JOC The Journal of Organic Chemistry

Article

PSEUDOCRYPTAND HOSTS FOR PARAQUATS & DIQUATS

Jason W Jones, Terry Leon Price, Feihe Huang, Lev N. Zakharov,
Arnold L. Rheingold, Carla Slebodnick, and Harry William Gibson

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02812 • Publication Date (Web): 22 Dec 2017

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

PSEUDOCRYPTAND HOSTS FOR PARAQUATS & DIQUATS

Jason W. Jones,[a,¶] Terry L. Price, Jr.,[a,□] Feihe Huang,[a,§] Lev Zakharov,[b,£] Arnold L. Rheingold,[b] Carla Slebodnick [a] and Harry W. Gibson [a]

[a] Department of Chemistry and Macromolecules Innovation Institute, Virginia Tech, Blacksburg VA 24060

[b] Department of Chemistry, University of California, San Diego, La Jolla, CA 92093-0358

ABSTRACT

H-bonding interaction of acidic moieties (CH_2OH, COOH) at the 5- and 5'-positions of bis(1,3-phenylene)-32-crown-10 (**1**) with di- or tri-topic anions leads to enhanced formation of inclusion complexes with N,N'-dialkyl-4,4'-bipyridinium salts ("paraquats", **2**); the enforced folding of the crown ethers into pseudocryptands thus leads to pseudo-pseudorotaxanes. Strikingly, in the presence of the most effective anion (trifluoroacetate, TFA) the apparent bimolecular association constants for crown-paraquat complexation increase by more than an order of magnitude and approach those for covalent cryptands derived from the crown ether.

Even though they may form pseudocryptands the picolinate, nicotinate and isonicotinate diesters **6** of *cis*-(4,4')-bis(hydroxymethyl)dibenzo-30-crown-10 do not exhibit enhanced binding of either diquat or paraquat relative to the starting diol in contrast to the picolinate ester of isomeric 5,5'-bis(hydroxymethyl)bis(*m*-phenylene)-32-crown-10, which displayed a higher binding constant than the starting diol. The results for the analogous reverse esters **7** derived from *cis*-(4,4')-dicarboxydibenzo-30-crown-10 and pyridylmethanols reveal weaker complexes with diquat than the normal esters **6**; however, surprisingly two reverse esters **7** complex paraquat more strongly than isomers **6**.

¶ Present address: The Chemours Company, Wilmington, DE 19899

□ Present address: Zestron Corporation, 11285 Assett Loop, Manassas, VA 20109

§ Present address: Department of Chemistry, Zhejiang University, Hangzhou, P. R. China

£ Present address: Department of Chemistry, University of Oregon, Eugene, OR, 97403

INTRODUCTION

In the field of host-guest chemistry there is an ongoing quest to find new higher binding systems, more facile syntheses, and new molecular recognition motifs.[1] This opens the door to the production of new materials which may be accessed more easily and/or possess unique properties. Our work initially focused on improved syntheses of dibenzo crown ethers,[1g,2,3] and then the much higher binding cryptands.[3,4] With each change the host synthesis was improved and/or higher binding was achieved, leading to more efficient host-guest combinations. As an illustration of the importance of this progression, if the goal is the production of supramolecular polymers, with every increase in binding, higher molecular weights are achieved.[5] Since the synthesis of the pyridyl dibenzo-30-crown-10 cryptands and the recent introduction of pseudocryptands achieving association constants close to those of the corresponding cryptands with paraquat,[6] effort has been put into exploring other pseudocryptands. Pseudocryptands are cyclic host compounds which contain one or two unconnected arms that non-covalently yield a cryptand-like structure upon guest binding; these compounds are an extension of the class of pseudomacrobicyclic compounds [7-10] that earlier were called lariat ethers [11a,11b] and now rigid U-shaped hosts called “tweezers”;[11c-11e] however, the arms of the lariat ethers were designed to interact with the guests, while in the present work some arms were designed to close the encapsulating host by interacting with each other or counter-anions of guests. **Figure 1** provides cartoon examples of pseudocryptands.

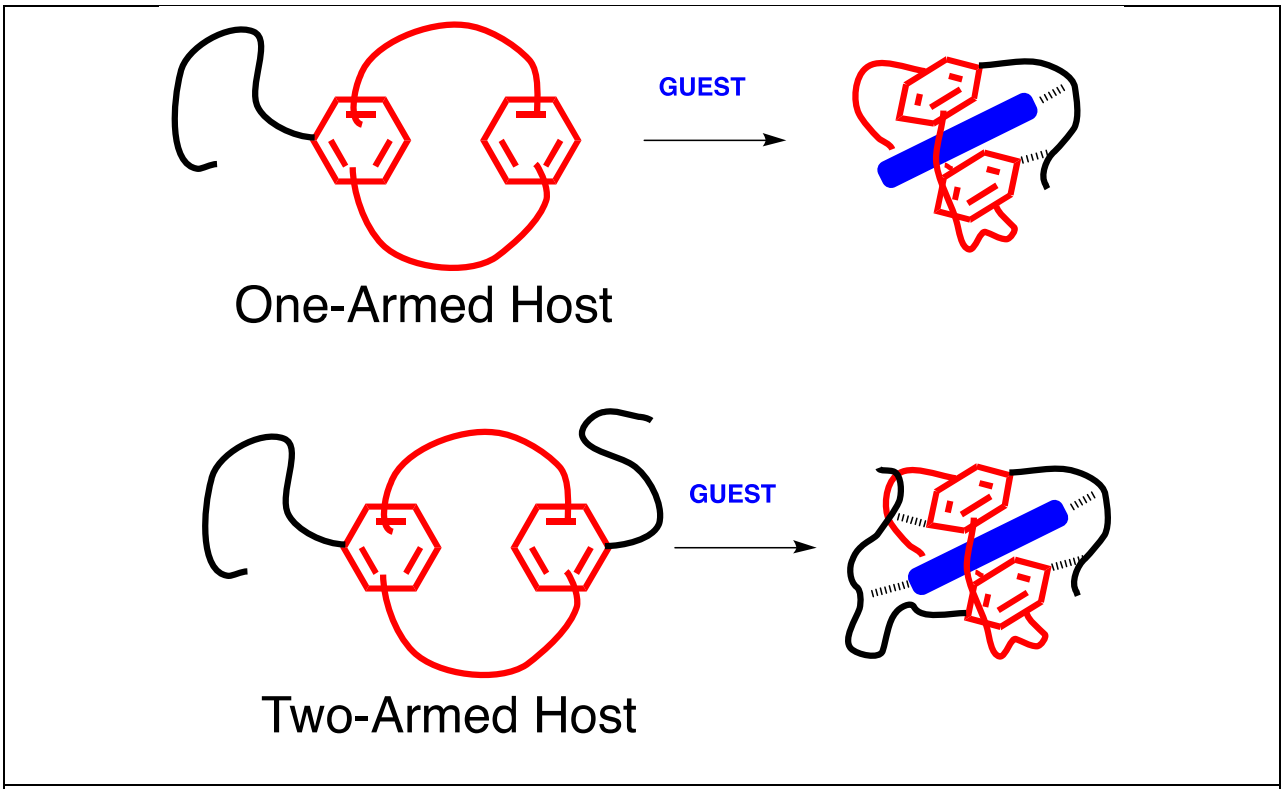


Figure 1. Pseudocryptand complexes formed from one- and two-armed hosts by interaction of the arms with either the guest and/or another part of the host.

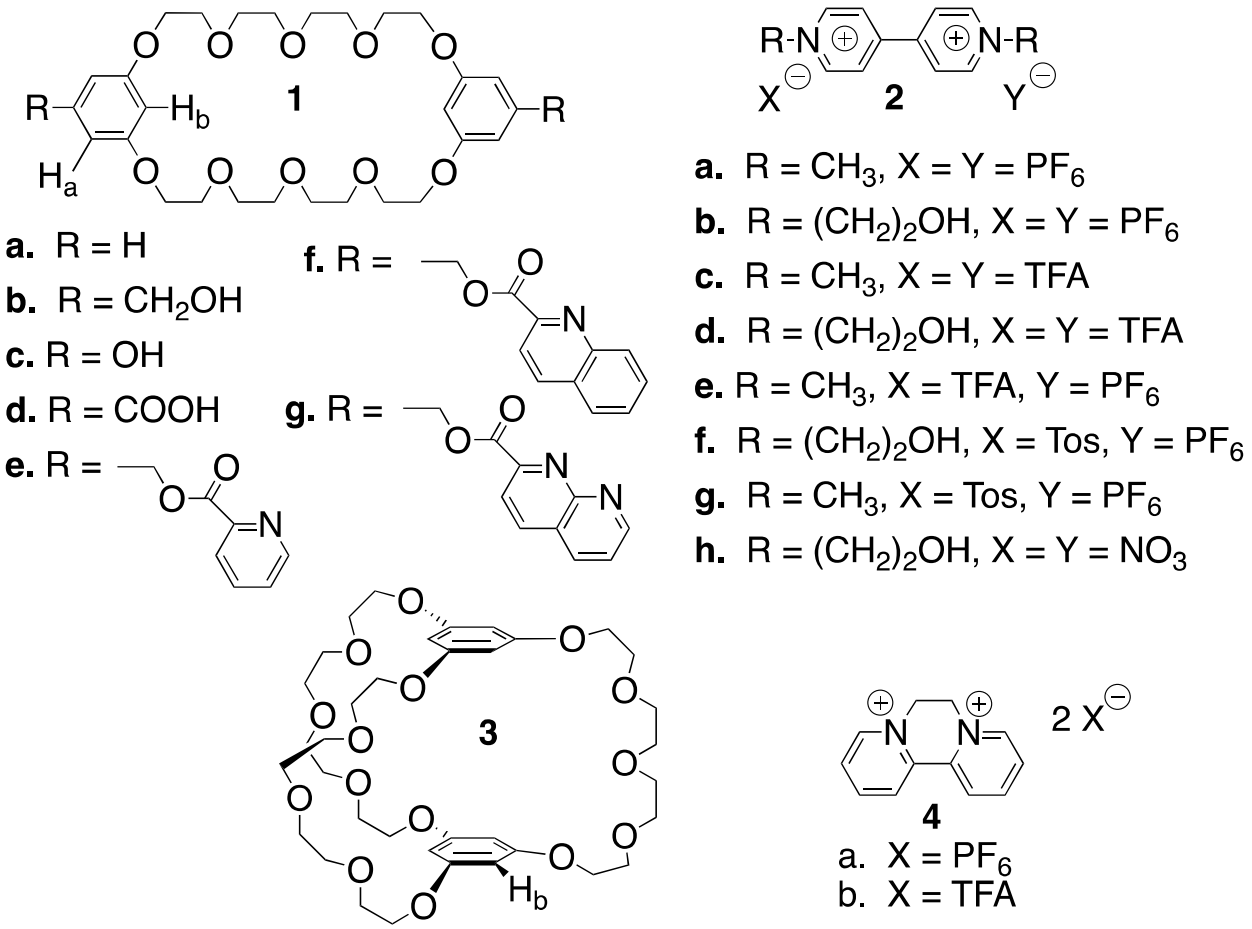
Useful crown ether derivatives are now available in high yields via K^+ templated syntheses [the Wang-Pederson-Wessels (WPW) protocol]. [1g,2,3,12] Here we explore two types of crown ether derivatives: in the first studies we examined use of counterions to bring about pseudocryptand formation through chelation of substituents on bis(*m*-phenylene)-32-crown-10 and the second series investigated the effects of the attachment of pyridyl ester moieties to dibenzo-30-crown-10.

RESULTS AND DISCUSSION

A. Anion Chelation of Derivatives of Bis(*m*-phenylene)-32-crown-10 (BMP32C10)

In the solid-state, one of the complexes formed between bis(5-hydroxymethyl-1,3-phenylene)-32-crown-10 (**1b**) and dimethyl paraquat **2a** was not a pseudorotaxane, but an exo- or taco-complex.[4a] The required folding of the host to adopt the taco-

complex suggested a favorable effect of constraining the flexible host molecule to the requisite folded shape,[13]



Scheme 1. Hosts and guest used in this study.

thereby minimizing the entropic penalty of reorganization. Indeed, when a covalent linker was used to do so in forming bicyclic host **3**, a 100-fold improvement in association constant (K_a) resulted, increasing from 5.5 x 10^2 M^{-1} in **1b•2a** to 6.0 x 10^4 M^{-1} in **3•2a**! [4a] Dynamic temperature studies indicated the increase in K_a resulted entirely from preorganization of **3**, i. e., the difference was entirely due to entropic factors,

results which were supported by X-ray structural analyses as nearly identical geometries and interactions were noted for **1b•2a** and **3•2a**.

Encouraged by these exciting results, we explored other methods to drive pseudorotaxane formation by enforcing the folding of BMP32C10 necessary for formation of taco complexes, thus reducing the entropic penalty for complexation, through hydrogen bonding of suitable 5- and 5'-substitutents with di- and tri-topic anions, i. e., formation of "pseudocryptands" [8] in a non-covalent or truly supramolecular manner. The anions were introduced as tetraalkylammonium salts.

As a control experiment, an acetone-d_6 solution of crown ether diol **1b** with two equivalents of tetra(*n*-butyl)ammonium hexaflurophosphate (*n*-Bu_4NPF_6) was studied. Neither ^{1}H (see SI, **Figure S1**) nor ^{19}F NMR resonances shifted for either of the two components, indicating that *n*-Bu_4NPF_6 does not form a complex with **1b**. Under similar conditions, ^{1}H (see SI, **Figure S2**) and ^{19}F NMR indicated that no interaction occurs between paraquat diol **2b** and *n*-Bu_4NPF_6.

In a second control experiment, we observed complexation of paraquat diol **2b** by crown ether diol **1b** in acetone-d_6. As discussed elsewhere,[14,15] a bright orange solution resulted upon mixing the host and guest components, indicative of a charge transfer event from the electron rich host to the electron deficient viologen. We then titrated *n*-Bu_4NPF_6 into the solution and noted that the time averaged ^{1}H NMR resonances of the crown ether shift towards their uncomplexed positions, qualitatively signaling a decrease in association (**Figure 2**). In light of a report that suggests **2a** to be *fully* ion paired in acetone-d_6,[16] this finding was unexpected: if the complex truly were 100% ion

paired, one would predict K_a not to vary. To explain this anomaly, we consider two possibilities.

First, it may be the case that Δ_0 changes for the system upon addition of *n*-Bu_4NPF_6; as a result, the observed chemical shift change of **Figure 2** would carry no qualitative meaning. We tested this possibility by studying a solution 0.9 mM in host **1b** and 100 mM in paraquat **2b** both before and after addition of 100 mM *n*-Bu_4NPF_6. The 100-fold excess of guest relative to host ensured near quantitative complexation of **1b**, enabling one to determine δ_{bound}, and thus Δ_0, by simple observation of the host resonances. As can be seen in **Figure 3**, the δ_{bound} signals do not change upon addition of *n*-Bu_4NPF_6. We conclude that Δ_0 is therefore unaffected by addition of *n*-Bu_4NPF_6.

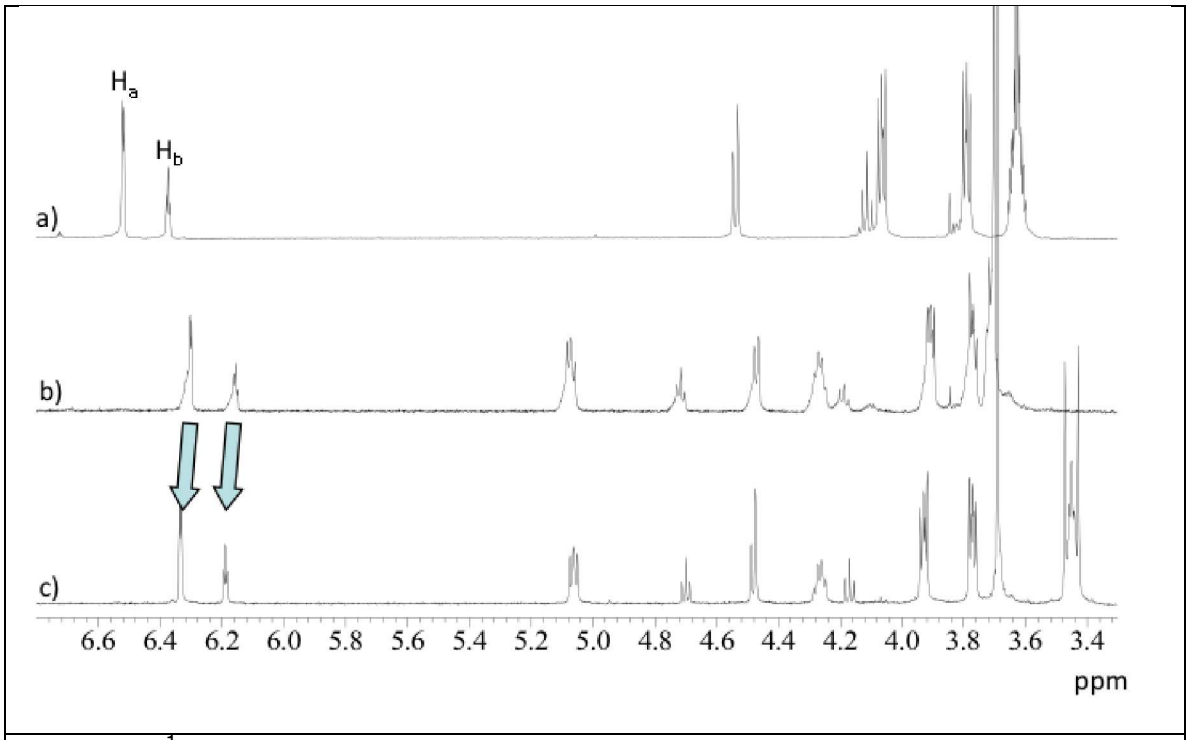


Figure 2. ^{1}H NMR spectra (400 MHz, 295 K, acetone-d_6) of a) crown diol **1b**; b) 2.00 mM **1b** + 2.00 mM paraquat diol **2b**; c) 2.00 mM **1b** + 2.00 mM **2b** + 4.63 mM *n*-Bu_4NPF_6.

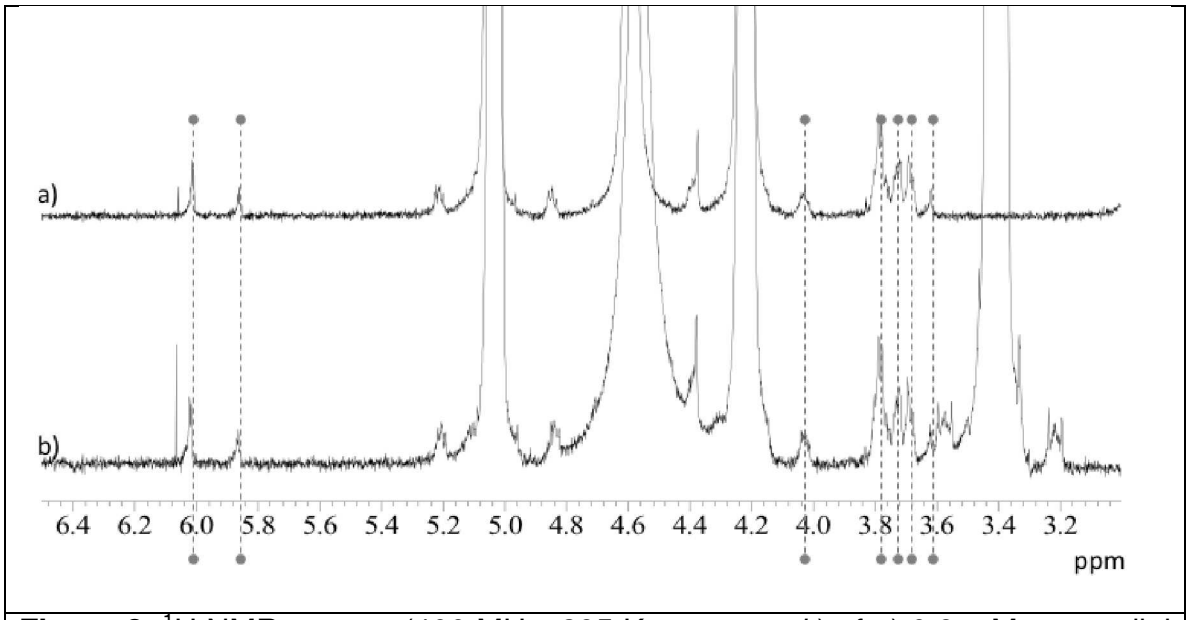


Figure 3. ^{1}H NMR spectra (400 MHz, 295 K, acetone-d_6) of a) 0.9 mM crown diol **1b** + 100 mM paraquat diol **2b** and b) 0.9 mM **1b** + 100 mM **2b** + 100 mM *n*-Bu_4NPF_6.

Because the result of **Figure 2** is reminiscent of a similar experiments with dibenzo-24-crown-8 and dibenzylammonium PF_6,[17,18] we considered the only remaining possibility: the complex **1b•2b** may not be fully ion paired. As a result of the ion pair dissociation constants (K_{ipd}) of *n*-Bu_4NPF_6 (1 to 5 x 10^{-2} M) [19a,19b] and analog **2a** (≈ 1 × 10^{-2} M) [20] in acetone, the paraquat under the influence of a large excess of PF_6^- would become more ion paired, thereby driving the complexation equilibrium towards starting materials, as observed in **Figure 2**. We believe this to be the reality, and speculate that minor percentages in the extent of complex ion pairing would otherwise be difficult to discern in this fast exchange system.

Therefore, we concluded that the reduction in binding was due to enhanced ion pairing of the paraquat diol (**2b**) by the added PF_6^-. The spectra were analyzed to estimate K_a. Because addition of *n*-Bu_4NPF_6 was shown not to influence δ_{bound}, Δ_0 was taken from earlier studies [21] to be 0.472 ppm for H_b. Based on this value, we calculated

K_a = 8.3 (□ 1.3) x 10^2 M^{-1} for **1b•2b** alone and K_a = 5.2 (□ 0.8) x 10^2 M^{-1} for **1b•2b** in the presence of *n*-Bu_4NPF_6, representing a significant 40% reduction in K_a.[22]

We showed that when mixed with crown diol **1b**, *n*-Bu_4NPF_6 does not interact with the host (**Figure S1**). Similarly, no interaction occurs between paraquat diol **2b** and *n*-Bu_4N PF_6 (**Figure S2**). However, addition of *n*-Bu_4NPF_6 to a solution of **1b**/**2b** caused signals to shift toward the uncomplexed state. Contrary to this result, as we previously reported [7] the ^{1}H NMR resonances of the crown signals in a solution of crown diol **1b** and paraquat diol **2b** all shifted towards their fully complexed positions upon addition of tetraethylammonium trifluoroacetate (Et_4NTFA), signaling an increase in association. Indeed, at 2.35 equivalents of added salt the apparent K_a value increased an impressive 14-fold. The observed upfield chemical shift upon addition of Et_4NTFA is especially noteworthy given the tendency of TFA^- to form a much tighter ion pair than PF_6^-,[17,18,19c] which, as demonstrated by **Figure 2**, would otherwise result in a downfield chemical shift of the complex. Indeed, in the absence of host **1b**, counterion exchange between **2a** or **2b** and Et_4NTFA results in the precipitation of **2c** or **2d**, respectively. Furthermore, parent crown ether **1a** without the hydroxymethyl groups complexed guest **2a** 43% more weakly in the presence of Et_4NTFA through increased ion pairing of the guest, indicating the critical importance of the hydroxyl moieties.[23] An X-ray crystal structure of the pseudocryptand complex **1b•2e** clearly showed the hydrogen bonding of the ditopic trifluoroacetate (TFA) anion with the hydroxyl groups of **1b**.[7] Later this motif was re-confirmed via X-ray crystallography of an analogous complex comprising the pseudocryptand formed from crown ether bisphenol **1c** and TFA anion and a bisparaquat.[24]

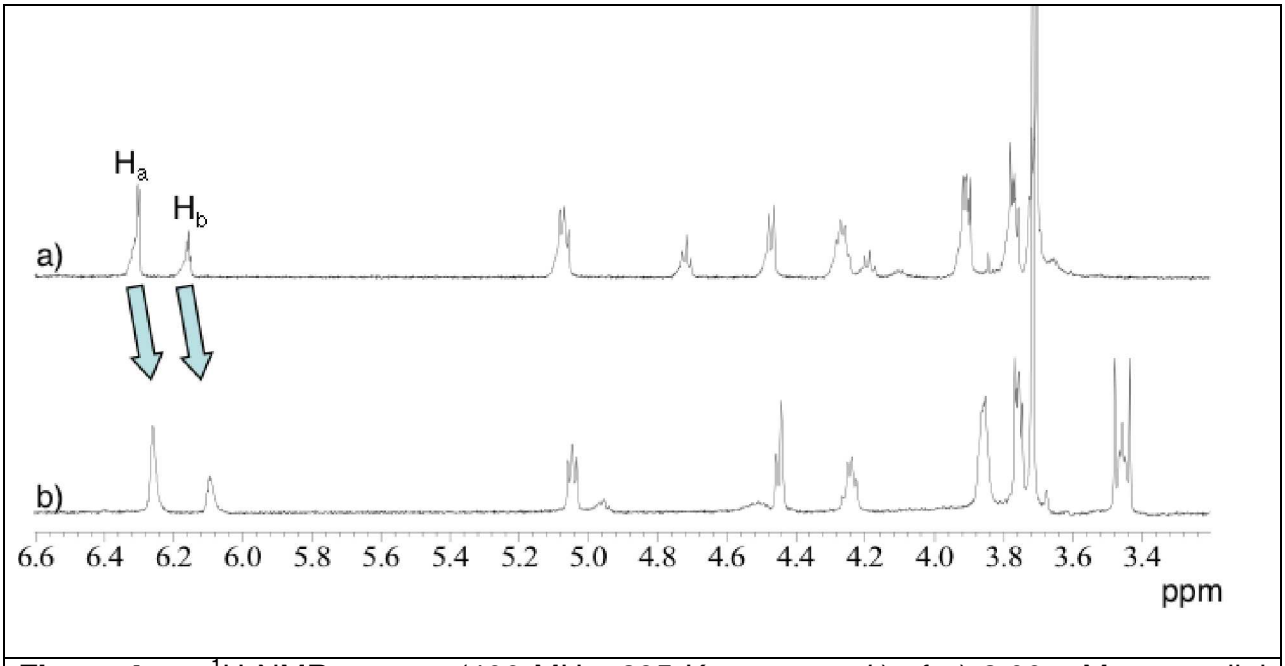


Figure 4. ^{1}H NMR spectra (400 MHz, 295 K, acetone-d_6) of a) 2.00 mM crown diol **1b** + 2.00 mM paraquat diol **2b** and b) 2.00 mM **1b** + 2.00 mM **2b** + 2.50 mM *n*-Bu_4NOTs.

In the case of dol **1b**, since no changes occurred in the ^{1}H NMR spectrum upon addition of ET_4NTFA we concluded that formation of the pseudocryptand structure is a cooperative process requiring the presence of both the guest and the anion, leading to complex **1b•2e**.

Based on these encouraging results we moved on to study the influence of other tetrabutylammonium salts on the complexation of host **1b** with guest **2b**. Using the same approach the tridentate tosylate anion (OTs^-) increased $K_{a,exp}$ 1.6 fold (to K_a = 920 M^{-1}, **Figure 4**, **Table 1**). Again in view of the fact that tetra(*n*-butyl)ammonium tosylate (*n*-Bu_4NOTs) is more ion paired (K_{ipd} = 2.5 x 10^{-3} M) [19d] than *n*-Bu_4NPF_6 it might have been expected that complexation would be retarded. A single crystal of the resultant mixed anion complex **1b•2f** was grown and the X-ray diffraction structure (**Figure 5**) shows that in this solid state structure only two oxygen atoms of the tosylate anion interact with one of the hydroxyl groups of host **1b** at O--H distances of 2.70 and 1.96 Å

(a and h in **Figure 5**); one of the oxygen atoms of the TsO interacts strongly with the 2- and 3-protons of one pyridyl ring of the paraquat guest (b and c In **Figure 5**). Presumably in solution, however, the anion does bind both OH groups of the host to form a pseudocryptand, but the solid state structure does not comprise a pseudocryptand. Notably the remaining PF_6 anion interacts with both □□hydrogens of the paraquat; that is, the complex is ion paired. Other details of the structure are similar to analogous complexes: π-stacking of the aromatic rings at 3.6 Å and multiple interactions of the protons of the guest with oxygen atoms of the host.

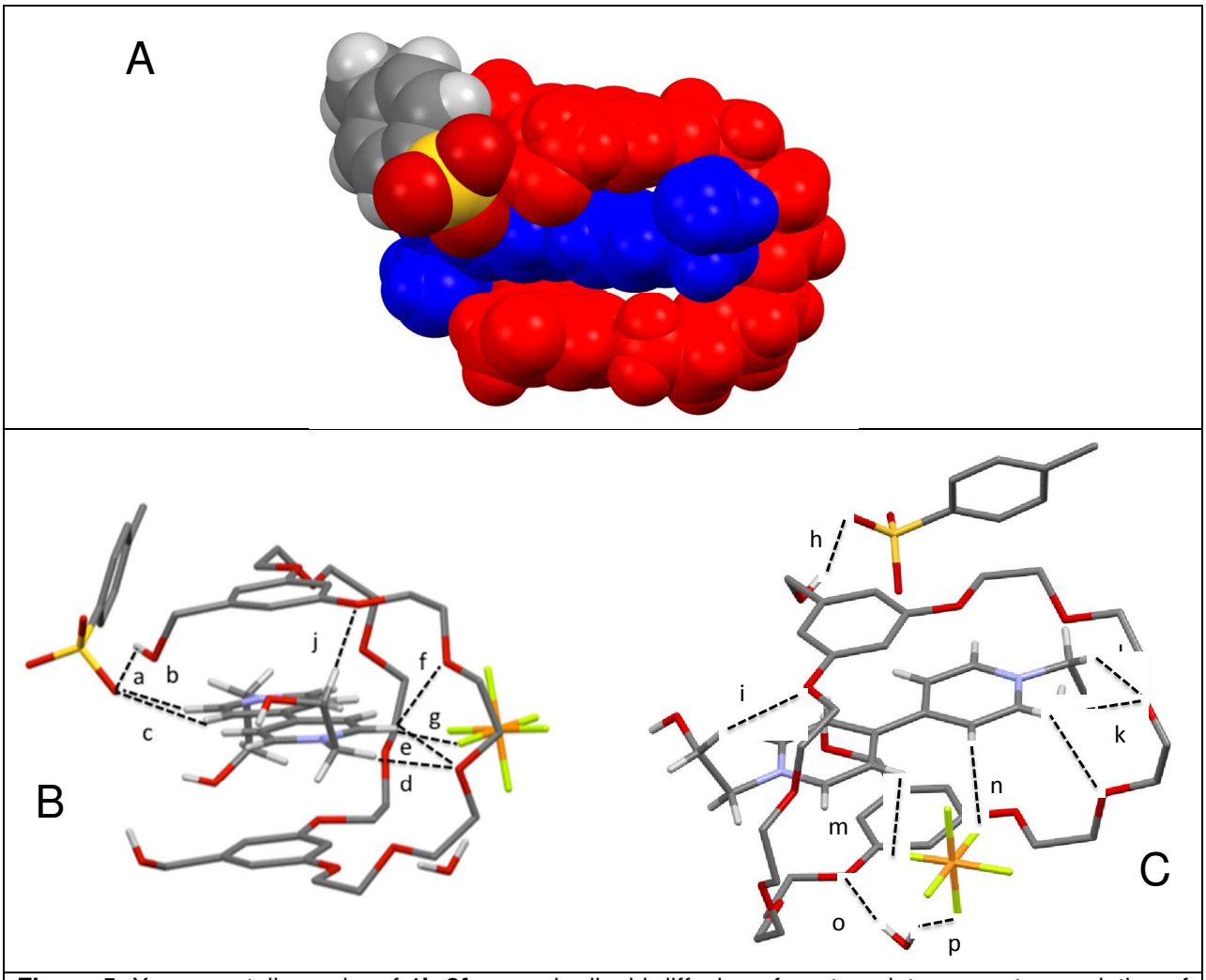


Figure 5. X-ray crystallography of **1b•2f** grown by liquid diffusion of pentane into an acetone solution of the components. **A)** Space filling representation, showing the interaction of the tosylate with one hydroxyl group of the host and the 2- and 3-protons of the guest; the host is shown in red and the guest in blue; the hydrogens of the tosylate anion are white, the sulfur is yellow and the oxygens are red. **B)** Stick representation showing interactions of one tosylate oxygen with a hydroxyl proton of the host and the 2- and 3-protons of the guest and other interactions between host and guest as well as with the PF_6 counteranion. **C)** Stick representation showing interactions of another tosylate oxygen with the same hydroxyl proton of the host and other host-guest interactions. In **B** and **C** hydrogen atoms on the host and tosylate have been removed for clarity. Hydrogen-bond parameters: C---O(X) distances (Å), C-H---O(X) distances (Å), C-H ---O(X) angles (deg) a:----, 2.70, ---; b: ---, 2.49, ---; c: ---, 2.57, ---; d: 3.23, 2.26, 175.0; e: 3.62, 2.84, 140.2; f: 3.29, 2.58, 131.7; g: 2.92, 2.31, 122.0; h: ---, 1.96, ---; i: 3.64, 2.71, 157.4; j: 3.12, 2.45, 127.8; k: 3.37, 2.51, 151.0; l: 3.40, 2.53, 147.1; m: 3.03, 2.51, 115.2; n: 3.53, 2.64, 157.4; o: ---, 2.21,---; p: ---, 1.93, ---. Centroid to centroid distance between phenyl rings: 7.08 Å; distance between centroids of top phenyl ring and that of paraquat: 3.57 Å; distance between centroids of bottom phenyl ring and that of paraquat: 3.58 Å. Angle between phenyl planes of the host: 1.60 °. Angle between top phenyl plane and PQ plane: 3.45 °. Angle between bottom phenyl plane and PQ plane: 5.05 °. Torsion angle of bipyridinium rings: 1.81 °.

The interaction of crown diol **1b** with dimethyl paraquat **2a** and *n*-Bu_4NOTs led to a 1.5-fold increase in K_a (**Table 1**).[7] The resulting complex **1b•2g** is superficially similar to **1b•2f** as shown in **Figure 6**. However, the torsion angle of the paraquat is quite different from that in **Figure 5**: 20.7 vs. 1.8 ^{o}!! Again the tosylate anion interacts with only one of the hydroxy groups of the crown diol (a In **Figure 6**). But now instead of the other oxygen atom of the tosylate interacting with the 2- and 3-protons of one of the paraquat rings as in **Figure 5**, it now interacts with the 3-protons of both paraquat rings (b and c In **Figure 6**).

Interestingly, there is an element of unpredictability in use of chelating anions. This is demonstrated by enhanced complexation of crown ether diol **1b** with diquat (**4a)** in the presence of Et_4NTFA, yielding **1b•4b**, as previously reported.[26a] Contrary to the above results (**Figures 5** and **6**) the two hydroxyl groups of the host crown ether in **1b•4b** are linked not by one of the anions, but rather by an adventitious water molecule (f and g in **Figure 7**); the TFA anions do interact with the methylene protons of the paraquat guest (b and c in **Figure 7**). The water in this case is the hydrogen bond donor and the diol the acceptor, as opposed to the case of **1b•2e***,* in which the TFA anion is the hydrogen bond acceptor and the diol is the donor.[7] However, the oxygen atom of the water molecule interacts with the 3- and 3'-hyrdrogen atoms of the diquat (i and j in **Figure 7**). In this case the water closes the pseudocryptand (f and g in **Figure 7**) and not the TFA anion.

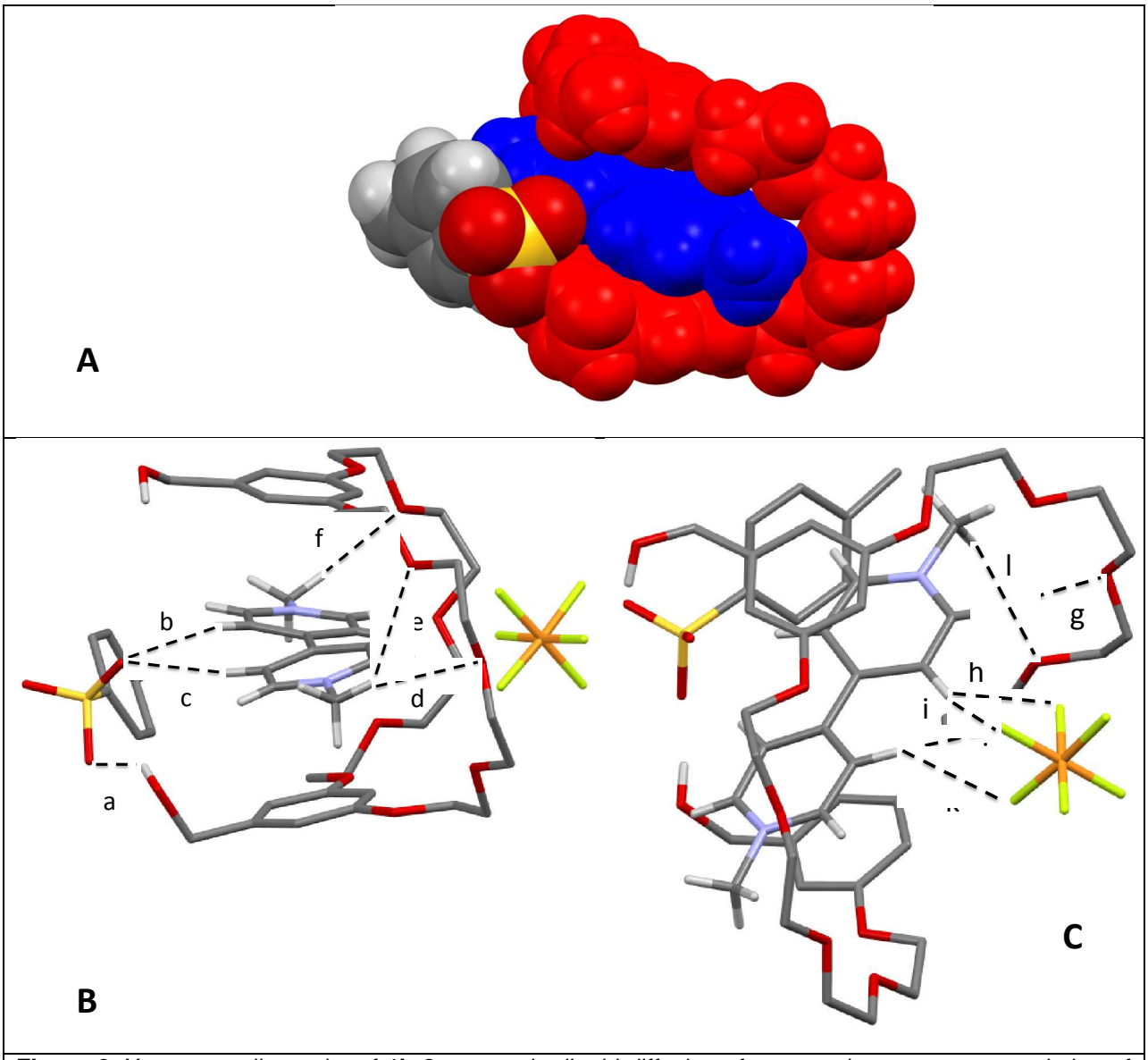


Figure 6. X-ray crystallography of **1b•2g** grown by liquid diffusion of pentane into an acetone solution of the components. **A)** Space filling representation, showing the interaction of the tosylate with one hydroxyl group of the host and the 3- and 3'-protons of the guest; the host is shown in red and the guest in blue; the hydrogens of the tosylate anion are white, the sulfur is yellow and the oxygens are red. **B)** Stick representation showing interactions of one tosylate oxygen with a hydroxyl proton of the host and the 3- and 3'-protons of the guest and other interactions between host and guest. **C)** Stick representation showing other host-guest interactions and interactions with the PF_6 anion. In **B** and **C** hydrogen atoms on the host and tosylate have been removed for clarity. Hydrogen-bond parameters: C---O(X) distances (Å), C-H---O(X) distances (Å), C-H ---O(X) angles (deg) a:----, 2.06, ---; b: 3.13, 2.31, 144.8; c: 3.64, 2.82, 169.6; d: 3.57, 2.62, 164.9; e: 3.49, 2.79, 129.6; f: 3.28, 2.44, 139.8; g: 3.38, 2.51, 153.6; h: 3.23, 2.46, 138.7; i: 3.62, 2.77, 151.1; j: 3.48, 2.54, 173.3; k: 3.46, 2.72, 135.6; l: 3.400, 2.84, 117.7. Centroid to centroid distance between phenyl rings: 7.17 Å; distance between centroids of top phenyl ring and that of paraquat: 3.55 Å; distance between centroids of bottom phenyl ring and that of paraquat: 3.52 Å. Angle between phenyl planes of the host: 15.35 °. Angle between top phenyl plane and PQ plane: 8.60 °. Angle between bottom phenyl plane and PQ plane: 6.90 °. Torsion angle of bipyridinium rings: 20.69 °.

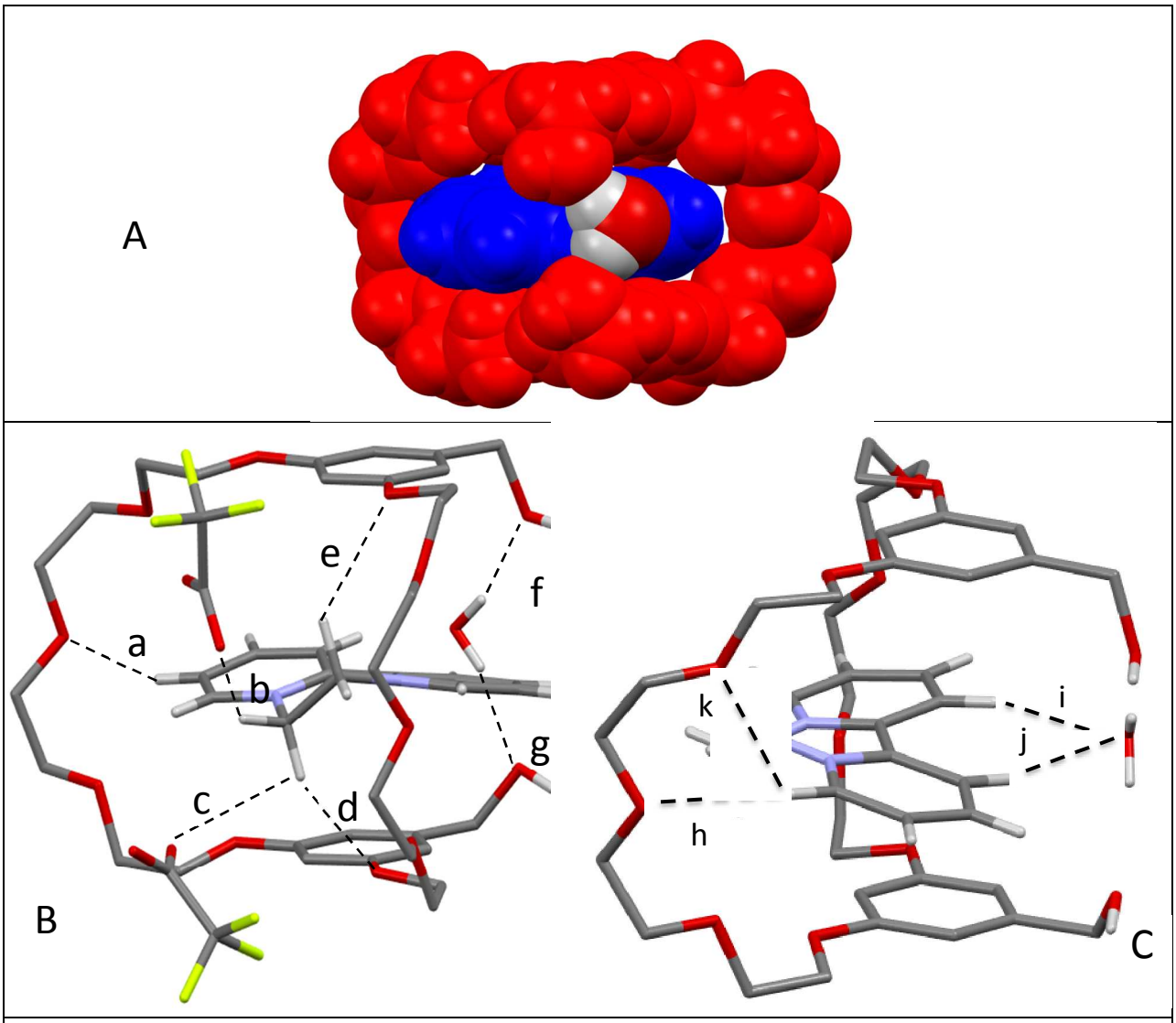


Figure 7. X-ray crystallography of **1b•4b** grown by vapor diffusion of pentane into acetone at room temperature. **A)** Space filling representation with counterions removed, showing the pseudocryptand structure resulting from water chelation; the host is shown in red and the guest in blue; the hydrogens of water are white and the oxygen is red. **B)** Stick representation showing interactions of the counterions with the methylene protons and other interactions. Hydrogen atoms on the host have been removed for clarity. Carbons are gray, hydrogens are white, nitrogens are blue, oxygens are red and fluorines are yellow-green. **C)** Stick representation showing interactions of the guest with water and the host. Counterions and hydrogen atoms on the host have been removed for clarity. Carbons are gray, hydrogens are white, nitrogens are blue and oxygens are red. Hydrogen-bond parameters: C---O(X) distances (Å), C-H---O(X) distances (Å), C-H ---O(X) angles (deg) a: 2.80, 3.66, 151.9; b: 2.41, 3.13, 128.4; c: 2.89, 3.22, 100.4; d: 2.52, 3.39, 146.6; e: 2.63, 3.78, 132.2; f: 2.00, 2.81, 166.0; g: 2.00, 2.84, 167.0; h: 2.59, 3.45, 150.9; i: 2.46, 3.39, 166.9; j: 2.45, 3.36, 162.2; k: 2.62, 3.22, 120.9. Centroid to centroid distance between phenyl rings: 6.98 Å. Angle between phenyl planes of the host: 1.16 °. Angle between top phenyl plane and DQ plane: 0.48 °. Angle between bottom phenyl plane and DQ plane: 1.49 °. Torsion angle of bipyridinium rings: 17.6 °.

Incremental addition of teta(*n*-butyl)ammonium nitrate (*n*-Bu_4NO_3) to an acetone-d_6 solution 2.00 mM in both BMP32C10 diol (**1b)** and paraquat diol PF_6 (**2b**) caused diminution in the extent of complexation initially, as noted both by chemical shift changes and lessening of the intense yellow-orange color of the initial solution, and then precipitation and finally total loss of the guest from solution. This experimental result indicates that nitrate salt **2g** is insoluble in acetone. Indeed precipitation of **2g** was observed upon addition of *n*-Bu_4NNO_3 to **2b** in acetone.

As expected, the non-chelating tetrafluoroborate (BF_4^-) anion of tetra(*n*-butyl)ammonium tetrafluroborate (*n*-Bu_4NBF_4) reduced association of paraquat diol **2b** with crown diol **1b**. (**Figure S3**, SI). Likewise, addition of tetra(*n*-butyl)ammonium trifluoromethanesulfonate (*n*-$Bu_4NCF_3SO_3$) also diminished apparent K_a values, a result of the reduced basicity of trifluoromethanesulfonate (triflate) anion relative to TFA (**Figure S4**, SI). At the other extreme, addition of the more basic acetate (CH_3COO^-) anion via tetra(*n*-butyl)ammonium acetate (*n*-$Bu_4NCH_3CO_2$) to **1b**/**2b** resulted in electron transfer reactions,[25] which destroyed the guest ligand.

Noting that the dicarboxylic acid host **1d** should more readily H-bond to di- and tri-topic anions than host **1b** due to its higher acidity, we explored its complexation with paraquat **2a** in the presence of Et_4NTFA and found a 47-fold increase in K_a to 3.4 x 10^4 M^{-1} (**Table 1**). This finding is significant, especially considering that this value is within a factor of two of that determined for the covalent cryptand analog **3** (6.1 x 10^4 M^{-1}, **Table 1**). In the case of diacid **1d** ^{1}H NMR spectra (see SI, Figure S8) show definite interactions with Et_4NTFA, suggesting that a pseudocryptand is in dynamic equilibrium

with its components in the absence of the guest species. Thus, this system contrasts with **1b•2e**, in which pseudocryptand formation requires the guest.

Table 1. Comparison of binding constants (K_a) of various pseudocryptand and cryptand systems in acetone-d_6 at 22 °C. Values determined from the chemical shift of H_b for each host.

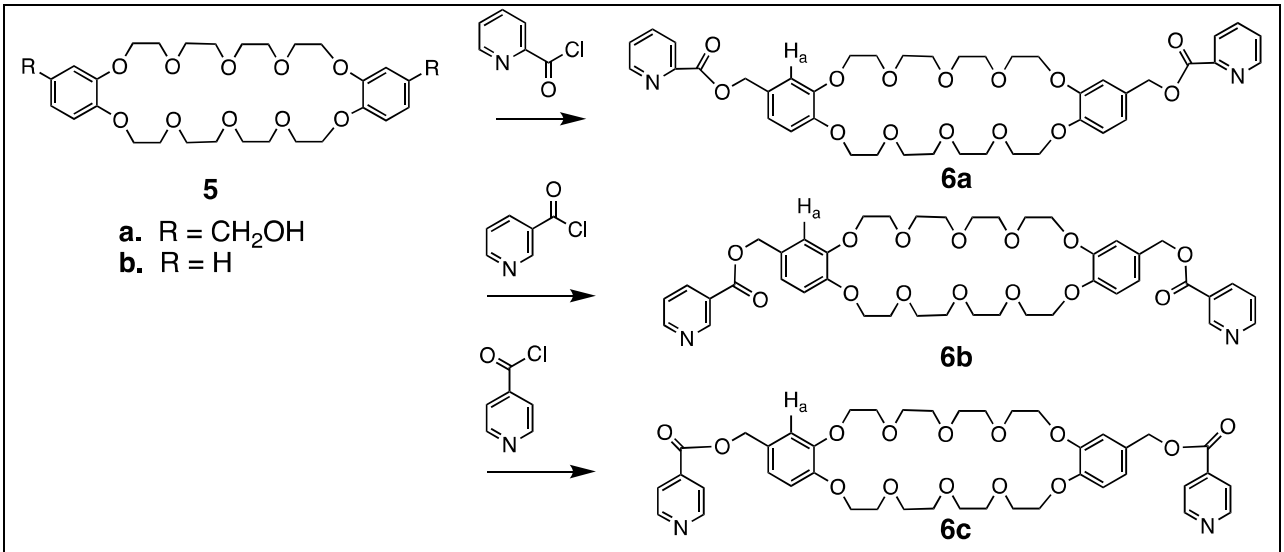
Host 2.00 mM	Guest 2.00 mM	Additive (Equiv.)	App. K_a (M^{-1})	Change in K_a
1a	**2b**	0	61 [23]	---
1a	**2b**	Et_4NTFA 1.25	48 (± 19)	0.79 x
1a	**2b**	Et_4NTFA 3.75	35 (± 17)	0.57 x
1b	**2a**	0	570 [4a]	---
1b	**2a**	n-Bu_4NOTs (1.00)	920 [7]	1.6 x
1b	**2b**	0	830 [7]	---
1b	**2b**	n-Bu_4NPF_6 (2.32)	520 [7]	0.63 x
1b	**2b**	Et_4NTFA (1.18)	5.63×10^3 [7]	6.8 x
1b	**2b**	Et_4NTFA (2.35)	1.20×10^4 [7]	14 x
1b	**2b**	n-Bu_4NOTs (1.00)	1.86 (± 0.35) x 10^3	2.2 x
1a	**4a**	0	390 [14]	---
1b	**4a**	0	2.8×10^3 [26a]	---
1d	**2a**	0	70 [a]	---
1d	**2a**	Et_4NTFA (1.00)	3.4×10^4	47 x
3	**2a**	0	6.1×10^4 [a, 4a]	---
3	**4a**	0	2.0×10^4 [26b]	---

[a] At 21 °C.

The results with addition of tetralkylammonium salts to solutions of hosts and guests are summarized in Table 1. With non-chelating hosts such as **1a** addition of any salt results in diminution of the binding constant, because the guest becomes more ion paired. With chelating hosts such as **1b** and **1d** addition of PF_6 salts decreases K_a for the same reason; however, anions that interact to form pseudocryptands, i. e., TFA and OTs, increase K_a as a result, offsetting the ion pairing effect.

B. Pyridyl Esters of *cis*-Dibenzo-30-crown-10 Diol

Previously the syntheses of cryptands such as **3** were low yielding; this has been remedied now in the case of the dibenzocrown ether-based pyridyl cryptands.[4b] However, we previously showed that easily prepared diesters **1e** – **1g** displayed significanltly enhanced binding constants with paraquats.[6] That naturally begged the question: would corresponding pyridyl diesters of dibenzo-30-crown-10 similarly be elevated? A series of three isomeric dibenzo-30-crown-10 diol pyridyl esters (**6**) was synthesized (**Scheme 2**) and association constants with paraquat and diquat were determined by isothermal titration calorimetry **(Tables 2** and **3**; see SI Figures S19 and S20 for examples); in all cases 1:1 stoichiometry was observed. An ^{1}H NMR-based Job plot (**Figure 8**) confirmed the expected 1:1 stoichiometry for **6a** with diquat.



Scheme 2. Synthesis of pyridyl esters of **6a** – **6c** of dibenzo-30-crown-10 diol (**5a**).

Table 2. Association constants and thermodynamic parameters for complexation of hosts **5a**, **5b**, **6a**-**6c** with diquat (**4a**, acetone, 25 ℃ via ITC).

HOST	10^{-3} K_a (M^{-1})	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (eu)
5b	17 [a]	---	---	---
5a	50 [b]	---	---	---
6a	40.6 (± 1.9)	-6.28 (± 0.29)	-17.4 (± 0.1)	-37.3 (± 1.8)
6b	4.36 (± 0.10)	-4.96 (± 0.11)	-17.3 (± 0.2)	-41.4 (± 1.1)
6c	3.50 (± 0.09)	-4.83 (± 0.13)	-17.7 (± 0.2)	-43.2 (± 1.3)

[a] By uv/vis: ref. 27.
[b] By uv/vis: ref. 28.

Table 3. Association constants and thermodynamic parameters for complexation of hosts **5a**, **6a**-**6c** with paraquat **2a** (acetone, 25 °C via ITC).

HOST	K_a (M^{-1})	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (eu)
5a	1.1×10^3 [a]	---	---	---
6a	207 (± 5)	-3.16 (± 0.08)	-4.31 (± 0.04)	-3.86 (± 0.10)
6b	785 (± 12)	-3.95 (± 0.06)	-10.2 (± 0.1)	-21.0 (± 0.35)
6c	162 (± 11)	-3.95 (± 0.20)	-5.60 (± 0.08)	-8.66 (± 0.60)

[a] By uv/vis: ref. 29.

The ITC data indicate that association constants for esters **6** with diquat PF_6 (**4a**) were lower than those with starting diol **5a**; this is presumed to be due to a combination of electronic and steric effects. Likewise with paraquat PF_6 (**2a**), binding with esters **6** is weaker than that with the starting diol **5a**, presumably for similar reasons. Interestingly however, the dipicolinate, **6a**, gave the highest association constant with diquat, while the dinicotinate, **6b**, is advantageous for binding paraquat. Looking first at the diquat series (**Table 1**), as the pyridyl ring's attachment is moved from the 2- position to 4-position, ΔH remains the same within experimental error, while ΔS becomes more negative due to a more extensive rearrangement for binding the guest. With **6b** and

paraquat the higher association constant (**Table 2**) results from a much larger enthalpy change than the other isomers.

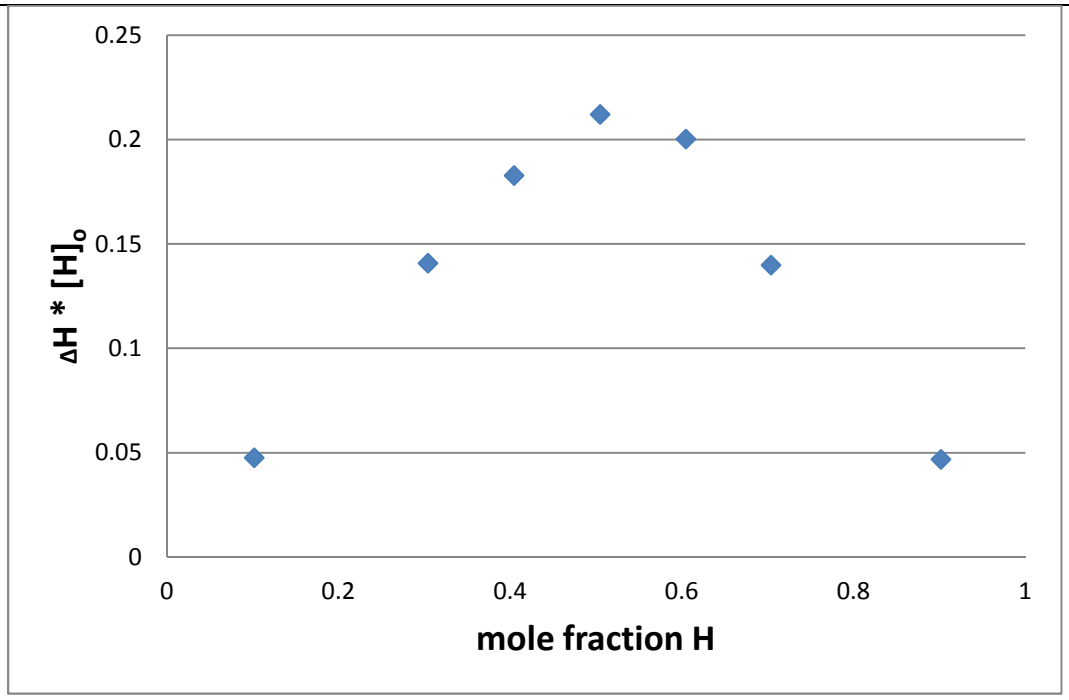


Figure 8. 500 MHz ^{1}H NMR Job Plot titration of **6a** with diquat **4a** in acetone-d_6 at room temperature ([**6a**] + [**4a**] = 0.97 mM); H_a used for analysis.

There is a correlation between enthalpy and entropy changes for the complexation of complexes **6** with the two bpyridinium guests as shown in **Figure 9**. Others have reported similar results and rationalized them.[30]

Table 4 lists association constants for similar bis(*m*-phenylene)-32-crown-10 pseudocryptands we reported previously;[6,10] compound **6a** is analogous to 32-crown-10 version **1e**, while compounds **1f** and **1g** were strategically evolved to increase π–stacking of the aroyl groups and thus cooperative binding with paraquat. The paraquat binding of **1e** is an order of magnitude higher than **6a**, but the diquat binding of **6a** is nearly two orders of magnitude higher than **1e**. It is worth pointing out that **6a** bound diquat better than host **1g**.

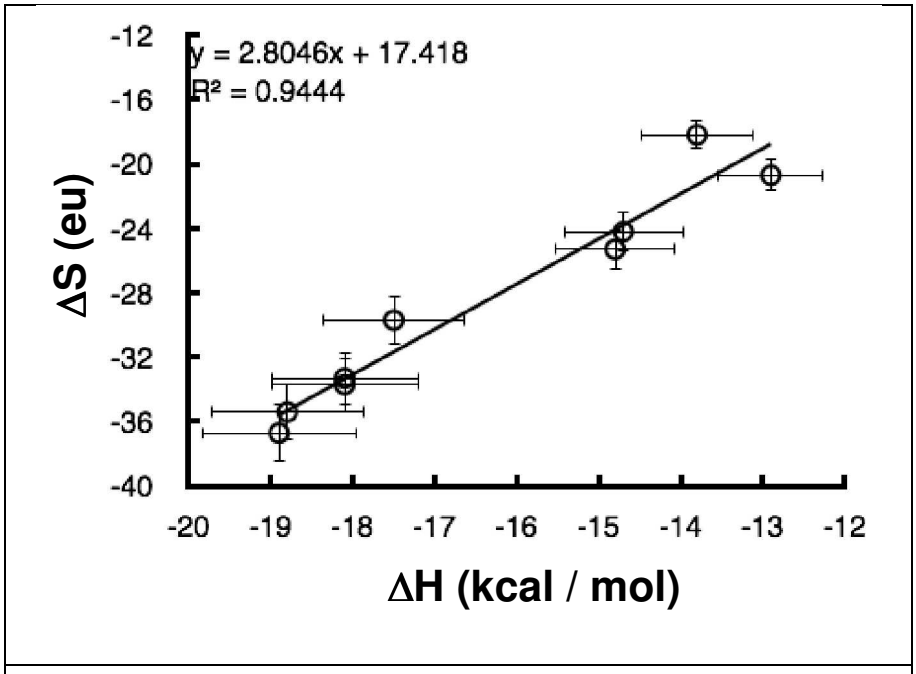


Figure 9. Correlation of ΔH and ΔS for complexes **6** with paraquat **2a** and diquat **4a** (Tables 2 and 3). Error bars: 5 %.

Table 4. Association constants (K_a) Hosts **1e**–**1g** with paraquat **2a** [6] and diquat **4a**.[10]

Complex	10^{-3} K_a (M^{-1})
1e•2a	3.1 [a]
1f•2a	12.4 [a]
1g•2a	250 [b]
1e•4a	0.77 [c]
1f•4a	0.56 [d]
1g•4a	32 [d]

[a.] value obtained in $CDCl_3$/CDCN (1/1, v/v) via ^{1}H NMR.
[b.] value obtained in $CHCl_3$/CHCN (1/1, v/v) via ITC.
[c.] value obtained in acetone-d_6 at 25 °C via ^{1}H NMR.
[d.] value obtained in acetone at 25 °C via ITC.

Both 2D NOESY and X-ray crystallography were employed to probe the 3D structures of the complexes. 2D NOESY spectra were taken in acetone-d_6 at room temperature for DQ PF_6 (**4a**) with all three esters **6**. The X-ray crystal structure of **6b•4a** is shown in **Figure 10**.

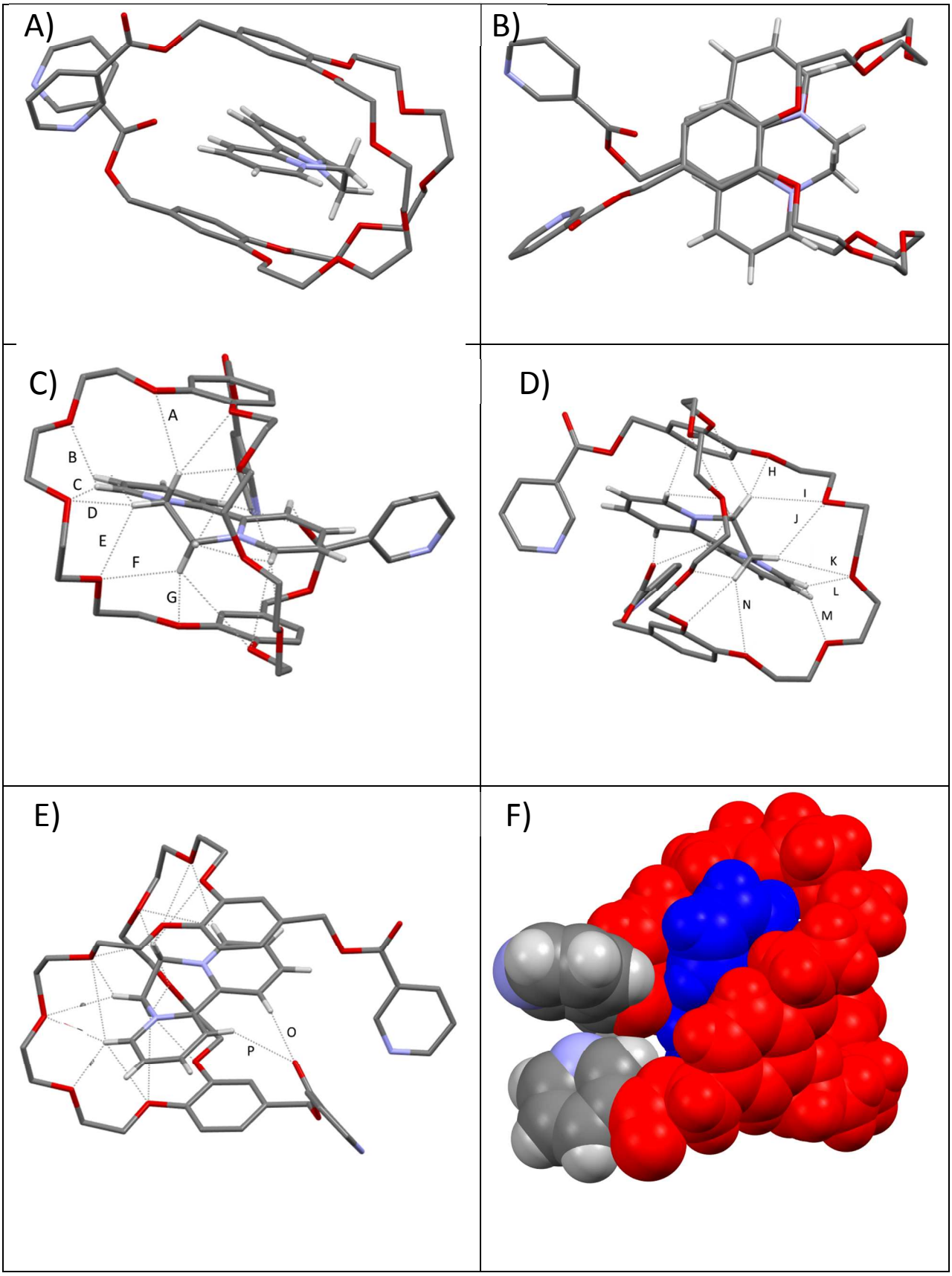

A)
B)
C)
A
B
C
D
E
F
G
D)
H
I
J
K
L
M
N
E)
O
P
F)

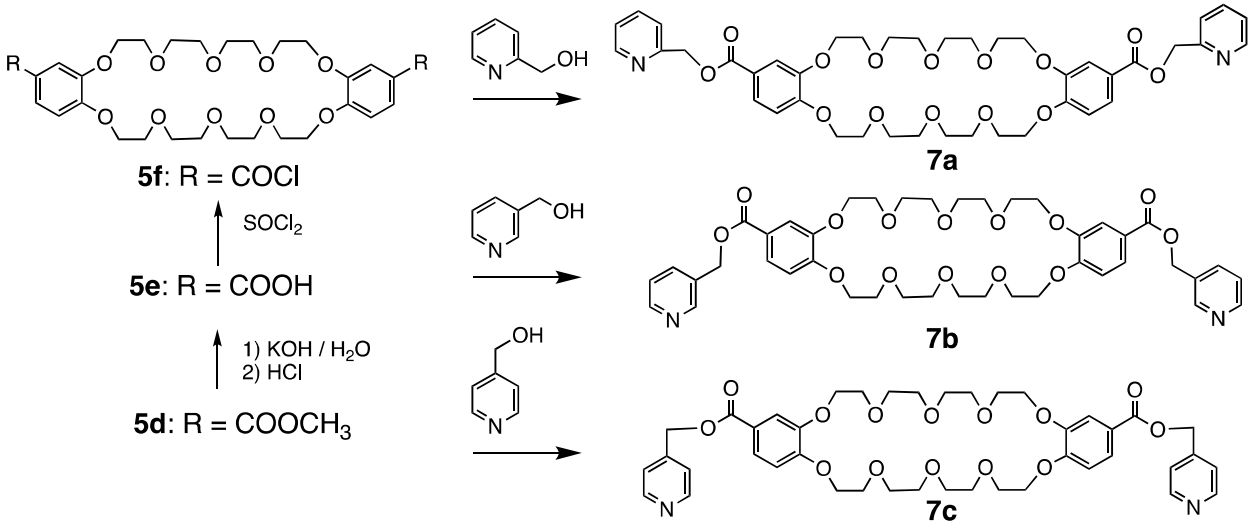
Figure 10. X-ray crystallography of **6b•4a** grown by slow vapor diffusion of ether into acetone (crystal structure contains a reasonable amount of disorder; counter ions, solvent, artifacts, and non-guest hydrogens have been removed for clarity; carbons are gray, hydrogens are white, nitrogens are blue, and oxygens are red. **A)** side view; **B)** top down view; **C)** hydrogen bonding to the *m*-ethyleneoxy chain; **D)** hydrogen bonding to the *p*-ethyleneoxy chain; **E)** hydrogen bonding at the ester. Hydrogen-bond parameters: C---O distances (Å), C-H---O distances (Å), C-H ---O angles (deg) A: 3.455, 2.887, 117.29; B: 3.088, 2.405, 128.55; C: 3.605, 2.843, 137.98; D: 3.072, 2.093, 170.35; E: 3.031, 2.541, 110.42; F: 3.117, 2.458, 123.64; G: 3.320, 2.451, 146.20; H: 3.340, 2.447, 149.74; I: 3.421, 2.739, 126.35; J: 3.278, 2.808, 109.76; K: 3.619, 2.722, 150.96; L: 3.281, 2.399, 154.19; M: 2.954, 2.230, 132.31; N: 3.679, 3.170, 113.52; O: 3.445, 2.470, 173.75; P: 3.265, 2.470, 141.24. **F)** Space-filling representation with the host in red and the guest in blue showing closure of the pseudocryptand by the embracing pyridine moieties; the pyridyl nitrogen of one ester group is 3.34 Å from the carbonyl carbon of the other ester moiety while the adjacent pyridyl 2-H interacts with the carbonyl oxygen at 3.26 / 2.52 Å / 134.6 °. Angle between phenyl planes of the host: 1.86 °. Angle between top phenyl plane and DQ plane: 1.38 °. Angle between bottom 4phenyl plane and DQ plane: 1.53 °. Torsion angle of bipyridinium rings: 17.5 °.

NOESY experiments (see SI, Figures S16-S18) with complexes of **6a–c** with diquat **4a** indicate no detectable interactions between the pyridine rings and the diquat cation, suggesting that in solution diquat sits in a cupped pocket formed by the crown (similar to other taco structures observed for dibenzo-30-crown-10 systems).[3,28,29] However, it is suspected that in complex **6a•4a**, the pyridyl rings are π-stacked on the basis of a NOESY correlation between protons A (6-H) and D (3-H) on opposite sides of the pyridyl ring. In the complexes of **6b** and **6c**, this correlation was not observed, suggesting that the pyridyl units point outwards and are not π –stacked; this explains the higher K_a observed for **6a** vs. **6b** and **6c**.

In the X-ray crystallographic structure of **6b•4a**, **Figure 10**, most of the hydrogen bonding occurs between the ethyleneoxy units and diquat, while the pyridyl nitrogen atoms sit too far away to play an active role with the guest. However, the interaction of one pyridyl nitrogen with th carbonyl carbon of the other ester moiety coupled with its 2-proton interacting with the ester ether oxygen effectively seals the pseudocryptand.

C. *cis*-Dibenzo-30-crown-10 Dicarboxylic Esters of Pyridyl Alcohols

By use of the crown ether diacid chloride and the corresponding pyridylmethanols we envisioned a stronger interaction of the more basic nitrogen atom with paraquat and diquat guests. Hence, the "reverse esters" **7a** – **7c** were prepared from the acid chloride **5f** and the isomeric pyridylmethanols (**Scheme 3**). These hosts were then examined with diquat (**Table 5**) and paraquat (**Table 6**) by ITC (see SI Figures S39-S44).



Scheme 3. Synthesis of dibenzo-30-crown-10 dicarboxylic esters **7a**-**7c** of pyridylmethanols.

Table 5. Association constants and thermodynamic parameters for complexation of hosts **7a**-**7c** with diquat (**4a**, acetone, 25 °C via ITC).

HOST	K_a (M^{-1})	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (eu)
7a	556 (± 90)	-3.74 (± 0.10)	-3.83 (± 1.97)	-0.30 (± 6.96)
7b	696 (± 30)	-3.88 (± 0.03)	-6.42 (± 0.12)	-8.52 (± 0.51)
7c	636 (± 23)	-3.82 (± 0.02)	-4.46 (± 0.08)	-2.15 (± 0.34)

The complexations of reverse esters **7** with diquat PF_6 (**4a**) are one to two orders of magnitude weaker in terms of K_a than "normal esters" **6** (**Table 2**). Such a reduction in binding strength is consistent with the electronic effect of reversing the ester moiety, since in **7** the electron withdrawing effect supposedly weakens the ability of the aromatic rings to participate in charge transfer interactions with the cationic guest.

Table 6. Association constants and thermodynamic parameters for complexation of hosts **7a**-**7c** with paraquat **2a** (acetone, 25 °C via ITC).

HOST	K_a (M^{-1})	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (eu)
7a	427 (± 29)	-3.59 (± 0.05)	-4.41 (± 0.15)	-2.75 (± 0.67)
7b	633 (± 47)	-3.82 (± 0.05)	-4.98 (± 0.17)	-3.89 (± 0.78)
7c	423 (± 28)	-3.58 (± 0.04)	-6.20 (± 0.21)	-8.79 (± 0.84)

Surprisingly, however, the binding of paraquat PF_6 by reverse esters **7** is stronger in two cases by factors of ca. two-fold in K_a (**Table 6**) than the isomeric normal esters of **Table 3**. The reasons for this generally enhanced binding of esters **7** are not clear in the absence of crystal structural

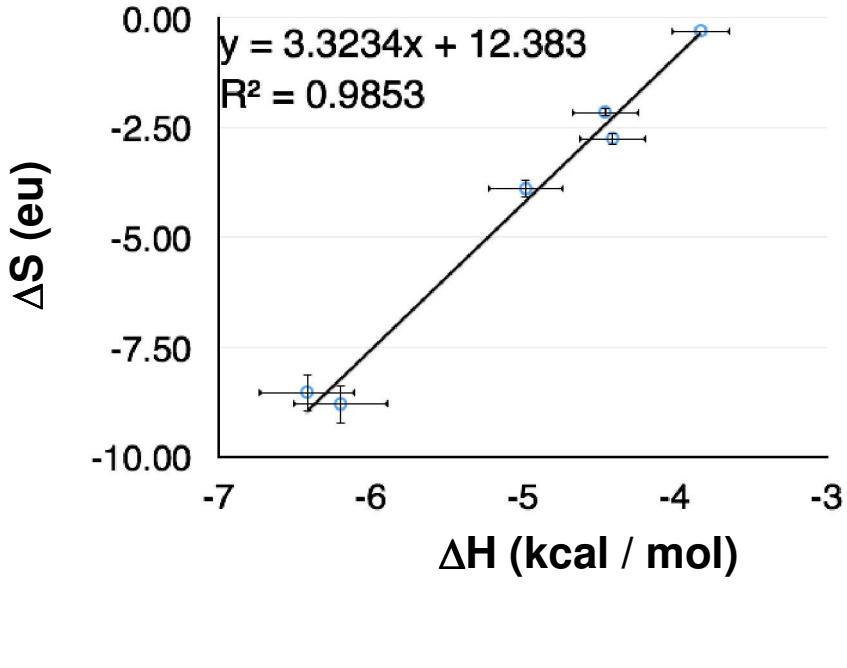


Figure 11. Correlation of ΔH and ΔS for complexes **7** with paraquat **2a** and diquat **4a** (Tables 2 and 3). Error bars: 10 %.

information. However, we speculate that perhaps in this case the increased electron density on the pyridyl nitrogen atoms offsets the decreased electron density of the aromatic rings of the hosts.

As observed in series **6** (**Figure 9**) the data for interaction of reverse esters **7** with diquat and paraquat reveal a linear correlation of the enthalpy and entropy changes associated with complex formation (**Figure 11**).

CONCLUSIONS

The use of counter-anions to link acidic moieties at the 5- and 5'-positions of bis(*m*-phenylene-32-crown-10) is a simple means of enhancing the binding of the host with paraquat derivatives by more than an order of magnitude in apparent K_a.

The placement of the 2-pyridyl carboxylate group in the dibenzo-30-crown-10 diol diester provided the best overall binding constant, **6a•4a** (diquat), in this series of diesters. However, all of these hosts (**6a**–**6c**) were worse in terms of the binding strength than the parent crown diol **5a** both with diquat and paraquat.[28,29] These results are in contrast to those obtained with the analogous bis(*m*-phenylene)-32-crown-10 pyridyl derivatives (**1e**-**1g**, **Table 4**), all of which possessed higher binding constants than parent diol **1b**. The results for reverse esters **7** reveal weaker complexes with diquat than normal esters **6**; however, surprisingly, reverse esters **7a** and **7c** complex paraquat more strongly than isomers **6a** and **6c**.

EXPERIMENTAL

General Information: 1a,[33] **1b**,[34] **1c**,[34] **2a**,[31] **2b**,[32] **3**, [4a] **5a** [3] and **5d** [3] were prepared as described in the literature. All other reagents were purchased from commercial suppliers and used without further purification except where noted. ^{1}H NMR spectra

were obtained on JEOL ECLIPSE-500, BRUKER-500, and AGILENT-NMR-vnmrs400 spectrometers. ^{13}C NMR spectra were collected at 125 MHz and 101 MHz on these instruments, respectively. HR MS were obtained using an Agilent LC ESI TOF system and acetonitrile solvent. Reagents were purchased and used as received without further purification, except for DCM, which was dried by distillation over CaH. ITC results were obtained using an MCS system from Microcal, Inc.

NMR Studies of Complexation: For all complexation studies, precisely weighed amounts of each component were added to a 5.00 mL volumetric flask (±0.02 mL) equipped with a ground glass stopper to make a moderately concentrated (nominally 16 mM) master solution. This solution was then sequentially diluted (no more than four sequential dilutions per master solution) as needed by transferring exactly half of the higher concentration solution to a clean volumetric flask by means of to-deliver volumetric pipettes (±0.006 mL) and diluting to the 5.00 mL mark. The fresh solutions were passed through a filter before 0.500 mL of each solution component (both host and guest) at a specified concentration was transferred via a to-deliver pipette to a 5 mm NMR tube. ^{1}H NMR data were collected on a temperature controlled spectrometer (400 MHz). Errors are reported by assuming a 5% variation in Δ/Δ_0 values.

Determination of K_a for Bis(5-carboxy-*m*-phenylene)-32-crown-10 (1d) with Parquat Diol Bis(hexafluorophosphate)(2b): The following data were collected in acetone-d_6 at 21.4 ± 0.1 ^{o}C with constant [**1d**] = 8.484 mM. Analysis using the

[2b] (mM)	**δ_b (ppm)**	**δ_b (ppm)**

0.00	6.757	7.152
14.64	6.520	6.967
28.54	6.428	6.895
47.11	6.370	6.846
58.28	6.344	6.829
71.70	6.325	6.811
94.95	6.297	6.792
121.40	6.279	6.777

iterative Cresswell-Allred method [21,35] afforded the following values from the data for H_a and H_b, respectively: $K_a = 70 \pm 6$ and 70 ± 5 M^{-1}.

Example of ITC Titration Method: Two different ITC titration methods were used for this work; in each the first data point was ignored to avoid preimixing error. Low gain titrations with paraquat PF_6 (**2a**) employed 25 aliquots using host in the cell (5.00 mM) and guest in the syringe (75.0 mM). High gain titrations with diquat PF_6 (**4a**) employed 100 aliquots using host in the cell (0.990 mM) and guest in the syringe (15.0 mM). For both methods acetone was used as the solvent and experiments were conducted at 25°C. The following is a detailed description of titration of crown ether **6a** with diquat PF_6 (**4a**); the other systems were done similarly with slightly different concentrations. Host **6a** was loaded into the cell of the instrument at a concentration of 0.994 mM, while a 250 µL ITC syringe was loaded with diquat PF_6 (**4a**) at a concentration of 15.00 mM. The instrument was set to high gain (high sensitivity). The titration was achieved through 100 injections of 2.50 µL every 180 s; a primary filter period of 2 s and a

secondary filter period of 4 s were applied (filter period switch time was set to 120 s). A background titration used exactly the same titration conditions with the exception that the solution of **6a** in the cell was replaced with acetone. The heats for the dilution experiment were subtracted from the heats for the titration of diquat PF_6 (**4a**) with **6a**. Analysis of the data was carried out using software provided by the manufacturer. A "One Set of Sites" model was used; stoichiometries other than 1:1 provided unsatisfactory fits and the "One Set of Sites" model was justified by an NMR-based Job Plot.

^{1}H NMR Job Plot Titration: A diquat solution was made at 0.968 mM and **6a** at 0.987 mM, both in deuterated acetone. NMR solutions were made at ratios of host/guest: 9.00/1.00, 7.00/3.00, 6.00/4.00, 5.00/5.00, 4.00/6.00, 3.00/7.00, and 1.00/9.00. Aromatic hydrogen H_a (**Scheme 2**) of the crown was observed for the titration due to its large chemical shift change.

General procedure 1, acid chlorides. Picolinoyl Chloride: Thionyl chloride (18.0 mL, 247 mmol) was added to a flask containing picolinic acid (4.35 g, 35.4 mmol) with magnetic stirring under nitrogen. The reaction mixture was allowed to stir at room temperature for 48 h, followed by removal of the excess thionyl chloride using evaporation to provide the desired product, 5.00 g (100%). No further purification was performed; the product was used directly.

General procedure 2. Dipicolinate Ester of *cis*(4,4')-Bis(hydroxymethyl)dibenzo-30-crown-10 (6a). Picolinoyl chloride (3.21 g, 22.7 mmol) was added to a flask with magnetic stirring, freshly distilled DCM (125 mL), and pyridine (2.9 mL, 36 mmol). The mixture was stirred briefly and crown diol **5a** (0.38 g, 0.64 mmol) was added and the

flask was placed under nitrogen to stir at room temperature for 48 h. Solvent was removed by rotary evaporation and the residue was dissolved in chloroform (50 mL). The mixture was washed with water (10 mL x 1), 2% $NaHCO_3$ (10 mL x 3), water (10 mL x 1), 1 M HCl (until the aqueous wash was clear) and water again until pH 7. The organic layer was dried over sodium sulfate and solvent was removed by rotary evaporation. The crude material was purified using column chromatography: neutral alumina eluting with 96:4 chloroform:methanol to give the desired product, a colorless solid, 0.45 g (87%), mp 97.1-99.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (m, 2H), 8.12 (m, 2H), 7.82 (m, 2H), 7.46 (m, 2H), 7.06 – 7.00 (m, 4H), 6.85 (d, J = 8 Hz, 2H), 5.36 (s, 4H), 4.14 (m, 8H), 3.89 – 3.82 (m, 8H), 3.78 – 3.72 (m, 8H), 3.69 – 3.64 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 149.9, 149.2, 148.9, 148.1, 137.0, 128.7, 126.9, 125.3, 122.4, 115.1, 114.0, 70.9, 70.7, 69.7, 69.2, 67.5 (21 peaks expected and 17 peaks found due to ethyleneoxy peak overlap). HR MS: m/z 824.3567, $[M + NH_4]^+$, calcd. for $(C_{42}H_{54}N_3O_{14})^+$ m/z 824.3600, error 4.0 ppm; m/z 807.3306, $[M + H]^+$, calcd. for $(C_{42}H_{51}N_2O_{14})^+$ m/z 807.3335, error 3.6 ppm.

Nicotinoyl Chloride: General procedure 1 was used to produce a solid (3.68 g, 100%) using thionyl chloride (15.0 mL, 206 mmol) and nicotinic acid (3.20 g, 26.0 mmol).

Isonicotinoyl Chloride: General procedure 1 was used to produce a solid (3.69 g, 100%) using: thionyl chloride (10 mL, 138 mmol) and isonicotinic acid (3.21 g, 26.1 mmol).

Dinicotinate Ester of *cis*(4,4')-Bis(hydroxymethyl)dibenzo-30-crown-10 (6b): General procedure 2 was used with nicotinoyl chloride (3.00 g, 21.2 mmol), DCM (150 mL), pyridine (5.0 mL, 62 mmol), and crown diol **5a** (0.51655 g, 0.86574 mmol) to

produce a colorless crystalline solid (0.6655 g, 95%), mp 62.8-67.1°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (m, 2H), 8.77 (m, 2H), 8.30 (m, 2H), 7.38 (m, 2H), 6.98 (m, 4H), 6.87 (d, *J* = 8 Hz, 2H), 5.29 (s, 4H), 4.19 – 4.12 (m, 8H), 3.90 – 3.84 (m, 8H), 3.77 (m, 8H), 3.68 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 153.5, 151.0, 149.3, 149.0, 137.2, 128.5, 126.1, 123.3, 122.0, 114.8, 114.0, 70.9, 70.7, 69.7, 69.8, 69.2, 69.1, 67.1 (21 peaks expected and 19 peaks found due to ethyleneoxy peak overlap). HR MS: m/z 824.3584, $[M + NH_4]^+$, calcd. for $(C_{42}H_{54}N_3O_{14})^+$ m/z 824.3600, error 1.9 ppm; m/z 404.1687 $[M + 2H]^{+2}$, calcd. for $(C_{42}H_{52}N_2O_{14})^{+2}$ m/z 404.1704, error 4.2 ppm.

Diisonicotinate Ester of *cis*(4,4')-Bis(hydroxymethyl)dibenzo-30-crown-10 (6c): General procedure 2 using isonicotinoyl chloride (3.69 g, 26.1 mmol) DCM (125 mL), pyridine (2.8 mL, 34.8 mmol), and crown diol **5a** (0.34 g, 0.570 mmol) produced a colorless solid (0.42 g, 91%), mp 85.8 – 88.2 □. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (m, 4H), 7.84 (m, 4H), 7.00 – 6.95 (m, 4H), 6.86 (d, *J* = 8 Hz, 2H), 5.28 (s, 4H), 4.15 (m, 9H), 3.90 – 3.85 (m, 8H), 3.78 – 3.74 (m, 8H), 3.67 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 150.6, 149.3, 149.0, 137.4, 128.3, 122.9, 122.1, 114.9, 114.0, 70.9, 70.7, 69.7, 69.7, 69.2, 69.1, 67.5 (19 peaks expected and 17 peaks found due to ethyleneoxy peak overlap). HR MS: m/z 824.3615, $[M + NH_4]^+$, calcd. for $(C_{42}H_{54}N_3O_{14})^+$ m/z 824.3600, error 1.8 ppm; m/z 807.3340 $[M + H]^+$, calcd. for $(C_{42}H_{51}N_2O_{14})^+$ m/z 807.3335, error 0.6 ppm.

***cis*(4,4')-Dicarboxydibenzo-30-crown-10 (5e):** A solution of 2.98 g (4.57 mmol) of crown ether diester **5d**, 100 mL of 10 % aq. NaOH and 100 mL of THF was heated at reflux for 18 h. The THF was removed by rotary evaporation and the aqueous mixture was brought to pH 1 with conc. HCl. The mixture was cooled and filtered; the colorless

solid was dried on the frit, 2.85 g (100%), mp 208.4-210.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (dd, J = 8, 2 Hz, 2H), 7.43 (d, J = 2 Hz, 2H), 7.03 (d, J = 8 Hz, 2H), 4.17 – 4.12 (m, 4H), 4.12 – 4.08 (m, 4H), 3.76 (q, J = 4 Hz, 8H), 3.65 – 3.60 (m, 8H), 3.54 (dd, J = 6, 4 Hz, 9H). ^{1}H NMR (400 MHz, CD_3CN) δ 7.60 (dd, J = 8, 2 Hz, 2H), 7.48 (d, J = 2 Hz, 2H), 6.95 (d, J = 8 Hz, 2H), 4.17 – 4.11 (m, 8H), 3.85 – 3.78 (m, 8H), 3.70 – 3.66 (m, 8H), 3.64 – 3.60 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.1, 152.2, 147.6, 123.4, 123.1, 113.8, 112.4, 70.14, 70.13, 69.93, 69.91, 68.8, 68.7, 68.5, 68.4 (15 peaks expected and 15 peaks found). HR MS: m/z 642.2727 $[M + NH_4\}^+$, calcd. for $C_{30}H_{44}NO_{14}$ m/z 642.2756, error 3.0 ppm; 647.2284 $[M + Na]^+$, calcd. for $C_{30}H_{44}NaO_{14}$ m/z 647.2310, error 4.0 ppm; m/z 663.2021 $[M + K]^+$, calcd. for $C_{30}H_{44}KO_{14}$ m/z 663.2050, 4.4 error ppm.

***cis*(4,4')-Bis(chlorocarbonyl)dibenzo-30-crown-10 (5f):** General procedure 1 was used to produce a solid (0.36 g, 98 %) using thionyl chloride (5.0 mL, 70 mmol), crown ether diacid **5e** (0.35 g, 0.56 mmol) and 1 drop of DMF. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 9, 2 Hz, 2H), 7.53 (d, J = 2 Hz, 2H), 6.89 (d, J = 9 Hz, 2H), 4.25 – 4.15 (m, 8H), 3.95 – 3.87 (m, 8H), 3.80 – 3.73 (m, 8H), 3.72 – 3.65 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 155.1, 148.5, 127.3, 125.5, 115.2, 112.0, 71.03, 70.96, 70.73, 70.69, 69.5, 69.3, 69.2, 69.0 (15 signals expected and 15 signals found).

***cis*(4,4')-Dicarboxydibenzo-30-crown-10 Ester of Picolyl Alcohol (7a):** A solution of 0.4687 g (0.708 mmol) of diacid chloride **5f**, 0.60 mL (6.2 mmol) of 2-pyrdylmethanol and 1.5 mL of pyridine in 40 mL of DCM was stirred at room temperature for 22 h. The solution was filtered, washed with aq. $NaHCO_3$ (4x) and water (3x) and passed through a basic alumina plug with 98.5:1.5 DCM:MeOH. The solvent was removed from the

eluent and the solid was recrystallized from ether containing ca. 0.1 vol % DCM to afford 0.55 g (96 %) of colorless solid, mp 89.1-90.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (ddd, *J* = 5, 2, 1 Hz, 2H), 7.75 – 7.67 (m, 4H), 7.59 (d, *J* = 2 Hz, 2H), 7.42 (dt, *J* = 8, 1 Hz, 2H), 7.25 – 7.20 (m, 2H), 6.87 (d, *J* = 8 Hz, 2H), 5.44 (s, 4H), 4.22 – 4.16 (m, 8H), 3.93 – 3.86 (m, 8H), 3.80 – 3.74 (m, 8H), 3.71 – 3.66 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 156.2, 153.2, 149.4, 148.3, 136.8, 124.2, 122.8, 122.5, 121.7, 114.8, 112.3, 71.0, 70.9, 70.70, 70.69, 69.6, 69.5, 69.1, 68.9, 67.1 (21 signals expected and 21 signals found). HR MS: m/z 807.3332, 100%, $(M + H)^+$, calcd. for $(C_{42}H_{51}N_2O_{14})^+$ m/z 807.3335, error 0.4 ppm; m/z 404.1699, 49%, $(M + 2H)^{2+}$, calcd. for $(C_{42}H_{52}N_2O_{14})^{2+}$ m/z 404.1704, error 1 ppm; m/z 829.3139, 16%, $(M + Na)^+$, calcd. for $(C_{42}H_{50}N_2NaO_{14})^+$ m/z 829.3154, error 1.8 ppm.

***cis*(4,4')-Bis(carboxy)dibenzo-30-crown-10 Ester of Nicotinyl Alcohol (7b):** Using the same procedure as for **7a** with 0.4314 g (0.652 mmol) of diacid chloride **5f**, 0.60 mL (6.2 mmol) of 3-pyrdylmethanol and 1.5 mL of pyridine in 40 mL of DCM stirred at room temperature for 21.5 h yielded 0.50 g (95 %) of colorless solid, mp 89.1-90.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (m, 2H), 8.59 (dd, *J* = 5, 2 Hz, 2H), 7.76 (dt, *J* = 8, 2 Hz, 2H), 7.66 (dd, *J* = 8, 2 Hz, 2H), 7.53 (d, *J* = 2 Hz, 2H), 7.31 (ddd, *J* = 8, 5, 1 Hz, 2H), 6.84 (d, *J* = 8 Hz, 2H), 5.33 (s, 4H), 4.20 – 4.14(m, 8H), 3.92 – 3.86 (m, 8H), 3.78 – 3.74 (m, 8H), 3.70 – 3.65 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 153.2, 149.65, 149.60, 148.3, 136.0, 131.8, 124.1, 123.5, 122.3, 114.6, 112.2, 71.0, 70.9, 70.69, 70.67, 69.6, 69.4, 69.1, 68.9, 64.0 (21 signals expected and 21 signals found). HR MS: m/z 807.3343, 100%, $(M + H)^+$, calcd. for $(C_{42}H_{51}N_2O_{14})^+$ m/z 807.3335, error 1 ppm; m/z 404.1704, 24%, $(M + 2H)^{2+}$, calcd. for $(C_{42}H_{52}N_2O_{14})^{2+}$ m/z 404.1704, error 0 ppm.

***cis*(4,4')-Bis(carboxy)dibenzo-30-crown-10 Ester of Isonicotinyl Alcohol (7c):** Using the same procedure as for **7a** with 0.3499 g (0.529 mmol) of diacid chloride **5f**, 0.63 g (5.8 mmol) of 4-pyrdylmethanol and 1.5 mL of pyridine in 40 mL of DCM stirred at room temperature for 19 h yielded 0.40 g (93 %) of cream colored solid, mp 115.4-118.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.58 (m, 4H), 7.69 (dd, *J* = 8, 2 Hz, 2H), 7.56 (d, *J* = 2 Hz, 2H), 7.32 – 7.29 (m, 4H), 6.87 (d, *J* = 8 Hz, 2H), 5.33 (s, 4H), 4.22 – 4.15 (m, 8H), 3.93 – 3.87 (m, 8H), 3.79 – 3.74 (m, 8H), 3.70 – 3.66 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 153.3, 150.0, 148.4, 145.3, 124.2, 122.1, 121.8, 114.6, 112.2, 71.0, 70.9, 70.68, 70.66, 69.6, 69.4, 69.1, 68.8, 64.5 (19 signals expected and 19 signals found). HR MS: m/z 807.3368, 100%, $(M + H)^+$, calcd. for $(C_{42}H_{51}N_2O_{14})^+$ m/z 807.3335, error 4.1 ppm; m/z 404.1716, 39%, $(M + 2H)^{2+}$, calcd. for $(C_{42}H_{52}N_2O_{14})^{2+}$ m/z 404.1704, error 3.0 ppm; m/z 829.3176, 9%, $(M + Na)^+$, calcd. for $(C_{42}H_{50}N_2NaO_{14})^+$ m/z 829.3154, error 2.7 ppm.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ????

^{1}H, ^{13}C NMR, COSY and NOESYspectra; representative isothermal titration results. (PDF)

Crystallographic data of salt **2c** and complexes **1b•2f**, **1b•4b** and **6b•4a**. (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: hwgibson@vt.edu.

ORCID

Harry W. Gibson: 0000-0001-9178-6691

Present Addresses

¶ Present address: The Chemours Company, Wilmington, DE 19899

Present address: Zestron Corporation, 11285 Assett Loop, Manassas, VA 20109

§ Present address: Department of Chemistry, Zhejiang University, Hangzhou, P. R. China

£ Present address: Department of Chemistry, University of Oregon, Eugene, OR, 97403

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation for support of this work through the following awards: DMR0704076 and CHE-1507553. We thank Ms. Hanlie Wessels for obtention of some melting points and spectral data.

REFERENCES

1. a. Gong, H.-Y.; Rambo, B. M.; Lynch, V. M.; Keller, K. M.; Sessler, J. L. *Chem. Eur. J.* **2012**, *18*, 7803-7809;

b. Kikuchi, Y.; Takahagi, H.; Ono, K.; Iwasawa, N. *Chem. Asian J.* **2014**, *9*, 1001-1005;

c. Han, Y.; Meng, Z.; Ma, Y.-X.; Chen. C.-F. *Acc. Chem. Res.* **2014**, *47*, 2026-40;

d. Zhao, W.; Chu, J. Xie, F.; Duan, Q.; He, L.; Zhang, S. *J. Chromatog. A* **2017**, *1485*, 44-51;

e. Liu, Z.; Nalluri, S. K. M.; Stoddart, J. F. *Chem. Soc. Rev*. **2017**, *46*, 2459-2478;

f. Lipke, M. C.; Cheng, T.; Wu, Y.; Arslan, H.; Xiao, H.; Wasielewski, M. R.; Goddard, W. A.; Stoddart, J. F. *J. Am. Chem. Soc.* **2017**, *139*, 3986-3998;

g. Pederson, A. M.-P.; Price, T. L., Jr.; Slebodnick, C,; Schoonover, D. V.; Gibson, H. W. *J. Org. Chem.* **2017***, 82,* 8489-8496.

2. Gibson, H. W.; Wang, H.; Bonrad, K.; Jones, J. W.; Slebodnick, C.; Zackharov, L. N.; Rheingold, A. L.; Habenicht, B.; Lobue, P.; Ratliff, A. E. *Org. Biomol. Chem.* **2005**, *3*, 2114-2121.

3. Pederson, A. M. P.; Ward, E. M.; Schoonover, D. V.; Slebodnick, C.; Gibson, H. W. *J. Org. Chem.* **2008**, *73*, 9094-9101.

4. a. Bryant, W. S.; Jones, J. W.; Mason, P. E.; Guzei, I.; Rheingold, A. L.; Fronczek, F. R.; Nagvekar, D. S.; Gibson, H. W. *Org. Lett.* **1999**, *1*, 1001-1004;

b. Price, T. L., Jr.; Wessels, H. R.; Slebodnick, C.; Gibson, H. W. *J. Org. Chem.* **2017***, 82,* 8117-8122;

5. Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Miejer, E. W. *Science* **1997**, *278*, 1601-1604.

6. Niu, Z.; Slebodnick, C.; Schoonover, D.; Azurmendi, H.; Harich, K.; Gibson, H. W. *Org. Lett.* **2011**, *13*, 3992-3995.

7. Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Gibson, H. W. *J. Amer. Chem. Soc.* **2002**, *124*, 13378-13379.

8. a. Nabeshima, T.; Akine, S.; Saiki, T. *Rev. Heteroatom Chem.* **2000**, *22*, 219-239;

b. Heck, R.; Dumarcay, F.; Marsura, A. *Chem. Eur. J.* **2002**, *8*, 2438-2445;

c. Nabeshima, T.; Yoshihira, Y.; Saiki, T.; Akine, S.; Horn, E. *J. Am. Chem. Soc.* **2003**, *125*, 28-29;

d. Katoh, A.; Kudo, H.; Saito, R. *Supra. Chem.* **2003**, *2*, 79-84;

e. Nabeshima, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 969-991.

9. Huang, F.; Zakharov, L. N.; Rheingold, A. L.; Jones, J. W.; Gibson, H. W. *Chem. Commun.* **2003**, 2122-2123.

10. Niu, Z.; Price Jr, T. L.; Slebodnick, C.; Gibson, H. W. *Tetrahedron Lett.* **2016**, *57*, 60-63.

11. a. Gokel, G.W. *Chem. Soc. Rev.* **1992**, *21*, 39-47;

b. Elwahy, A. H. M.; Abbas, A. A. *J. Heterocyc. Chem.* **2008**, *45,* 1-65;

c. Burattini, S.; Greenland, B. W.; Hayes, W.; Mackay, M. E.; Rowan, S. J.; Colquhoun, H. M. *Chem. Mater.* **2011**, *23*, 6-8;

d. Zhu, Z.; Cardin, C. J.; Gan, Y.; Murray, C. A.; White, A. J. P.; Williams, D. J.; Colquhoun, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19442-19447;

e. Greenland, B. W.; Bird, M. B.; Burattini, S.; Cramer, R.; O'Reilly, R. K.; Patterson, J. P.; Hayes, W.; Cardin, C. J.; Colquhoun, H. M. *Chem. Commun.* **2013**, *49*, 454-456.

12. Wessels, H. R.; Gibson, H. W. *Tetrahedron* **2016**, *72,* 396-399.

13. The concept of preorganization traces its roots to the "lock and key" idea of Fisher [Fischer, E. *Chem. Ber.* **1894**, *27*, 2985-2993] and was highlighted in Nobel Prize winning work by Cram [Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, UK, 1994] and Lehn [Lehn, J.-M. *Supramolecular Chemistry*; VCH Publishers: New York, 1995].

14. Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1058-1061.

15. a) Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1064-1066.

b) Gillard, R. E.; Raymo, F. M.; Stoddart, J. F. *Chem. Eur. J.* **1997**, *3*, 1933-1940.

16. Huang, F.; Jones, J. W.; Slebodnick, C.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*, 14458-14464.

17. Jones, J. W.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125,* 7001-7004.

18. Gibson, H. W.; Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Slebodnick, C. *Chem. Eur. J.* **2011**, *17,* 3192-3206.

19. a. Goldfarb, D. L.; Longinotti, M. P.; H. Corti, R. *J. Solution Chem.* **2001**, *30,* 307-322;

b. Fry, A. J. *J. Org. Chem.*, **2015**, *80*, 3758–3765;

c. Dai, J.; Mendonsa, S. D.; Bowser, M. T.; Lucy, C. A.; Carr, P. W. *J. Chromatog. A* **2005**, *1069*, 225-234;

d. Savedoff, L. G. *J. Am. Chem. Soc.* **1966**, *88,* 664 – 667.

20. Gasa, T. B.; Spruell, J. M.; Dichtel, W. R.; Sorensen, T. J.; Philp, D.; Stoddart, J. F.; Kuzmic, P. *Chem. Eur. J.* **2009**, *15*, 106 – 116.

21. Gong, C.; Balanda, P. B.; Gibson, H. W. *Macromolecules* **1998**, *31*, 5278-5289. Δ_0 is defined as the average value calculated by Benesi-Hildebrand, Scatchard, and Creswell-Allred treatments.

22. Errors are reported by assuming a 5% variation in Δ / Δ_0 values.

23. Jones, J. W.; Bryant, W. S.; Bosman, A. W.; Janssen, R. A. J.; Meijer, E. W.; Gibson, H. W. *J. Org. Chem.* **2003**, *68*, 2385-2389.

24. Huang, F.; Guzei, I. A.; Jones, J. W.; Gibson, H. W. *Chem. Commun*. **2005**, 1693-1695.

25. Naik, D. B.; Moorthy, P. N. *J. Chem. Soc., Perkin Trans. 2* **1990**, *5*, 705-709.

26. a. Huang, F.; Slebodnick, C.; Switek, K. A.; Gibson, H. W. *Tetrahedron* **2007**, *63,* 2829-2839;

b. Huang, F.; Slebodnick, C.; Switek, K. A.; Gibson, H. W. *Chem. Commun.* **2006**, 1929-1931.

27. Colquhoun, H. M.; Goodings, E. P.; Maud, J. M.; Stoddart, J. F.; Williams, D. J.; Wolstenholme, J. B. *J. Chem. Soc., Chem. Commun.* **1983**, 1140-1142.

28. Kohnke, F. H.; Stoddart, J. F. *Tetrahedron Lett.* **1985**, *26*, 1681-1684.

29. He, C.; Shi, Z.; Zhou, Q.; Li, S.; Li, N.; Huang, F. *J. Org. Chem.* **2008**, *73*, 5872-5880.

30. a. Piguet, C. *Dalton Trans.* **2011**, *40*, 8059-8071;

b. Gilli, P.; Ferretti, V.; Gilli, G.; Borea, P. A. *J. Phys. Chem.* **1994**, *98*, 1515-1518;

c. Pan, A.; Biswas, T.; Rakshit, A. K.; Moulik, S. P. *J. Phys. Chem. B* **2015**, *119*, 15876-15884;

d. Lambert, F. L.; Leff, H. S. *J. Chem. Educ* **2009**, *86*, 94-98;

e. Starikov, E. B.; Nordén, B. *Chem. Phys. Lett.* **2012**, *538*, 118-120.

31. Ashton, P. R.; Campbell, P. J.; Chrystal, E. J. T.; Glink, P. T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J. F.; Tasker, P. T.; Williams, D. J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1865-1869.

32. Shen, Y. X.; Engen, P. T.; Berg, M. A. G.; Merola, J. S.; Gibson, H. W. *Macromolecules* **1992**, *25*, 2786-2788.

33. Delaviz, Y.; Gibson, H. W. *Polym. Commun.* **1991**, *32*, 103-105.

34. Gibson, H. W.; Nagvekar, D. S. *Can. J. Chem.* **1997**, *75*, 1375-1384.

35. Cresswell, C. G.; Allred, A. L. *J . Phys. Chem.* **1962**, *66*, 1469;