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Pseudocryptand-Type [2]Pseudorotaxanes Based on Bis(*meta*-phenylene)-32-Crown-10 Derivatives and Paraquats with Remarkably Improved Association Constants

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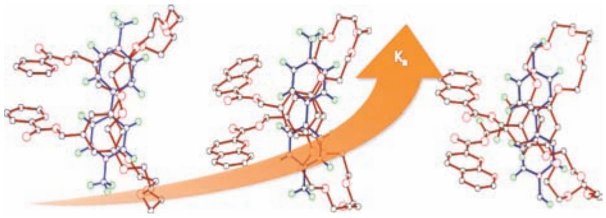
ABSTRACT



The first dual component pseudocryptand-type [2]pseudorotaxanes were designed and prepared via the self-assembly of synthetically easily accessible bis(*meta*-phenylene)-32-crown-10 pyridyl, quinolyl, and naphthyridyl derivatives with paraquat. The formation of the pseudocryptand structures in the complexes remarkably improved the association constant by forming the third pseudobridge via H-bonding with the guest and π-stacking of the heterocyclic units.

Pseudorotaxanes are mechanically interlocked molecular architectures consisting of linear molecular components ("guests") encircled by macrocyclic components ("hosts"). The design and preparation of novel and simple pseudorotaxanes systems[1] with high association constants are of great significance, since stable pseudorotaxanes are the fundamental building blocks for preparation of many novel, more advanced supramolecular species, such as rotaxanes, catenanes, polypseudorotaxanes, polyrotaxanes and polycatenanes,[2] which are expected to have unique properties and potential applications.[2,3] Crown ethers, e.g., **1**, and paraquat (*N,N*′-dialkyl-4,4′-bipyridinium) derivatives (Scheme 1) have been widely used in the construction of pseudorotaxanes.[4] Moreover, cryptands have proven to be much better hosts for

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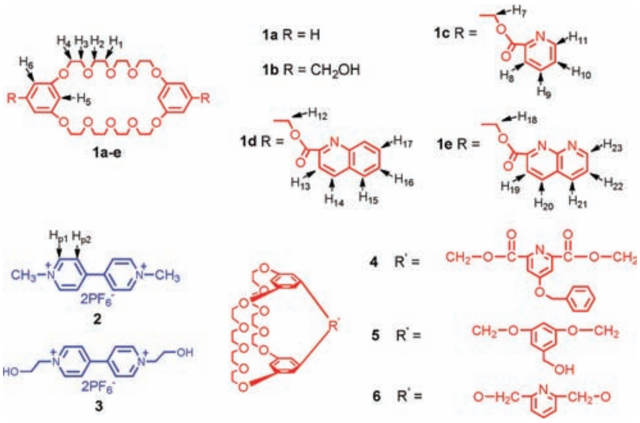
Scheme 1. Structures of Hosts **1a**–**e** and **4**–**6** and Paraquat Guests **2** and **3**



the paraquat derivatives due to preorganization and introduction of more binding sites;[5,6a] however, the synthetically lower accessibility of cryptands[5b–i,6a] (e.g., **4**[5b] and **5**[5c] in 21% and 42% yields, respectively, from **1b**) has limited their further applications. Our group first demonstrated that the complexes between a bis(*meta*-phenylene)-32-crown-10 (BMP32C10) derivative (**1b**) and paraquat derivatives instead of being pseudorotaxanes were folded into "taco" shapes (Supporting Information Figure S22) in the solid state, as proven by their X-ray crystal structures.[6a,7] Until recently,[6] almost all the complexes of bis(*meta*-phenylene)-32-crown-10 derivatives with paraquat derivatives (such as **2** and **3**[8]) had demonstrated "taco"-shaped structures, which expose one side of the paraquat salts. Inspired by these results, we tried to take advantage of the "taco"-shaped structures, which were tendentiously formed in the complexes of BMP32C10 derivatives with paraquat derivatives to design powerful new hosts with high association constants. Here we first report novel pseudocryptand-type[9] [2]pseudorotaxanes based on synthetically easily accessible BMP32C10 derivatives with remarkably improved association constants.

Crown ether **1c** was prepared via the EDCI/DMAP coupling between BMP32C10 diol (**1b**)[10] and picolinic acid in 94% yield. Equimolar solutions of **1c** and **2** in chloroform/acetonitrile (1/1, v/v) were deep yellow due to the charge-transfer interaction between the electron-rich aromatic rings of **1c** and the electron-poor pyridinium rings of **2**, evidence for complexation.

^{1}H NMR spectra of equimolar solutions of **1c** and **2** displayed only one set of peaks, indicating fast exchange.[7] After complexation, peaks corresponding to H_3, H_4, H_5, H_6, H_7, H_8, and H_{11} of **1c** and H_{p2} of **2** moved upfield, while H_1, H_2, and H_{10} of **1c** and H_{p1} of **2** moved downfield. The stoichiometry of the complex between **1c** and **2** was determined to be 1:1 by a Job plot[7,11] and confirmed by an electrospray ionization mass spectrum (ESI-MS): *m*/*z* 1137.07 $[\mathbf{1c}\cdot\mathbf{2}\text{-}PF_6]^+$, 993.13 $[\mathbf{1c}\cdot\mathbf{2}\text{-}2PF_6+H]^+$, 496.07 $[\mathbf{1c}\cdot\mathbf{2}\text{-}2PF_6+H]^{2+}$.[7] The K_a was determined to be $(3.1 \pm 0.3) \times 10^3\ M^{-1}$ in $CDCl_3/CD_3CN$ (1/1, v/v) based on the proton NMR data;[12] this value is 8-fold higher than the K_a of the simple BMP32C10 complex $\mathbf{1a}\cdot\mathbf{2}$ ($393 \pm 30\ M^{-1}$, in the same solvent).

We reasoned that the association constant increases because the folding of the central part of the crown ether, to form the "taco" complex with guest **2**, enables both pyridyl rings to participate in the complexation process by interaction with the α- and *β*-protons of the paraquat, as designed on the basis of the concept underlying lariat ethers.[13] This hypothesis was confirmed by X-ray diffraction analysis of crystals of **1c** and the complex of **1c** with **2** (Figure 1). The molecules of host **1c** by themselves assume a stair-step structure[7] common to bis(*m*-phenylene) crown ether derivatives,[14] placing the phenylene rings nearly parallel to each other but as far apart as possible by extension in opposite directions. In contrast, in the complex, **1c** is folded and the two pyridyl rings interact via face-to-face π-stacking,[14b,15] while the two N-atoms are pointed to the central cavity, resulting in a single-molecule

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[7] See Supporting Information.

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[12] ^{1}H NMR characterizations were done on solutions with constant [**1c**] and varied [**2**]. Based on these NMR data, Δ_o, the difference in δ values for proton H_6 of **1c** in the uncomplexed and fully complexed species was 0.559 ppm as the *y*-intercept of a plot of $\Delta = \delta - \delta_u$ vs $\mathbf{1c}/[\mathbf{2}]_0$ in the high initial concentration range of **2**. K_a was calculated from $K_a = (\Delta/\Delta_0)/[(1 - \Delta/\Delta_0)([\mathbf{2}]_0 - \Delta/\Delta_0[\mathbf{1c}]_0)]$. For $\mathbf{1d}\cdot\mathbf{2}$ the Δ_o value for H_6 was 0.494 ppm; the K_a value was determined analogously.

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pseudocryptand host[9] structure. Paraquat salt **2** is threaded through the central cavity of the pseudocryptand, and the complex is stabilized by H-bonds between the O- and N-atoms of **1c** with H-atoms on the paraquat salt **2** and offset face-to-face π-stacking between the phenylene rings of **1c** and the pyridinium rings of **2**. As a result, a pseudocryptand-type [2]pseudorotaxane is formed. It is noteworthy that the ester ether oxygens and the nitrogens of both pyridyl units identically interact with the β-protons of the guest. Moreover, the formation of the pseudocryptand structure of **1c·2** in solution was confirmed by 1D-NOESY experiments.[7]

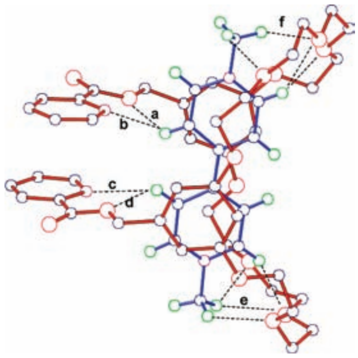

Figure 1. X-ray structure of **1c·2**. O-atoms, red; C-atoms, black; N-atoms, purple; H-atoms, green. **1c** is red. **2** is green. The same settings are used in the following crystal structures. Solvent molecules, PF_6^- ions, and hydrogens except the ones on **2**, and disordered atoms were omitted for clarity. Selected H-bond parameters: H···O(N) distances (Å), C···O(N) distances (Å), C–H···O(N) angles (deg): (a) 2.56, 3.14, 120; (b) 2.41, 3.12, 131; (c) 2.67, 3.39, 134; (d) 2.54, 3.17, 124; (e) 2.53, 3.27, 132; (f) 2.43, 3.23, 139.

Since the improved K_a of **1c·2** was clearly due to pseudocryptand-type [2]pseudorotaxane structure formation, favored by π-stacking of the pyridyl units, we next chose to incorporate quinoline groups, which afford larger aromatic profiles.[16] The bisquinolyl compound **1d** was prepared via EDCI/DMAP coupling between BMP32C10 diol (**1b**) and quinaldic acid in 98% yield. In ^1H NMR spectroscopy the complexation was a fast-exchange process. A Job plot[7,11] indicated that the stoichiometry between **1d** and **2** was 1:1, as confirmed by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry: m/z 1092 [**1d**·**2**-2PF$_6$]$^+$.[7] The K_a was determined to be $(12.4 \pm 1.3) \times 10^3$ M^{-1} in $CDCl_3/CD_3CN$ (1/1, v/v),[12] which is a 31-fold increase compared with the K_a for simple crown ether **1a** with **2** and a 4-fold increase relative to **1c·2**. Interestingly, this K_a value is even higher than those of some synthetically less accessible cryptand complexes with **2**, such as **5·2** and **6·2**.[17]

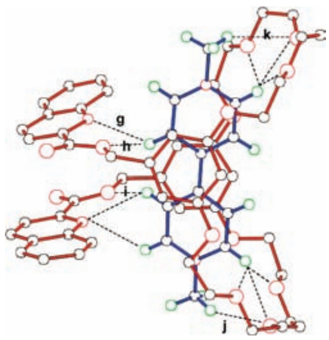

Figure 2. X-ray structure of **1d·2**. Solvent molecules, PF_6^- ions, hydrogens except the ones on **2**, and disorder were omitted for clarity. Selected H-bond parameters: H···O(N) distances (Å), C···O(N) distances (Å), C–H···O(N) angles (deg): (g) 2.61, 3.34, 134; (h) 2.57 3.20 125; (i) 2.59, 3.19, 121; (j) 2.50, 3.39, 150; (k) 2.17, 3.05, 150.

Similarly, X-ray analysis of a single crystal of **1d·2** demonstrated the pseudocryptand-type [2]pseudorotaxane structure (Figure 2), as expected, revealing offset face-to-face π-stacking of the quinoline rings and lone-pair-π interactions between carbonyl oxygen atoms and quinoline rings.[18] Paraquat salt **2** is threaded through the central cavity of the pseudocryptand, and the complex is stabilized by H-bonds between the O- and N-atoms of **1d** with H-atoms on the paraquat salt **2** and offset face-to-face π-stacking between the aromatic rings of the host and guest. In contrast to the situation with **1c·2** the interactions of the two quinolyl units with the guest are not the same; one interacts with a β-proton only via both the ester ether oxygen and the nitrogen atoms, while the other interacts via the nitrogen with both α- and β-protons and the ester ether oxygen again interacts with a β-proton. Again, the formation of the pseudocryptand-type [2]pseudorotaxane in solution was confirmed by 1D-NOESY experiments.[7]

Based on the crystal structure of pseudocryptand-type [2]pseudorotaxane **1d·2**, we realized that the 8-carbon of the quinoline ring in the complex is close to the α-H (H_{p1}, short distance: 3.63 Å), β-H (H_{p2}, short distance: 3.65), and benzyl proton H_6 of guest **1d** (short distance: 2.84 Å). As a result, if the 8-position carbon is replaced by an H-bond acceptor, it is possible to form extra H-bonds, which can stabilize the pseudocryptand [2]pseudorotaxane structure even more. Also, the replacement of the 8-carbon by an H-bond acceptor can eliminate the repulsion between the H-atom on the 8-carbon and α-H (H_{p1}, short distance: 2.91 Å), β-H (H_{p2}, short distance: 3.09 Å), and the benzyl proton H_6 of **1d** (short distance: 2.28 Å), which disfavor the

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(17) The K_a of **4·2** and **5·2** were reported[5d] as $(6.3 \pm 0.6) \times 10^3$ and $(9.4 \pm 0.9) \times 10^3$ M^{-1} in $(CD_3)_2CO$, respectively. It should be noted that the solvent affects the association constants. However, the association constants in $(CD_3)_2CO$ and $CDCl_3/CD_3CN$ will not differ greatly.

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formation of the pseudocryptand-type [2]pseudorotaxane structure. Therefore, the 1,8-naphthyridyl group, which has N-atoms at the 1- and 8-positions, was chosen to be incorporated into BMP32C10.

The bisnaphthyridyl compound **1e** was prepared via EDCI/DMAP coupling between BMP32C10 diol (**1b**) and 2-naphthyridyl carboxylic acid in 93% yield. ^{1}H NMR spectroscopy showed that the complexation between **1e** and **2** was fast exchange. Isothermal titration calorimetry (ITC)[19] indicated the stoichiometry between **1e** and **2** was 1:1, as confirmed by ESI-MS: *m*/*z* 1239.43 $[\mathbf{1e}\cdot\mathbf{2}\text{-}PF_6]^+$.[7] The K_a was determined to be $(2.5 \pm 0.2) \times 10^5\ M^{-1}$ in $CHCl_3/CH_3CN$ (1/1, v/v) by ITC,[7,19] a 625-fold increase compared with the K_a for simple crown ether **1a** with **2** and a 20-fold increase relative to **1d·2**. To the best of our knowledge, this K_a value is the highest reported for BMP32C10 derivatives with **2** and, most important, it is comparable to even the best cryptand hosts, such as **4** ($K_a = (9.0 \pm 1.8) \times 10^5\ M^{-1}$ in acetone).[5b]

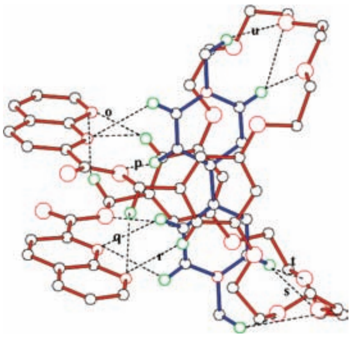

Figure 3. X-ray structure of **1e·2**. Solvent molecules, PF_6^- ions, and hydrogens except the ones involved in H-bond formation were omitted for clarity. Selected H-bond parameters: H···O(N) distances (Å), C···O(N) distances (Å), C−H···O(N) angles (deg): (o) 2.59, 3.47, 155; (p) 2.73, 3.23, 114; (q) 2.58, 3.32, 134; (r) 2.52, 3.31, 153; (s) 2.41, 3.23, 146; (t) 2.51, 3.32, 144; (u) 2.42, 3.38, 164.

As expected, the crystal structure of the complex **1e·2** demonstrated its pseudocryptand-type [2]pseudorotaxane arrangement (Figure 3), similar to the complex of **1d·2**. **1e** is folded and the two naphthyridyl rings interact via offset face-to-face π-stacking and lone-pair-π interactions between carbonyl O-atoms and naphthyridyl rings, while the four N-atoms are pointed to the central cavity, resulting in a single-molecule pseudocryptand host.[9] Paraquat salt **2** is threaded through the central cavity of the pseudocryptand, and the complex is stabilized by H-bonds between O- and N-atoms of **1e** with H-atoms on the paraquat salt **2** and offset face-to-face π-stacking between the aromatic rings of the host and guest. As expected, the N-atoms at the 8-position do interact with α-H (H_{p1}, short distance: 3.33 Å) β-H (H_{p2}, short distance: 3.38 Å). However, these interactions appear to be weak due to the relative long distances. However, the N-atoms at the 8-position formed relatively strong H-bonds with benzyl protons H_6 (short distances: 2.588 and 2.516 Å) and weak H-bonds with CH_2 protons H_{18} (short distances: 3.019 and 2.913 Å). These H-bonds provide extra linkages which stabilize the pseudocryptand-type [2]pseudorotaxane arrangement. Also, the two naphthyridyl arms of **1e** are much closer to threaded guest **2** compared with the **1d·2** system due to the removal of repulsions between the H-atom connected with the 8-carbon and α-protons (H_{p1}) and β-protons (H_{p2}) in the latter. As a result, the N-atoms at the 1-position can interact with both α-protons (H_{p1}) and β-protons (H_{p2}) and provide extra H-bonds relative to the **1d·2** system. Clearly, these H-bonds stabilize the pseudocryptand-type [2]pseudorotaxane arrangement. Therefore, the association constant increased remarkably, reflecting $\Delta G_{298} = -7.4$ kcal/mol. Again, the formation of the pseudocryptand-type [2]pseudorotaxane in solution was confirmed by 1D-NOESY experiments.[7]

In summary, pyridyl, quinolyl, and naphthyridyl based bis(*meta*-phenylene)-32-crown-10 diesters were designed and prepared efficiently in high yields (93–98%) from diol **1b**. Via the self-assembly of a paraquat derivative with these new hosts, the first dual component pseudocryptand-type [2]pseudorotaxanes[20] were prepared. The formation of pseudocryptand structures improves the association constants remarkably (from 393 M^{-1} to $2.5 \times 10^5\ M^{-1}$, doubling ΔG_{298} from −3.5 to −7.4 kcal/mol). The present protocol provides a facile method to prepare pseudorotaxane systems with relatively high association constants. Our current efforts are focused on extending this motif to prepare real cryptand and analogous hosts for construction of supramolecular polymers and polyrotaxanes.

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Supporting Information Available. Synthesis of **1c**, **1d**, and **1e**; Job plots, mass spectra and X-ray crystallographic files (CIF) for **1c**, **1c·2**, **1d·2**, **1e·2**; 1D NOESY spectra of **1c·2**, **1d·2**, **1e·2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Because the ^{1}H NMR titration method is not suitable for systems with association constants $> 10^4\ M^{-1}$, such as **1e·2**, ITC was employed. (a) Jelesarov, I.; Bosshard, H. R. *J. Mol. Recognit.* **1999**, *12*, 3–18. (b) Velazquez-Campoy, A.; Freire, E. *Nat. Protoc.* **2006**, *1*, 186–191. (c) Freyer, M. W.; Lewis, E. A. In *Methods in Cell Biology*; Correia, J. J., Dietrich, H. W., Eds.; Academic Press: 2008; Vol. 84, p 79.

(20) We previously reported a three-component pseudocryptand-based [2]pseudorotaxane complex: Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Gibson, H. W. *J. Am. Chem. Soc.* **2002**, *124*, 13378–13379. Later a pseudocryptand dimer formed from three components was reported: Huang, F.; Zakharov, L. N.; Rheingold, A. L.; Jones, J. W.; Gibson, H. W. *Chem. Commun.* **2003**, 2122–2123.