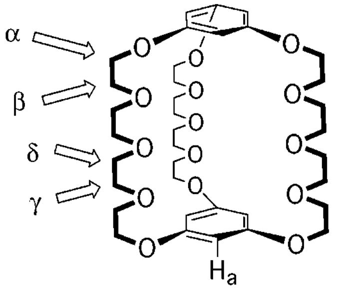
(12) Delaviz, Y.; Gibson, H. W. *Polym. Commun.* **1991**, *32*, 103.

(13) Gibson, H. W.; Nagvekar, D. S. *Can. J. Chem.* **1997**, *75*, 1375.

(14) (a) Crystals of **1a**:**2b** were grown by diffusion of hexane into an equimolar acetone solution of the components. X-ray diffraction was carried out on an Enraf-Nonius CAD4 diffractometer equipped with Cu K radiation (λ = 1.541 84 Å) and a graphite monochromator. Data were collected to θ = 75°. Crystal data: $C_{30}H_{44}O_{12}$:[$C_{12}H_{14}N_2$](PF_6)$_2$:1/2(C_3H_6O):1/2(H_2O), FW 1110.9, monoclinic space group $P2_1/c$, a = 10.7679(8), b = 15.677(1), and c = 2.453(4) Å, β = 93.196(8)°, V = 5469(1) Å^3, Z = 4, D_c = 1.349 g cm^{-3}, T = 297 K, μ = 16.0 cm^{-1}. Convergence was achieved with R = 0.118, R_w = 0.143, and maximum residual density 0.72 e Å^{-3} for 5502 data having $I > 1\sigma(I)$ (of 11712 unique data). (b) The structures were solved by direct methods using SIR (Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Polidori, G.; Spagna R.; Viterbo, D. *J. Appl. Crystallogr.* **1989**, *22,* 389) and refined by full-matrix least squares, using the Enraf-Nonius MolEN programs (Fair, C. K. *MolEN, An Interactive System for*

On the basis of the suggestion implicit in the structure of **1a**:**2b** that closure of a second ring would enhance the strength of the complexation and the historical success of cryptands in affording higher association constants and hence more efficient routes to such supramolecular assemblies, bis(1,3,5-phenylene)tri(1,4,7,10,13-pentaoxatridecyl) (**3**) was synthesized in one step from bisphenol **2d**[16] and tetra(ethylene glycol) ditosylate in 38% yield using the pseudo-high-dilution technique.[13] **3** was characterized by ^{1}H and ^{13}C NMR and MS.[17]



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When **1a** and **3** were mixed in acetone, the yellow color ($\lambda_{max} = 396$ nm) typical of such charge-transfer inclusion complexes formed immediately. ^{1}H NMR spectroscopy (Figure 3) indicated that exchange was rapid and complexation was strong on the basis of the significant upfield shifts of the bipyridinium protons, the aromatic proton, and the α-OCH_2 protons of **3** and the downfield shift of the γ- and δ-OCH_2 protons of **3**, qualitatively similar to those observed for other bisphenylene crown ether–paraquat complexes.[8,9] Solutions of **1b** and **3** behaved similarly.

A Job plot based on NMR data demonstrated that the complex was of 1:1 stoichiometry. The NMR data afforded an estimate of the association constant[18,19] for **1a**:**3**, $K_a = 6.1 \times 10^4$ M^{-1} at 23.4 °C in acetone-d_6, corresponding to $\Delta G = -92$ kJ/mol, a value which at this point must be regarded as preliminary in view of the difficulty in measuring such high association constants accurately by NMR.[20] This is among the highest values reported for crown ether complexes of paraquats.[21] For **1a**:**2b** the NMR data yielded[18,19] $K_a = 5.7 \times 10^2$ M^{-1} ($\Delta G = -53$ kJ/mol) under the same conditions. The 100-fold increase in K_a at 23 °C for the complex of bicyclic crown ether **3** vs that of simple crown ether **2b** represents nearly a doubling of ΔG. Thus, as expected, the bicyclic system **3** is a stronger host for complexation with paraquat. Again **1b** interacted with **3** in an analogous manner and the K_a value was similar.

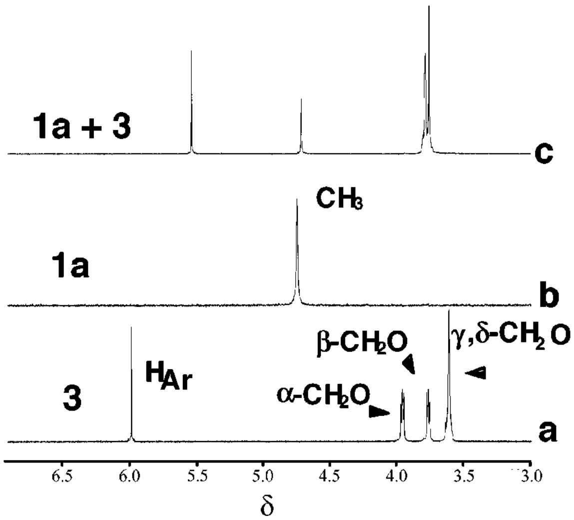

Figure 3. Partial ^{1}H NMR spectra (400 MHz, acetone-d_6, 21 °C) of (a, bottom) bicyclic crown ether **3** (2.69 mM), (b, middle) paraquat (**1a**, 2.69 mM), and (c, top) a solution of both **1a** and **3** (2.69 mM each).

The 1:1 complex **1a**:**3** was detected directly by FABMS. Two relevant peaks were observed: *m/z* 1057.45 for the complex after loss of a PF_6 counterion and *m/z* 912.62 for the complex after loss of a PF_6 counterion and a neutral PF_6. This fragmentation pattern has been observed in many pseudorotaxanes and catenanes derived from paraquat derivatives.[8,9]

X-ray diffraction results (Figure 4) confirmed the 1:1 stoichiometry and the structure of the "pseudorotaxane-

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Crystal Structure Analysis; Enraf-Nonius: Delft, The Netherlands, 1990). Non-hydrogen atoms were treated anisotropically except those of the disordered solvent molecules. Hydrogen atoms were placed in calculated positions, except those on the water molecules and the paraquat methyl groups, which were placed from difference maps. Acetone H atoms were not located. (c) Crystals of **1a**:**3** were grown by evaporation of an equimolar acetone solution of the two components. X-ray diffraction was carried out on a Siemens P4/CCD diffractometer equipped with Mo Kα radiation ($\lambda = 0.710\ 73$ Å) and a graphite monochromator. Data were collected to $\theta = 22.5°$. Crystal data: $C_{36}H_{54}O_{15}$:$C_{12}H_8N_2(PF_6)_2$:H_2O:C_3H_6O, FW 1297.09, triclinic space group *P*-1, $a = 25.0865$ (1), $b = 11.1315$ (2), and $c = 23.4900$ (2) Å; $\alpha = 90.00$, $\beta = 107.671$ (1), $\gamma = 90.00°$; $V = 6250.08$ (12) Å^3, $Z = 4$, $D_c = 1.378$ g cm^{-3}, $T = 213(2)$ K, $\mu = 0.173$ cm^{-1}. Convergence was achieved with $R = 0.0825$, $R_w = 0.2291$, and maximum residual density 0.836 e·Å^{-3} for 5130 data having $I > 2\sigma(I)$.

(15) Fyfe, M. C. T.; Stoddart, J. F. *Adv. Supramol. Chem.* **1999**, *5*, 1.

(16) Bisphenol **2d** was derived from 5-benzyloxyresorcinol [Nagvekar, D.; Gibson, H. W. *Org. Prep. Proced. Int.* **1997,** *29,* 240] via **2c** using the methodology reported for other derivatives of bis(*m*-phenylene)-32-crown-10 (ref 13). Details are given in the Supporting Information.

(17) ^{1}H NMR ($CDCl_3$) $\delta = 3.69$ (m-, γ-, δ-OCH_2, 24H), 3.81 (t, $J = 4.6$ Hz, β-OCH_2, 12H), 3.93 (t, $J = 4.6$ Hz, α-OCH_2, 12H) and 6.00 (s, 6H). ^{13}C NMR ($CDCl_3$) $\delta = 67.47$, 69.66, 70.64, 70.94, 94.20 and 160.41. FABMS (3-nitrobenzyl alcohol, NBA) *m/z* (rel intensity): 749.1 [$(M + Na)^+$, 100%], 727.2 [$(M + H)^+$ 32%], and 705.3 [$(M + Na)^+ - C_2H_4O$, 15%]. High-resolution FABMS (3-NBA): *m/z* 749.3373 $(M + Na)^+$ [calcd for $C_{36}H_{54}O_{15}Na$, 749.3373].

(18) The association constants were estimated on the basis of the chemical shift of proton H$_a$ of the uncomplexed cryptand **3** or crown ether **2b** and the observed signals in the presence of varied amounts of **1a** (titration).

(19) Using the iterative Creswell–Allred method: Gong, C.; Balanda, P. B.; Gibson, H. W. *Macromolecules* **1998**, *31*, 5278.

(20) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K.. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Series Eds.; Pergamon Press: New York, 1996; Vol. 8, Davies, J. E. D., Ripmeester, J. A., Vol. Eds., Chapter 10, pp 425–482.

(21) Nolte and co-workers reported that a bicyclic molecule containing two tetra(ethyleneoxy) bridges and a diphenylglycouril bridging moiety complexes **1a** with $K_a = 2.0 \times 10^4$ M^{-1} (in acetone at room temperature: Schenning, A. P. H. J.; deBruin, B.; Rowan, A. E.; Kooijman, H.; Spek, A. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2132), i.e., 1/3 of the value we observe for **1a**:**3**. Rowan et al. (Rowan, A. E.; Aarts, P. P. M.; Koutstaal, K. W. M. *Chem. Commun.* **1998**, 611) recently reported that a "porphyrin capped molecular clip" having crown ether and diphenylglycouril components formed a "pseudorotaxane-like" complex with **1a** with $K_a = 6.0 \times 10^5$ M^{-1}, in a less polar solvent system (1:1 MeCN–$CHCl_3$, room temperture). It should be noted that this host is also a cryptand containing a very strong electron donor, the porphyrin unit.

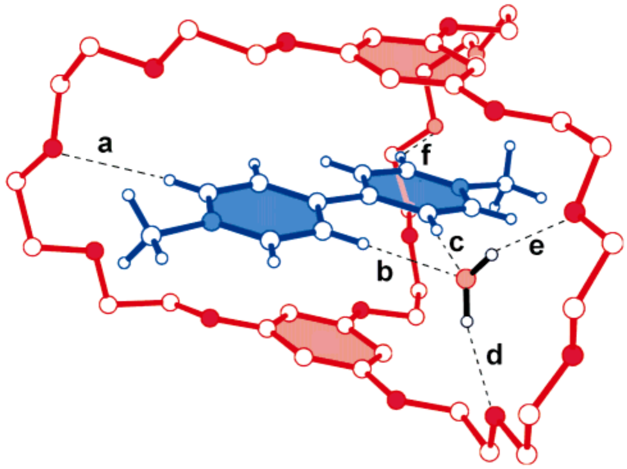

Figure 4. Solid-state structure of **1a**:**3** as determined by X-ray crystallography[14b,c] (solvent molecules and counterions omitted for clarity except as noted). H-bond distances in Å: **a** = 2.63, **b** = 2.34, **c** = 2.29, **d** = 2.05, **e** = 2.07, **f** = 2.75. H-bond angles (C−H- -O or O−H- -O) in degrees: **a** = 149, **b** = 179, **c** = 175, **d** = 160, **e** = 165, **f** = 152.

like” [22] inclusion complex of **1a**:**3**. Note that the position and orientation of the paraquat guest unit in this complex are very similar to those features in the simple crown complex **1a**:**2b** (Figure 2). As in **1a**:**2b** (Figure 2) there are four H-bonds emanating from the paraquat unit. Two of the α-protons of **1a** are involved in H-bonding with ether oxygen atoms, whereas in previously reported bisphenylene pseudorotaxane systems all four α-protons are involved in such H-bonding.[8,9] Moreover, in **1a**:**3** two adjacent β-protons are H-bonded to a water molecule, which in turn is H-bonded to two ethereal oxygen atoms. This is believed to be the first reported inclusion complex with demonstrated H-bonding of the β-protons of paraquat. As expected for a π-stacking interaction, the aromatic rings of the cryptand in **1a**:**3** are nearly (9.8°) parallel, with a 6.94 Å centroid−centroid separation; the paraquat moiety, whose rings are twisted 5.8° out of planarity, lies nearly parallel to and nearly symmetrically between the two arylene units of **3**. In comparison to the structure of **1a**:**2b** (Figure 2), the aromatic rings of the cryptand in **1a**:**3** are closer to the paraquat unit and to each other.

Thus, we have demonstrated the enhanced ability (relative to simple macrocycle **2b**) of a readily prepared bicyclic crown ether (**3**) to form paraquat-based “pseudorotaxanes-like” [22] inclusion complexes. Current efforts are focused on extension of the use of such preorganized host structures to other systems.

Acknowledgment. We acknowledge financial support of this research by the National Science Foundation through Individual Investigator Award CHE-9521738. Mass spectral data were obtained from the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954).

Supporting Information Available: Synthetic procedures for **2c**, **2d**, and **3**. Crystal data, structure refinement details, and SHELXTL files (.res) for **1a**:**2b** and **1a**:**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) This term was used by Stoddart et al. to describe analogous inclusion complexes of **1a** and **1b** with bis(*p*-phenylene)-34-crown-10 (BMP34C10) (Ashton, P. R.; Philp, D.; Reddington, M. V.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1680). A referee suggested that **1a**:**3** is not a “true” pseudorotaxane because **1a** is not long enough to extend outside the cavity of **3**. This is a somewhat subjective point since the methyl groups of **1a** protrude only slightly from the cavity. In the case of **1b**:**3**, however, **1b** is long enough to do so, as clearly shown by single-crystal X-ray analyses with BMP34C10 in our own work (Shen, Y. X.; Engen, P. T.; Gibson, H. W.; Merola, J. S. *Abstracts of Papers*, 201st National Meeting of the American Chemical Society, Atlanta, GA, April 1991; American Chemical Society: Washington, DC, 1991: ORGN 325. Shen, Y. X.; Engen, P. T.; Berg, M. A. G.; Merola, J. S.; Gibson, H. W. *Macromolecules* **1992**, *25*, 2786) and that of Stoddart (above reference). We thus anticipate that **1b**:**3** is a “true” pseudorotaxane.