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FULL PAPER

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An Inhospitable Cryptand: the Importance of Conformational Freedom in Host-Guest Complexation

Harry W. Gibson,[a]* Feihe Huang,[a,b] Run Zhao,[b] Li Shao,[b] Lev N. Zakharov,[c,d] Carla Slebodnick,[a] Arnold L. Rheingold [c]

Dedication. To the creative pioneers of supramolecular chemistry: Wasserman, Schill, Zollenkopf, Harrison and Zilkha and co-workers.

Abstract: Two new cryptands were synthesized from bis(5-bromomethyl-1,3-phenylene)-32-crown-10 (**4**). The third arms, containing 19 or 21 atoms, were installed via Williamson ether syntheses with bisphenols containing 2,6-disubstituted pyridines. 2,6-Diaminopyridine was converted to the bis(*p*-hydroxybenzoyl) derivative **3** for the first cryptand (**5**) and 2,6-dicarboxypyridine was converted to the bis(*p*-hydroxybenzylamide) **9** for the second cryptand (**10**). Cryptand **5** did not complex viologen derivatives **11–13** to an extent detectable by ^{1}H NMR. We attribute the lack of complexation between viologen derivatives and **5** to its lack of conformational flexibility that prevents π-stacking, a necessary component for complexation of viologens. In contrast longer and more flexible cryptand **10** did complex dimethyl paraquat (**11**) with K_a = 1.6 (± 0.2) x 10^3 M^{-1} in acetone at 23 °C, probably by π-stacking with the *p*-oxybenzyl moieties of the host, made available by its enhanced flexibility.

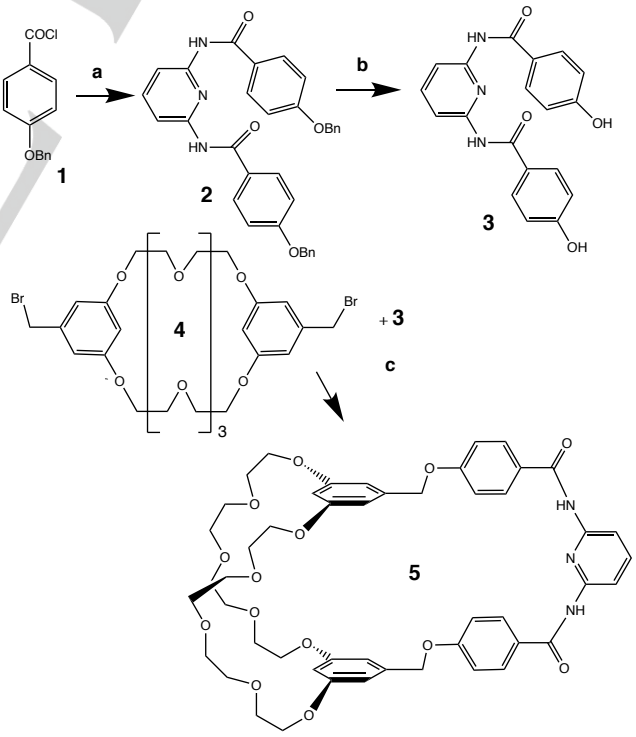
Introduction

In our quest to find hosts that bind viologens (*N*,*N*'-dialkyl-4,4'-bipyridinium salts) and/or diquats (*N*,*N*'-ethylene-2,2'-bipyridinium salts) very strongly, over the last two decades we developed cryptands from crown ethers,[1] the best of which provide binding constants in the range from 10^5 to > 10^6 M^{-1} at 25 °C.[1c,1d,1f,1h,1j,1m-1p] We also developed templated, high-yielding syntheses of dibenzo crown ethers [1i,2] as well as a templated method for converting dibenzo and bis(*m*-phenylene) crown ethers to dilactone cryptands whose third arms contain 2,6-dicarboxypyridine units as effective additional binding sites.[3] However, not all cryptands provide strong binding with viologens. Here we report two such cryptands designed along these lines.

Results and Discussion

a. Sytheses of New Cryptands

The cryptands we investigated earlier displayed very strong binding with viologens, forming pseudorotaxanes; these hosts contained pyridine rings in the third arms, prepared from pyridine-2,6-dicarboxylic acid and the crown ether diols. In the belief that a similar design using Williamson ether ring closures but incorporating a diamino pyridine as a binding site would result in even more powerful viologen binding, i. e., dilactams instead of dilactones, cryptand **5** was prepared according to **Scheme 1**. 2,6-Diaminopyridine was reacted with *p*-benzyloxybenzoyl chloride (**1**)[4] to afford the new protected bisphenol **2**; deprotection via hydrogenolysis afforded new bisphenol **3** essentially quantitatively. Cyclization via Williamson ether condensation of bis(5-bromomethyl-1,3-phenylene)-32-crown-10 (**4**)[5] with **3** produced the desired cryptand **5** in modest untemplated yield.



Scheme 1. Synthesis of cryptand **5**. **a**. 2,6-diaminopyridine/Et_3N, DCM, RT, 60%. **b**. H_2/Pd/C, EtOH, RT, 98%. **c**. K_2CO_3/*n*-Bu_4NI, DMF, RT-110 °C, 41%.

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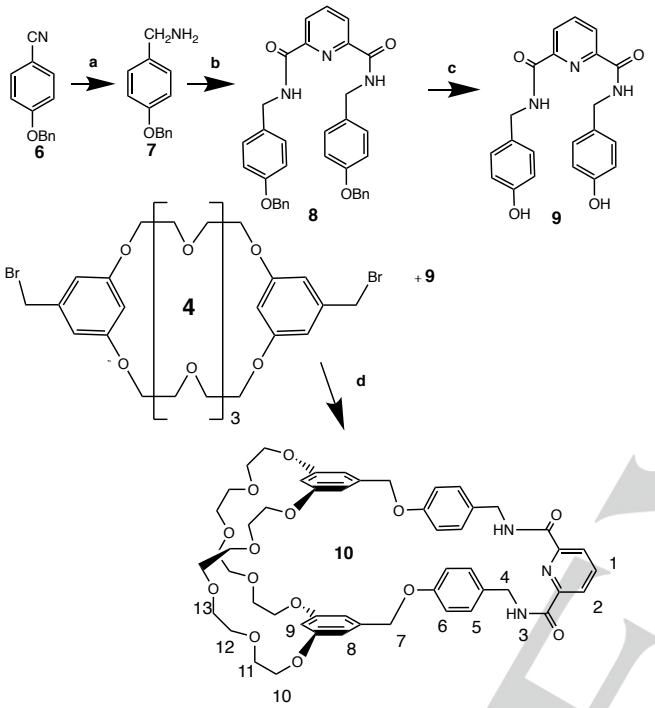
As an alternative we also prepared cryptand **10** via the route indicated in **Scheme 2.** Here *p*-benzyloxybenzylamine (**7**), a known compound,[6] was prepared from the corresponding nitrile **6**.[7] The amine **7** was reacted with 2,6-pyridinedicarbonyl chloride to produce new protected bisphenol **8**, which upon hydrogenolysis afforded the new bisphenol **9**. Williamson ether cyclization of **4** and **9** yielded the new cryptand **10**, again in modest untemplated yield.

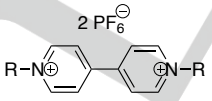
The intermediates and both cryptands were characterized satisfactorily via NMR and mass spectrometry.



Scheme 2. Synthesis of cryptand **10**. **a**. LAH/$AlCl_3$, Et_2O, RT, 91%. **b**. pyridine-2,6-dicarbonyl chloride/Et_3N, THF, RT, 82%. **c**. H_2/Pd/C, EtOH, RT, 99%. **d**. K_2CO_3/KCl/*n*-Bu_4NI, DMF, RT-110 °C, 41%.

b. Studies of Complexation of Cryptand 5 with Viologens

To probe the abilities of the cryptand to complex viologens, three compounds were selected; **11**, **12** and **13** were prepared as previously reported.[8,9]



11: R = CH_3
12: R = CH_2CH_2OH
13: R = $CH_2CH_2OOCNHC_6H_5$

The proton NMR spectra of cryptand **5** and its solutions with the three viologen derivatives are shown in **Figure 1**; a mixed solvent system was used because the viologens are not sufficiently soluble in $CDCl_3$. Strikingly, it can be seen that no change of chemical shifts corresponding to hydrogen atoms of host **5** can be observed, indicating that the expected complexations did not occur! This was confirmed by the lack of color in the solutions; usually hosts with aromatic rings form charge transfer complexes with viologens, leading to colors varying from yellow to dark orange or red.[1,10] Moreover, attempts to grow crystals from the solutions yielded only mixtures of the cryptand and the guest; no complexes resulted. The question is: why? Our first thought was that instead of being a cryptand, **5** is really a [1]rotaxane or a *pseudo*[1]catenane, as shown schematically in **Figure 2**.

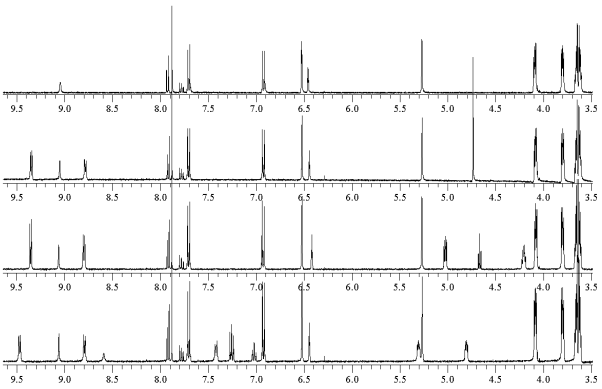


Figure 1. ^{1}H NMR spectra (400 MHz, 2.5:1 v:v CD_3COCD_3:$CDCl_3$, 22 °C) of 2.29 mM **5** (top), 2.29 mM **5** and 2.22 mM **11** (second from top), 2.29 mM **5** and 2.22 mM **12** (third from top), and 2.29 mM **5** and 2.22 mM **13** (bottom).

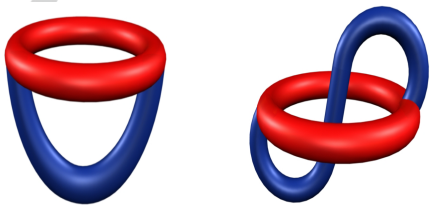


Figure 2. Schematic representation of a) left, a cryptand and b) right, its isomer, a [1]rotaxane or a *pseudo*[1]catenane.

[1]Rotaxanes have been reported, but they all consist of cyclic hosts bearing a long linear substituent with a bulky terminal group,[11] so the structure shown in **Figure 2** is better called a *pseudo*[1]catenane. *Pseudo*[1]catenanes have also been reported; these consist of *in-out* isomerization of fused or nearly fused ring systems;[11a,12] nearly fused means that the ring juncture on the initial macrocyclic is rather short, ca. four atoms. Some systems called *quasi*[1]catenanes [13] have also been reported; these consist of two rings sharing a spiro linkage constructed by step-wise chemistry a la Schill.[14] It seems that no *pseudo*[1]catenane of the sort shown in **Figure 2** formed by hydrogen bond induced self-threading across the width of the initial macrocycle has been reported. Therefore, we believe such a structure would be unique at this time.

In comparison to the previous cryptands[1] we examined, the third arms in **5** and **10** differ in two important ways: 1) the arm is longer, in **5** containing 19 atoms and in **10** 21 atoms, as opposed to 9-13 atoms in previous cryptands and 2) the presence of the amide groups in place of ether or ester moieties. These two factors could allow the third arm to thread through the cavity of the crown ether simply by inverting one of the phenylene rings in a process driven by hydrogen bonding of the amide NH moieties with the ether oxygen atoms as shown in **Figure 3,**

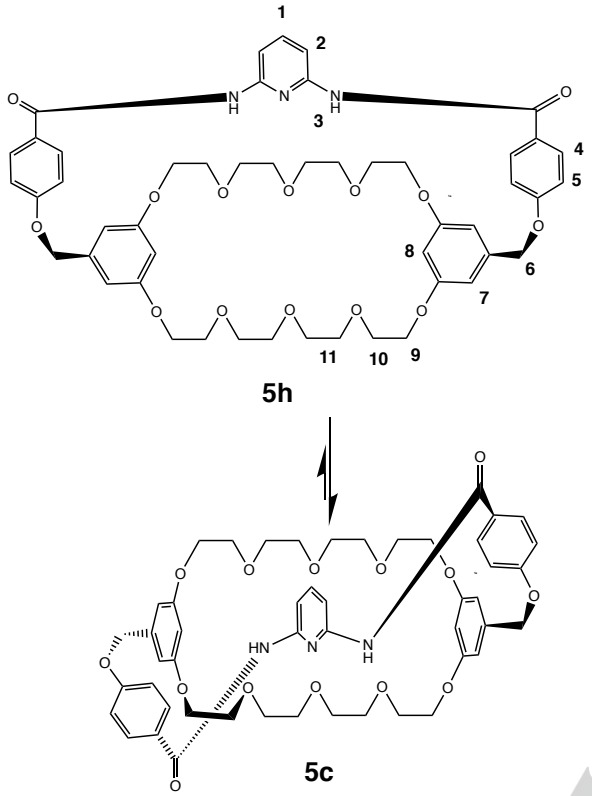


Figure 3. Possible equilibration of cryptand **5h** (**h** for host) to isomeric **5c** (**c** for *pseudo*[1]catenane via inversion of one of the *m*-phenylene rings of the crown ether driven by hydrogen bonding of the amide moieties to the ether oxygen atoms.

c. The Influence of Solvent Polarity on Purported Equilibration of Cryptand 5

To provide evidence for the putative formation of the *pseudo*[1]catenane isomer **5c**, ^{1}H NMR spectra were recorded in solvents of varying polarity as shown in **Figure 4**. Note that in chloroform the N-H protons (labeled *3*) yield two distinct and sharp, but unequal signals, while in the mixed solvent and DMSO only one broader signal is observed. In the latter two cases hydrogen bonding of **5** with the solvents is possible. Correspondingly the signals for the ethyleneoxy protons (labeled *9 – 11*) are shifted downfield in $CDCl_3$ as expected for hydrogen bonding of the amide NHs to the ether oxygen atoms. In $CDCl_3$ the hydrogen bonding could either be inter- or intra-molecular, the latter corresponding the **5c**. This result is not conclusive, however. The NOESY spectrum (see SI) did not reveal any through-space interactions indicative of **5c**.

Turning to Corey-Pauling-Kortun (CPK) models we sought confirmation of the ability of **5** to self-thread. However, they showed that self-threading is not possible for cryptand **5** because the linkages in the third arm are too rigid to allow this. As shown in **Figure 5** the rigidity forces the cavity to be open and apparently receptive to guests. Therefore, the reason for the lack of complexation of viologens is not self-threading. *What then is the reason for this unexpected inhospitality??*

d. Crystal Structure of Cryptand 5

With great anticipation a suitable crystal of the cryptand was grown from a chloroform:acetone (2.5:1.0 v:v) solution and subjected to X-ray diffraction. In the event, as shown in **Figure 6**, we were disappointed to find that in the solid state there was no evidence of self-threading of the type depicted in **Figure 3**. Instead, from the single molecule perspective (**Figure 6a**) the structure was open as initially expected from the CPK modeling.

However, a look at the packing (**Figure 6b**, **6c**, **6d**) reveals that the molecules are inter-nested in infinite chains oriented antiparallel to each other, consistent with the open clam-shell-like structure of the individual molecule. The closely packed molecules are held together by hydrogen bonds (**α** and **β**) to adventitious bridging water molecules between the amide NHs and ether oxygen atoms, in addition to dispersion forces.

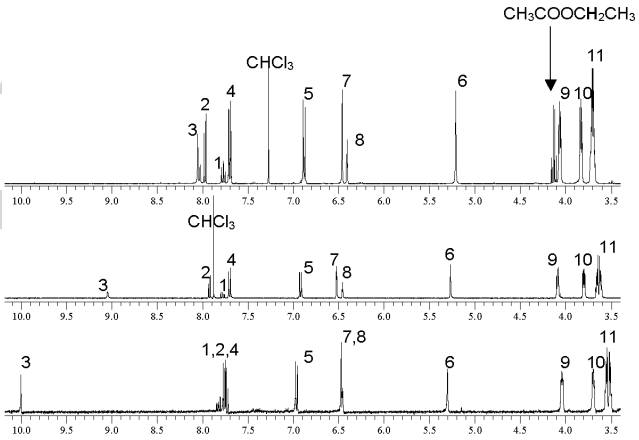


Figure 4. ^{1}H NMR spectra (400 MHz, 22 °C) of **5** in $CDCl_3$ (top), in 2.5:1 v:v $CD_3COCD_3/CDCl_3$ (middle), and DMSO-d_6 (bottom). For numbering see **Figure 3**. Peak assignments made via COSY; see SI.

Figure 5. Photographs of a CPK model of cryptand **5** showing its open cavity.

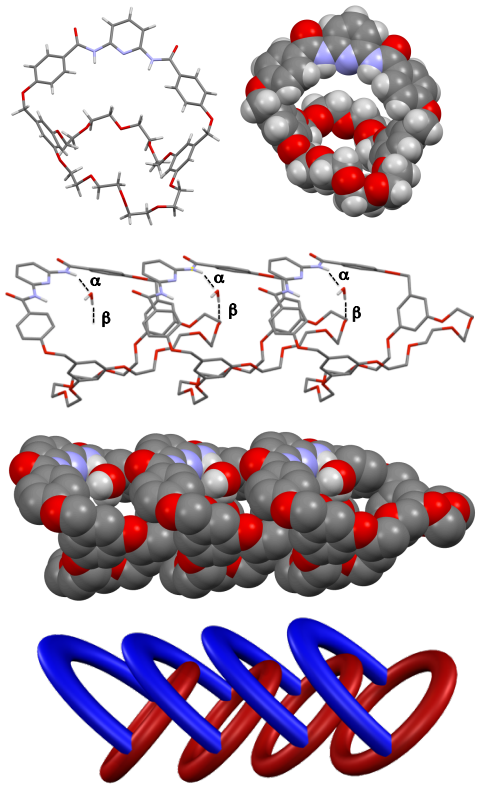


Figure 6. X-ray crystal structure of cryptand **5** (CCDC no. pending): a) top, stick and space filling representations of the individual molecule; b) middle, stick representation of the truncated infinite chain of inter-nested cryptand molecules (with non-interacting hydrogen atoms deleted); distance (angle) N--O 2.93 Å, (N)H—O (**α**) 2.11 Å (155.67 °), O—O 2.84 Å, (O)H—O (**β**) 1.95 Å (172.15 °); c) second from bottom, space filling representation (with non-interacting hydrogen atoms deleted) of the truncated infinite chain of inter-nested cryptand molecules; d) bottom, cartoon representation of inter-nested cryptand molecules. Disordered solvent molecules are not shown.

Inasmuch as self-threading of **5** is impossible, its lack of complexation with viologens must be attributed to something else. We initially suggested that aggregation in solution analogous to that observed in the crystal structure, leading to dimers, trimmers etc., prevented viologen complexation; the lack of complexation of **5** with viologens at 2.00 mM concentrations would thus imply that the dimerization constant is quite high, i. e., > 8 x 10^4 M^{-1}, to consume ≥ 91% of the cryptand.

However, an astute and dutiful reviewer suggested a more plausible explanation. As shown in **Figure 6a** and confirmed by CPK models, the rigidity of the pyridyl-containing arm places the 1,3,5-phenylene rings of the cryptand 10.40 Å apart (centroid to centroid) and maintains them in a nearly orthogonal arrangement (80.19 °). Complexation of viologens is primarily driven by π-stacking of the electron poor pyridinium rings with the electron rich aromatic rings of the host, which requires a parallel arrangement and separation of the latter by ca. 7 Å; here the conformational rigidity of **5** prevents this interaction. This is shown in **Figure 7**; guest **11** is easily accommodated in the large cavity of crypand **5**, but the 1,3,5-phenylene rings of the cryptand cannot π-stack with it nor can the aromatic rings of the *p*-oxybenzoyl moiety, which lie 10.69 Å apart at a 56.36 ° angle. Hence there are no non-covalent binding forces to form a complex between **5** and **11**.

e. Studies of Complexation of Cryptand 10 with a Viologen

At this juncture we did not hold much hope that cryptand **10** would be receptive to viologen guests. However, to our surprise, in fact, dimethyl paraquat (**11**) did form a 1:1 complex with **10** in acetone as shown in **Figure 8**. Note that protons H_7, H_8, H_9 and H_{10} on the host **10** move upfield strongly upon complexation, as do protons H_b and H_c of the guest paraquat; protons H_4 and H_5 move downfield and the ethylenexy protons merge into one signal. These chemical shift changes are consistent with previous observations of viologen complexes of cryptands based on bis(*m*-phenylene)-32-crown-10.[1a,1d,1l]

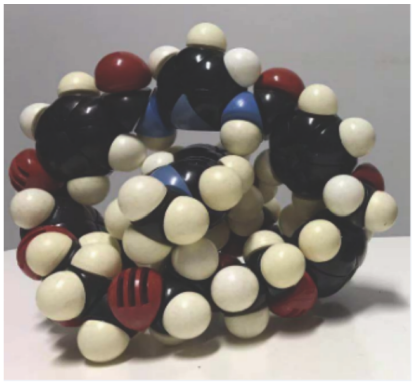


Figure 7. Photograph of a CPK model of viologen **11** in the flattened cavity of cryptand **5.**

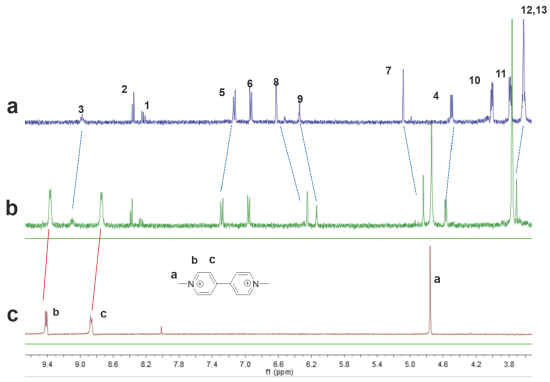


Figure 8. Partial ^{1}H NMR spectra (400 MHz, acetone-d_6, 23 °C): **a**) 1.00 mM cryptand **10**, **b**) 1.00 mM **10** + 1.00 mM paraquat (**11**), **c**) 1.00 mM paraquat (**11**). For numbering of the cryptand, see **Scheme 2**.

By the Job plot (**Figure 9**) the stoichiometry of the complex was established to be 1:1. The chemical shift of the fully complexed cryptand (Δ_o) was determined and this value was then used to calculate the binding constant of **10**:**11**, K_a = 1.6 (± 0.2) x 10^3 M^{-1} at 23 °C.[15] This value, however, is 1000-fold lower that similar cryptands with shorter third arms.[1d] This K_a is 3–fold higher than that of bis(*m*-phenylene)-32-crown-10 itself, which displays K_a = 0.55 x 10^3 M^{-1} with paraquat **11** under these conditions.[1b]

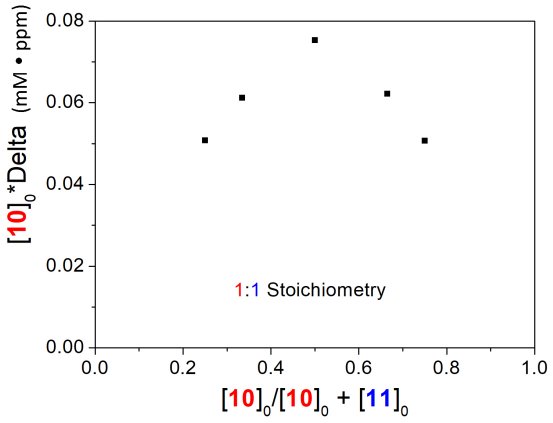


Figure 9. Job plot for interaction of cryptand **10** with dimethyl paraquat (**11**) in acetone-d_6 at 23 °C. Total concentration = 1.00 mM.

A new question is raised: why do **5** and **10** behave so differently in complexation experiments with viologens? We conclude that the longer third arm of **10** relative to that in **5** renders it more flexible, consistent with CPK models and with the fact that **10** is not a crystalline material; the addition of the two benzylic methylene groups in **10** relieves the rigidity induced through conjugation of the doubly aromatic amide linkages of **5**. The lower K_a of cryptand **10** with **11** relative to earlier cryptands probably reflects the remaining rigidity of the third arm, which as with host **5** probably prevents π-stacking of the 1,3,5-phenylene rings of the cryptand with the guest as indicated in **Figure 10**. However, this model also reveals that the two *p*-oxybenzyl moieties are nearly parallel and able to sandwich guest **11** by π-stacking. Unfortunately we were unable to obtain crystals of the host–guest complex **10**:**11** suitable for X-ray diffraction to assess this hypothesis.

Conclusions

Two new dilactam cryptands, **5** and **10**, based on bis(*m*-phenylene)-32-crown-10 and containing long third arms were prepared. NMR experiments showed that **5** did not complex any of the three viologens tested. X-ray crystallography revealed that the 1,3,5-phenylene rings of **5** in the solid state were nearly orthogonal with each other and were too far apart to π-stack with viologens, CPK models indicated the conformational rigidity of the structure, which disallowed reorganization to accommodate the guest. In contrast cryptand **10** did complex dimethyl paraquat (**11**), with K_a = 1.6 (± 0.2) x 10^3 M^{-1} in acetone at 23 °C; the more flexible third arm of **10** allows the two *p*-oxybenzyl aromatic rings to be parallel and we propose that they interact with the guest via π-stacking to stabilize the complex. These results re-emphasize the fact that having the right components for complexation is not sufficient; achieving the proper geometric orentations through conformational flexibility is also necessary.

Figure 10. Photograph of a CPK model of cryptand **10** showing its open cavity and nearly parallel *p*-oxybenzyl aromatic rings.

Experimental Section

Measurements, Materials: ^{1}H NMR spectra were obtained on JEOL Eclipse-500, Bruker 500 and Agilent NMR vnmrs400 spectrometers; ^{13}C NMR spectra were collected on these instruments at 126, 126 and 101 MHz, respectively. ^{1}H NMR splitting abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), h (heptet); coupling constants, *J*, are in Hz. High resolution mass spectra (HR MS) were obtained on a JEOL Model HX 110. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Reagents were purchased and used as received unless otherwise noted. *p*-Benzyloxybenzoyl chloride,[4] bis(5-bromomethyl-1,3-phenylene)-32-crown-10 (**4**) [5] and *p*-benzyloxybenzonitrile [6] were prepared via literature procedures.

2,6-Bis(*p*-benzyloxybenzoylamino)pyridine (2). Before the reaction, dichloromethane (DCM) was dried over molecular sieves and triethylamine was dried over KOH. A solution of *p*-benzyloxybenzoyl chloride[4] (**1**, 9.87 g, 40 mmol) in dry DCM (40 mL) was added dropwise to an ice-cooled mixture of 2,6-diaminopyridine (2.19 g, 20 mmol) and dry triethylamine (5.60 mL, 40 mmol) in dry DCM (120 mL). The mixture was stirred for 12 h at room temperature (RT); then the reaction was quenched with 20 mL of water, the organic layer was separated, washed with water, dried with magnesium sulfate, and concentrated under reduced pressure. The crude product was recrystallized from ethanol to give pure **2** (5.01 g, 60%), mp 226.1–227.0 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 5.22 (4H, s), 7.14 (4H, d, *J* = 9 Hz), 7.42 (10H, m), 7.86 (3H, m), 8.02 (4H, d, *J* = 9 Hz), and 10.31 (2H, s). HR MS FAB+ *m/z*: calcd. for $[M+H]^+$, $(C_{33}H_{28}N_3O_4)^+$: 530.20743; found: 530.20868 (error 0.43 ppm).

2,6-Bis(*p*-hydroxybenzoylamino)pyridine (3). A positive pressure (~ 40 psi) of H_2 was maintained for 48 h over a vigorously shaken suspension of 1.20 g (2.27 mmol) of benzyl ether **2** and 0.10 g Pd/C in 50 mL of anhydrous ethanol. After removal of the catalyst by filtration, the solvent was rotoevaporated to afford **3**, 0.77 g (98%), mp 285.8–286.5 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 4.34 (2H, s), 6.83 (4H, d, *J* = 9 Hz), 7.81 (3H, s), 7.88 (4H, d, *J* = 9 Hz), and 10.10 (2H, s). HR MS FAB+ *m/z*: calcd. for $[M+H]^+$, $(C_{19}H_{16}N_3O_4)^+$: 350.11353; found: 350.11371 (error 0.51 ppm).

Cryptand 5. A solution of 1.50 g (2.08 mmol) of crown ether dibromide **4** in 40 mL of DMF and a solution of 0.725 g (2.08 mmol) of bisphenol **3** in 40 mL of DMF were made. On the first day 10 mL of each solution were added into a stirred suspension containing potassium carbonate (2.87 g, 20.8 mmol) and tetrabutylammonium iodide (5 mg) in 1600 mL of DMF at

RT. After that, 5 mL of each were added every two days. After complete addition, the reaction mixture was stirred at 110 °C for 7 days. The cooled mixture was evaporated to remove DMF, treated with chloroform, and filtered. Removal of chloroform afforded a crude product which was purified by flash column chromatography (silica), eluting with 1:1 v:v hexane/ethanol and gradually increasing to ethyl acetate to give 0.77 g (41%) of **5**, mp 213.4-214.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ (ppm): 8.05 and 8.02 (2H, s), 7.97 (2H, d, *J* = 8 Hz), 7.77 (1H, t, *J* = 8 Hz), 7.70 (4H, d, *J* = 9 Hz), 6.87 (4H, d, *J* = 9 Hz), 6.46 (2H, d, *J* = 2 Hz), 6.41 (4H, t, *J* = 2 Hz), 5.21 (4H, s), 4.06 (8H, t, *J* = 5 Hz), 3.83 (8H, t, *J* = 5 Hz), and 3.70 (16H, m). ^{1}H NMR (400 MHz, 2.5:1 v:v CD_3COCD_3:$CDCl_3$, 22 °C) δ (ppm): 9.05 (2H, s), 7.92 (2H, d, *J* = 8 Hz), 7.78 (1H, t, *J* = 8 Hz), 7.70 (4H, d, *J* = 9 Hz), 6.92 (4H, d, *J* = 9 Hz), 6.52 (2H, d, *J* = 2 Hz), 6.46 (4H, t, *J* = 2 Hz), 5.27 (4H, s), 4.09 (8H, t, *J* = 5 Hz), 3.80 (8H, t, *J* = 5 Hz), and 3.63 (16H, m). ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 10.00 (2H, s), 7.82 (1H, m), 7.77 (4H, d, *J* = 8 Hz), 7.74 (1H, br), 7.72 (1H, m), 6.96 (4H, d, *J* = 8 Hz), 6.47 (4H, d, *J* = 4 Hz), 6.46 (2H, d, *J* = 4 Hz), 5.30 (4H, s), 4.04 (8H, t, *J* = 4 Hz), 3.70 (8H, t, *J* = 6 Hz), and 3.52 (16H, m). HR MS FAB+: calcd. for $[M+H]^+$, $(C_{49}H_{56}N_3O_{14})^+$ 910.37568; found 910.37579 (error 0.12 ppm).

4-Benzyloxybenzylamine (7). First 2.4 g (18 mmol) of $AlCl_3$ was added to a 250 mL three-necked round bottom flask with 35 mL of Et_2O and equipped with a magnetic stirrer. The resultant solution was added dropwise into another 500 mL three-necked round bottom flask filled with a mixture of 0.69 g (18 mmol) of $LiAlH_4$, 3.15 g (15 mmol) of 4-benzyloxybenzonitrile (**6**)[6] and 30 mL of Et_2O and equipped with a magnetic stirrer. The reaction mixture was kept at RT for 3 h. Water (100 mL) was added dropwise to the flask. The organic and water layers were separated. The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield the product (2.91 g, 91%), mp 116.2–117.5 °C; lit. mp 117 °C.[6] ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 3.95 (2H, s), 5.14 (2H, s), 7.06 (2H, d, *J* = 9 Hz), 7.39 (7H, m), and 8.16 (2H, br, s).

2,6-Bis(*p*-benzyloxybenzylaminocarbonyl)pyridine (8). To a solution of 4-benzyloxybenzylamine (**7**, 2.13 g, 10 mmol) and Et_3N (2.5 mL, 18 mmol) in THF (50 mL) was added 2,6-pyridinedicarbonyl dichloride (0.98 g, 4.8 mmol) in THF (30 mL) dropwise at RT. The resulting mixture was allowed to stir at RT for 12 h and poured into 150 mL of water. Solvents were removed with a rotoevaporator. The resultant solid mixture was recrystallized from ethanol to afford a colorless solid, 2.19 g (82%), mp 204.8–205.3 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 9.82 (2H, t, *J* = 7 Hz), 8.22 (3H, m), 7.36 (10H, m), 7.24 (4H, d, *J* = 9 Hz), 6.97 (4H, d, *J* = 9 Hz), 5.08 (4H, s), and 4.53 (4H, d, *J* = 7 Hz). LR MS FAB+ (NBA) *m/z* 558.1 $[M + H]^+$; HR MS FAB+ (NBA/PEG): *m/z* calcd. for $[M]^+$, $(C_{35}H_{31}O_4N_3)^+$, 557.23146; found 557.23187 (error 0.7 ppm).

2,6-Bis(*p*-hydroxybenzylaminocarbonyl)pyridine (9). A positive pressure (40 psi) of H_2 was maintained for 48 h over a vigorously shaken suspension of 1.60 g (2.87 mmol) of **8** and 0.10 g of Pd/C in 50 mL of anhydrous ethanol. After the removal of catalyst by filtration, the solvent was rotoevaporated to afford **9** as a colorless solid, 1.07 g (99%), mp 172.2–173.8 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 22 °C) δ (ppm): 9.80 (1H, t, *J* = 7 Hz), 9.19 (2H, s), 8.22 (4H, m), 7.13 (4H, d, *J* = 9 Hz), 6.72 (4H, d, *J* = 9 Hz), and 4.49 (4H, d, *J* = 7 Hz). LR MS FAB+ (NBA) *m/z:* 378.1 $[M + H]^+$; HR MS FAB+ (NBA/PEG) *m/z:* calcd. for $[M + H]^+$, $(C_{21}H_{20}O_4N_3)^+$, 378.14483; found 378.14517 (error –0.90 ppm).

Cryptand 10. A solution of 0.500 g (0.690 mmol) of crown ether dibromide **4** and 0.234 g (0.690 mmol) of bisphenol **9** in 40 mL of DMF was added via a syringe pump at 0.50 mL/h to a suspension containing 0.960 g (6.90 mmol) of potassium carbonate, 0.520 g (6.90 mmol)) of potassium chloride, and 5.00 mg of tetrabutylammonium iodide in 500 mL of DMF at 110 °C. After complete addition, the reaction mixture was stirred at 110 °C for 6 days. The cooled mixture was evaporated to remove DMF, extracted with chloroform, and filtered. Removal of chloroform afforded a crude product, which was purified by flash column chromatography (silica), eluting with ethyl acetate and gradually increasing to 1:1 ethyl acetate:methanol to afford **10** as a viscous oil, 0.26 g (40%), which did not crystallize. ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ (ppm): 8.42 (2H, d, *J* = 8 Hz), 8.10 (1H, t, *J* = 8 Hz), 7.81 (2H, t, *J* = 6 Hz), 7.24 (4H, d, *J* = 9 Hz), 6.93 (4H, d, *J* = 9 Hz), 6.51 (4H, d, *J* = 2 Hz), 6.38 (2H, t, *J* = 2 Hz), 4.93 (4H, s), 4.63 (4H, d, *J* = 6 Hz), 3.98 (8H, t, *J* = 5 Hz), 3.85 (8H, t, *J* = 5 Hz), and 3.68–3.75 (16H, m). LR MS FAB+ (NBA) *m/z*: calcd. for $[M]^+$, $(C_{51}H_{59}O_{14}N_3)^+$ 937.4; found 937.3. HR MS FAB+ (NBA/PEG) *m/z:* calcd. for $[M + H]^+$, $(C_{51}H_{60}O_{14}N_3)^+$, 938.40698; found 938.41180 (error 5.5 ppm).

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Keywords: cryptand, inhospitable non-host cryptand, viologen, pseudorotaxane complex, conformational flexibility

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15. ^{1}H NMR characterizations were done on solutions with constant $[\mathbf{10}]_0$ = 0.250 mM and varied $[\mathbf{11}]_0$ (0.500, 0.750, 1.00, 3.00, 5.00, and 15.0 mM). Based on these NMR data, Δ_0, the difference in δ values for aromatic proton H_9 of **10** in the uncomplexed and fully complexed species, was determined to be 0.3259 ppm as the y-intercept of a plot of $\Delta = \delta - \delta_u$ *vs.* $1/[\mathbf{11}]_0$. Then $p = \Delta/\Delta_0$; Δ = observed chemical shift change relative to uncomplexed species. The K_a value was calculated from $K_a = p/\{(1 - p)([\mathbf{11}]_0 - p[\mathbf{10}]_0)\}$ using the Δ value of a 1.00 mM **10** and **11** acetone solution.

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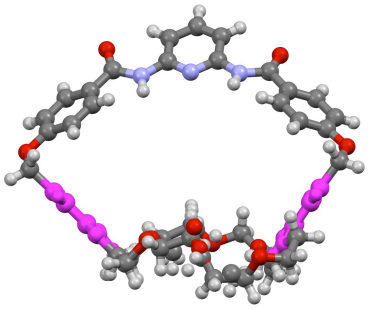

A conformationally rigid pyridyl cryptand does not bind viologens! The rigidity of the third arm of this cryptand causes the 1,3,5-phenylene rings (shown in pink) of the host to be nearly orthogonal and too far apart to π-stack with viologen guests. An analogous cryptand with a slightly longer and more flexible third arm does complex dimethyl paraquat.

An Inhospitable Cryptand: the Importance of Conformational Freedom in Host-Guest Complexation

Prof. Dr. Harry W. Gibson,* Prof. Dr. Feihe Huang, Run Zhao, Li Shao, Dr. Lev N. Zakharov, Dr. Carla Slebodnick, Prof. Dr. Arnold L. Rheingold

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