Improved Template-Directed Synthesis of Cyclobis(paraquat-*p*-phenylene)

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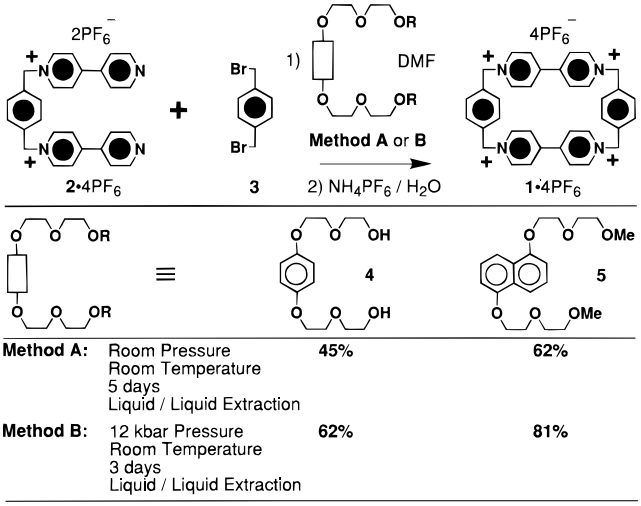
Since its template-directed synthesis (Scheme 1) was first reported[1] in 1988, cyclobis(paraquat-*p*-phenylene) (**1**$^{4+}$) has turned out to be an excellent receptor for substrates containing π-electron rich aromatic rings, such as hydroquinone and resorcinol derivatives,[2] dioxynaphthalene-based compounds,[3] biphenyl guests,[4] tetrathiafulvalene,[5] and indole[6] and their derivatives,[7] neurotransmitters,[8] aromatic amino acids,[9] and phenyl glycopyranosides[10] in both organic and aqueous solutions. In nonaqueous solvents, several factors determine[11] the binding ability of **1**$^{4+}$ toward a particular substrate. They include (i) the influence of the π-electron-donating ability of the aryl portion of the guest and its propensity to enter into aromatic $\pi-\pi$ stacking interactions[12] with the π-electron-accepting bipyridinium units in **1**$^{4+}$ and the additional stabilization gained as a result of (ii) [C−H···O] hydrogen bonding,[13] at least in appropriate substrates containing ether or ester oxygen atoms able to function as hydrogen bond acceptors, involving the acidic α-bipyridinium hydrogen atoms in **1**$^{4+}$ acting as hydrogen bond donors, and (iii) [C−H···π] interactions[14] in appropriate substrates containing electropositive aromatic hydrogen atoms that are able to enter into edge-to-face T-type interactions with the orthogonally-disposed *p*-xylyl spacers in **1**$^{4+}$. Clearly, the strength of complexation is solvent dependent and, since the counterions can be varied to render the tetracationic cyclophane either soluble in organic solvents (*e.g.* **1**·4PF$_6$) or in water (*e.g.* **1**·4Cl), **1**$^{4+}$ is a receptor with a wide substrate acceptance. Of course, the noncovalent bonding interactions that stabilize complexes will change their complexion considerably as the media range from low to high dielectric solvents. For example, hydrophobic forces probably come into play as a dominant source of complex stabilization in aqueous media. It follows that cyclobis(paraquat-*p*-phenylene) (**1**$^{4+}$) probably has a rosy future as a broad spectrum receptor. Already, it has found a special niche

Scheme 1



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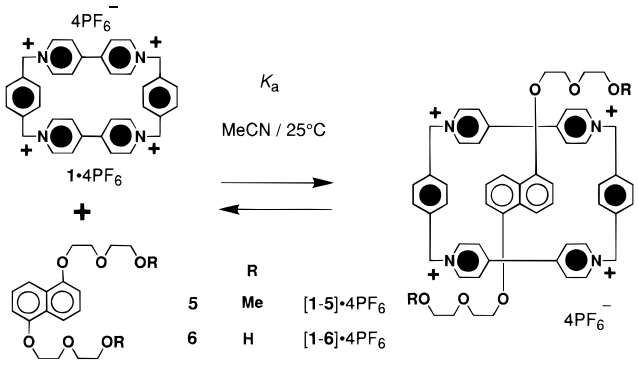

Figure 1. Complexation of the 1,5-dioxynaphthalene-based polyethers **5** and **6** by the tetracationic cyclophane **1**·4PF_6.

for itself in the self-assembly[15] of a rapidly growing series of interlocked molecular compounds, the so-called catenanes and rotaxanes.[16]

Following a reaction[2a,e] in which 1,1′-[1,4-phenylenebis(methylene)]bis(4,4′-bipyridinium) bis(hexafluorophosphate) (**2**·2PF_6) is heated under reflux for 2 days in MeCN with equimolar amounts of 1,4-bis(bromomethyl)benzene (**3**), counterion exchange (NH_4PF_6/H_2O) leads to the isolation of the tetracationic cyclophane $\mathbf{1}^{4+}$ as its tetrakis(hexafluorophosphate) salt in only 12% yield. This low yield was reproducible. Subsequently, it was discovered that the efficiency of the reaction, as reflected in both milder reaction conditions and in higher yields of $\mathbf{1}^{4+}$, could be improved[2e] by (i) changing the reaction solvent from MeCN to DMF, (ii) introducing a template into the reaction medium, and (iii) carrying out the (Menschutkin) reaction at ultra high pressures in the range of 10−15 kbars. Thus, a reaction carried out in DMF at room temperature and ambient pressure, employing 1,4-bis(2-(2-hydroxyethoxy)ethoxy)benzene **4** in 3 molar excess as a template, improved the yield of **1**·4PF_6 to 45%. When the reaction was repeated under the same conditions in an ultra high pressure reactor, the yield of **1**·4PF_6 rose to 62%, the best reported in the literature[2e] to date.

The growing interest[2−11] in cyclobis(paraquat-*p*-phenylene) ($\mathbf{1}^{4+}$), as an all-purpose electrochemically- and photochemically-addressable host, justifies the relentless search for more efficient ways of making it. Here, we report that the naphthalene-based template **5** provides a further fillip to the efficiency with which the template-directed synthesis of $\mathbf{1}^{4+}$ can be performed with and without specialized equipment and expertise.

Results and Discussion

1,5-Bis(2-(2-methoxyethoxy)ethoxy)naphthalene (**5**) and 1,5-bis(2-(2-hydroxyethoxy)ethoxy)naphthalene[17] (**6**) are bound (Figure 1) by the tetracationic cyclophane **1**·4PF_6 in solution. As a result of charge transfer interactions between the π-electron rich 1,5-dioxynaphthalene unit of the guest and the π-electron deficient bipyridinium units of the host, an intense purple color develops immediately when either **5** or **6** is mixed with **1**·4PF_6 in MeCN solution. As a result, UV-vis spectroscopy has been employed to investigate the stoichiometries as well as the stabilities of the corresponding complexes in solution. The continuous variations plots[18] illustrated in

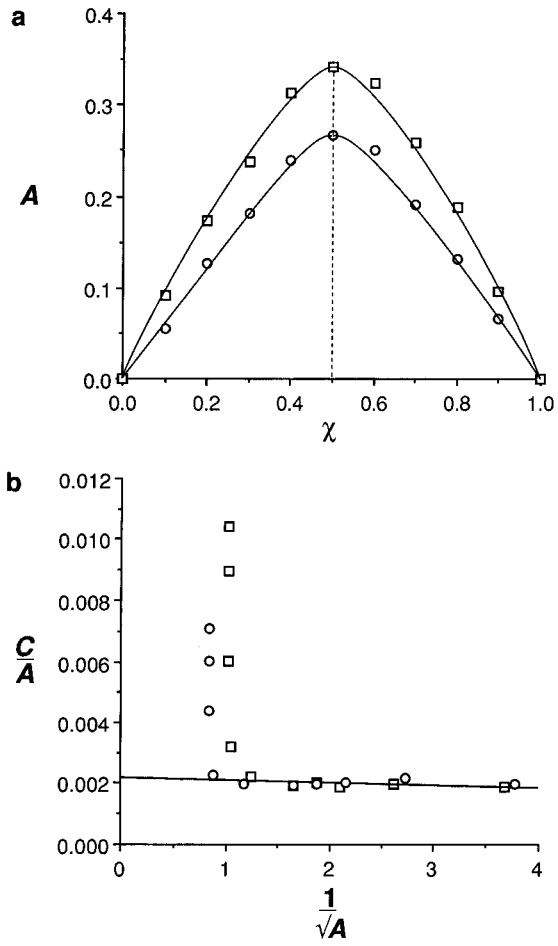

Figure 2. (a) Continuous variations plots of the absorbance *A* against the molar fraction χ of the host and (b) plots of the ratio between the concentration *C* and absorbance *A* against $1/\sqrt{A}$ for equimolar solutions of host and guest for the complexes (□) [**1**−**5**]·4PF_6 and (○) [**1**−**6**]·4PF_6 in MeCN.

Figure 2a were determined by employing total molar concentrations lower than 10^{-3} M in MeCN. In both cases, a maximum value of the absorbance *A* is observed when the molar fraction χ of the host is equal to 0.5, where the value of χ at the maximum is correlated to the stoichiometric coefficient *n* of the complex [host]−[guest]$_n$ by eq 1.

$$\chi = \frac{1}{1+n} \tag{1}$$

Thus, the concentrations of complexes [host]−[guest]$_n$ with $n \neq 1$ are negligible below 10^{-3} M. On the contrary, the plots illustrated in Figure 2b, determined by measuring the absorbance of equimolar MeCN solutions of host and guest having molar concentration *C*, where *C* is varied from 10^{-2} to 10^{-4} M, show deviation from linearity at *C* values higher than 10^{-3} M. These observations suggest that a 1:1 complex is the predominant species in solution when $C < 10^{-3}$ M. However, when $C > 10^{-3}$ M, complexes [host]−[guest]$_n$ with other stoichiometries, presumably, with $n > 1$, as suggested by an X-ray crystallographic analysis (*vide infra*) performed on the crystalline complex which is formed between **1**·4PF_6 and **5**, are also present in solution in the case of both guests **5** and **6**. In addition, K_a values higher than 5000 M^{-1} ($\Delta G° > 5$ kcal mol^{-1}) for both 1:1 complexes [**1**−**5**]·4PF_6 and [**1**−**6**]·4PF_6, *cf.*, $K_a = 2220 \pm 240$ M^{-1} and $\Delta G° = 4.6$

(17) For the synthesis of 1,5-bis(2-(2-hydroxyethoxy)ethoxy)naphthalene (**6**), see ref 1c.

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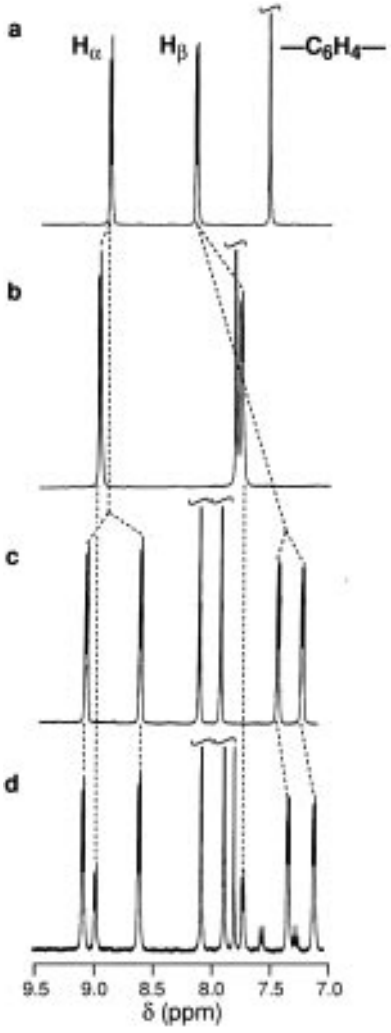

Figure 3. Partial ^{1}H-NMR spectra of (a) **1**·4PF_6, (b) an equimolar solution of **1**·4PF_6 and **4**, (c) an equimolar solution of **1**·4PF_6 and **6**, and (d) an equimolar solution of **1**·4PF_6, **4**, and **6** recorded in CD_3CN at −40 °C.

± 0.6 kcal mol^{-1} for the 1:1 complex [**1**−**4**]·4PF_6[2e], were derived by employing both the continuous variations and the dilution methods[18] in MeCN at 25 °C.

The ^{1}H NMR spectra, recorded at room temperature in CD_3CN, of equimolar solutions of either **5** or **6** and **1**·4PF_6 show broad resonances for the protons on both the host and guest, suggesting that "free" species and complexes are in slow exchange on the ^{1}H-NMR timescale. On the contrary, the ^{1}H-NMR spectra of the same solutions reveal (Figure 3c) sharp resonances when recorded at −40 °C. In contrast to the complex [**1**−**4**]·4PF_6 (Figure 3b) incorporating a hydroquinone-based guest, in the complexes formed between either **5** or **6** and **1**·4PF_6, the hydrogen atoms H_α and H_β attached to the α- and β-positions, respectively, in relation to the nitrogen atoms on the bipyridinium units, as well as those

(19) Coalescence of the two sets of resonances associated with the hydrogen atoms H_α, H_β, and [$-C_6H_4-$] is observed on warming up the solutions of the complexes. By employing the approximate coalescence treatment, the energy of activation $\Delta G^{\ddagger}_c$ associated with the decomplexation of [**1**−**5**]·4PF_6 and [**1**−**6**]·4PF_6 was measured using the hydrogen atoms H_α as the probe. A $\Delta G^{\ddagger}_c$ value of *ca.* 14.1 kcal mol^{-1} at the coalescence temperature T_c was determined for both complexes (T_c = 30 and 31 °C, k_c = 438 and 435 Hz, $\Delta\nu$ = 152 and 196 Hz for [**1**−**5**]·4PF_6 and [**1**−**6**]·4PF_6, respectively). For the approximate coalescence treatment, see: Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.

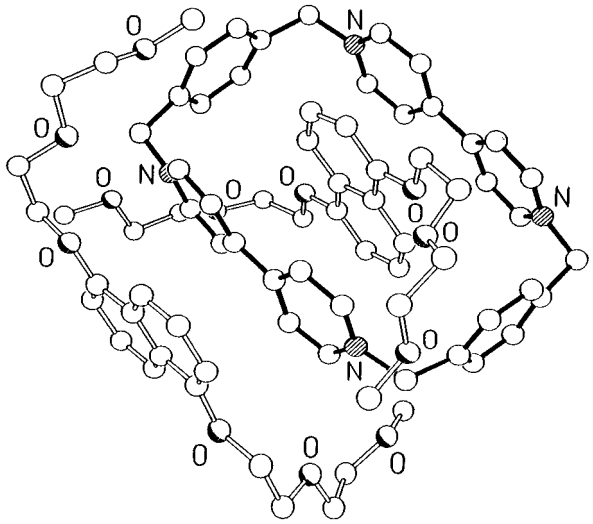

Figure 4. X-ray crystal structure of the 2:1 complex formed between the 1,5-dioxynaphthalene-based polyether **5** and the tetracationic cyclophane **1**·4PF_6 in the solid state.

associated with the phenylene hydrogen atoms [$-C_6H_4-$] attached to the *p*-xylene spacers of the host, give rise in each case to two sets of resonances,[19] as a result of the local C_{2h} symmetry imposed by the 1,5-dioxynaphthalene unit located within the cavity of the tetracationic host. In particular, the signals associated with H_β move to higher fields as a result of the shielding effect exerted by the 1,5-dioxynaphthalene unit. Consistently, dramatic upfield shifts are observed for the hydrogen atoms attached to the 4- and 8-positions of the 1,5-dioxynaphthalene unit which resonate at *ca.* δ 2.2 in the complexes [**1**−**5**]·4PF_6 and [**1**−**6**]·4PF_6.

The higher stabilities of the complexes [**1**−**5**]·4PF_6 and [**1**−**6**]·4PF_6 containing 1,5-dioxynaphthalene-based guests in comparison with the complex [**1**−**4**]·4PF_6, incorporating a hydroquinone-based guest, was also demonstrated by competitive binding experiments. The ^{1}H-NMR spectra, recorded at −40 °C in CD_3CN, of 1:1:1 solutions of either **5** or **6** and **4** and **1**·4PF_6 show (Figure 3d) the simultaneous formation of the complexes [**1**−**5**]·4PF_6 or [**1**−**6**]·4PF_6 and [**1**−**4**]·4PF_6. However, in both cases, a ratio of approximately 5:1 in favor of the complex containing the 1,5-dioxynaphthalene-based guest corresponding to a difference in the binding energies of *ca.* 1.6 kcal mol^{-1} was estimated by integrating the resonances associated with the hydrogen atoms H_β.

Crystals[20] of a complex between the 1,5-dioxynaphthalene derivative **5** and the tetracationic cyclophane **1**·4PF_6 were grown by vapor diffusion of *i*-Pr_2O into a MeCN solution containing equimolar amounts of **5** and **1**·4PF_6. An X-ray analysis reveals (Figure 4) that, in the solid state, a 1:2 stoichiometry exists between the tetracationic cyclophane **1**·4PF_6 and the 1,5-dioxynaphthalene derivative **5**. The superstructure provides an intriguing example of combined inclusion/clathration wherein one molecule of **5** is threaded through the center of $\mathbf{1}^{4+}$, while the other is positioned in a π−π stacking relationship alongside one of the bipyridinium units of $\mathbf{1}^{4+}$. The superstructural arrangement observed here is in marked contrast to that observed[2] for numerous 1:1 complexes formed between $\mathbf{1}^{4+}$ and a range of polyether/ester

(20) The LSIMS of an MeCN solution of these crystals shows peaks for the $[M - 2PF_6]^+$ and $[M - 3PF_6]^+$ ions arising from the 1:1 complex.

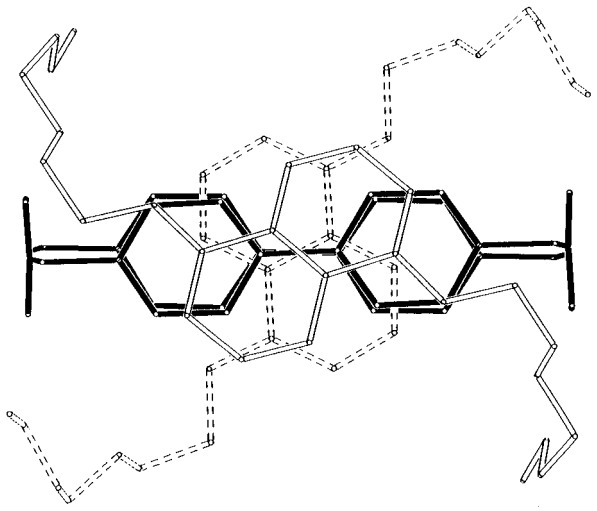

Figure 5. Relative orientation of the "inside" and "outside" 1,5-dioxynaphthalene units with respect to the plane defined by the four methylene groups of the tetracationic cyclophane in the crystal.

disubstituted benzene and naphthalene derivatives in which the complexes invariably have C_i symmetry. Here, the 1:2 (host:guest) complex has crystallographic C_2 symmetry about an axis passing through the centers of the two naphthalene rings and the two bipyridinium units (Figure 5). The two naphthalene-based template molecules are arranged so as to "embrace" one of the bipyridinium units of the tetracationic cyclophane. The complex is stabilized by a combination of $\pi-\pi$ aromatic,[21] [C−H···O],[22] and [C−H···π][23] interactions. An investigation of the packing of the 1:2 complexes reveals (Figure 6) the formation of polar stacks that extend along the C_2 axis.

The formation of a pseudorotaxane-like complex between the tetracationic cyclophane **1**·4PF_6 and the 1,5-dioxynaphthalene polyether **5** suggested strongly the possibility of employing **5** as the templating agent in the template-directed synthesis of **1**·4PF_6. Reaction (Scheme 1) of the bis(hexafluorophosphate) salt **2**•4PF_6 with the dibromide **3** in the presence of 3 mol equiv of the template **5** afforded the tetracationic cyclophane in a yield of 62%, *cf.* 45% in the case of **4**, after (i) continuous liquid−liquid extraction[24] of an aqueous solution of the crude mixture with CH_2Cl_2, (ii) purification of the residue by column chromatography, and (iii) counterion exchange (NH_4PF_6/H_2O). Performing the same reaction under ultrahigh pressure conditions enhances the efficiency of the template-directed synthesis affording the cyclophane in the remarkable yield of 81%, *cf.* 62% in the case of **4**.

(21) The mean interplanar separations between the "inside" 1,5-dioxynaphthalene residue and the "outside" and "inside" bipyridinium units are 3.32 and 3.37 Å, respectively, and the corresponding distance between the "outside" 1,5-dioxynaphthalene residue and the "inside" bipyridinium unit is 3.36 Å. Within the polar stacks between the "outside" 1,5-dioxynaphthalene residue and the "outside" bipyridinium unit, the mean interplanar separation is 3.32 Å.

(22) There are [C−H···O] hydrogen bonds between the H_α protons on the "inside" bipyridinium unit and the middle oxygen atom of the proximal polyether chains of both the "inside" and "outside" naphthalene-based threads. For the "inside" thread, the [C−H···O] hydrogen bonding geometries are [C···O], [H···O] distances, [C−H···O] angles: 3.30, 2.45 Å, 148°, and for the "outside" thread, 3.07, 2.39 Å, 127°, respectively.

(23) The [H···π] distances associated with the [C−H···π] interactions are 2.57 Å and the associated [C−H···π] angles are 146°.

(24) The templating agent **5** was recovered quantitatively from the organic layer after evaporation of the CH_2Cl_2 under reduced pressure.

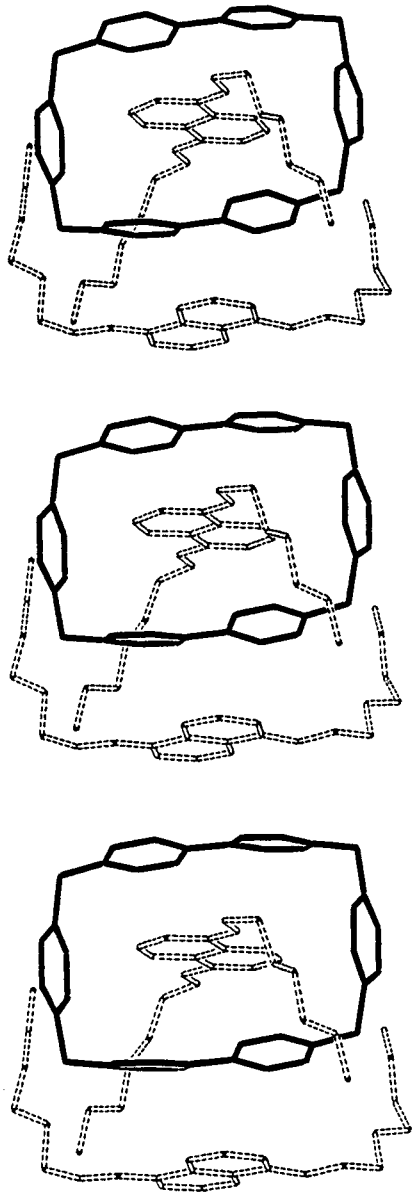

Figure 6. Packing diagram of the 2:1 complex formed between the 1,5-dioxynaphthalene-based polyether **5** and the tetracationic cyclophane **1**·4PF_6, showing the continuous donor−acceptor stack formed in the crystal.

Summary

The π-electron deficient bipyridinium-based receptor, cyclobis(paraquat-*p*-phenylene) binds π-electron rich guests with pseudorotaxane-like geometries as a result of π-π stacking, hydrogen bonding, and, in some instances, edge-to-face T-type interactions. This tetracationic cyclophane has also been incorporated into a wide number of mechanically-interlocked molecular compounds, such as catenanes and rotaxanes,[16] by means of appropriate self-assembling approaches.[15] Cyclobis(paraquat-*p*-phenylene) strongly binds the 1,5-dioxynaphthalene-based polyether, 1,5-bis(2-(2-methoxyethoxy)ethoxy)naphthalene, in solution as well as in the solid state. This observation suggested the possibility of employing 1,5-bis(2-(2-methoxyethoxy)ethoxy)naphthalene as the template in the template-directed synthesis of cyclobis(paraquat-*p*-phenylene). Indeed, the use of this π-electron rich guest as the template resulted in an improvement of the yield up to a remarkable 81%. The efficiency of this template-

directed synthesis is presumably a result of the high association constant for the binding[25] of 1,5-bis(2-(2-methoxyethoxy)ethoxy)naphthalene with cyclobis(paraquat-*p*-phenylene) to afford a pseudorotaxane-like complex, as revealed by UV-vis spectrophotometric analysis and ^{1}H-NMR spectroscopy in solution and by X-ray crystallographic analysis in the solid state.

Experimental Section

General. Solvents were dried according to literature procedures. Thin-layer chromatography (TLC) was carried out on alumina sheets coated with silica gel 60 (Merck 5554). The plates were inspected under UV light. Column chromatography was performed on silica gel 60 (Merck 9385, 230−400 mesh). Low resolution electron impact mass spectra (EIMS) were recorded operating at 70 eV. Liquid secondary ion mass spectra (LSIMS) were obtained employing a 35 keV cesium ion gun. Samples were dissolved in either a 3-nitrobenzyl alcohol or 2-nitrophenyl octyl ether matrix, previously coated on to a stainless steel probe tip. ^{1}H-NMR spectra were recorded at either 300 or 400 MHz. ^{13}C-NMR spectra were recorded at either 75.5 or 100.6 MHz. Microanalysis was performed by Analytical Labs in Lindbar, Germany.

1,5-Bis(2-(2-methoxyethoxy)ethoxy)naphthalene (5). 1,5-Dihydroxy-naphthalene (1.60 g, 10 mmol) and 1-chloro-2-(2-methoxyethoxy)ethane (2.77 g, 20 mmol) were added to a suspension of K_2CO_3 (4.14 g, 30 mmol) in dry MeCN (250 mL) under a nitrogen atmosphere. The suspension was stirred vigorously and heated under reflux for 3 days. After cooling down to rt, the solvent was evaporated off under vacuum, and CH_2Cl_2 (250 mL) was added to the residue. The mixture was washed with H_2O (3 × 200 mL), and the organic solution was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2: $MeCO_2Et/CH_2Cl_2$, 1:10) gave the title compound **5** as a yellow solid which was crystallized from MeOH (3.13 g, 7.90 mmol, 79%): mp 56 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.86 (d, 2H), 7.34 (t, 2H), 6.83 (d, 2H), 4.30 (t, 4H), 3.99 (t, 4H), 3.59 (t, 4H), 3.40 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.3, 126.7, 125.0, 114,6, 105.6, 72.0, 70.8, 69.8, 67.9, 59.0; EIMS *m*/*z* 364 for $[M]^{+\cdot}$. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.93; H, 7.67.

Cyclobis(paraquat-*p*-phenylene) Tetrakis(hexafluorophosphate) (1·4PF$_6$). Method A. 1,4-Bis(bromomethyl)benzene (**3**) (264 mg, 1 mmol), 1,1′-[1,4-phenylenebis(methylene)]-bis(4,4′-bipyridinium) bis(hexafluorophosphate) (**2**·2PF$_6$) (706 mg, 1 mmol), and 1,5-bis(2-(2-methoxyethoxy)ethoxy)naphthalene (**5**) (1092 mg, 3 mmol) were dissolved in dry DMF (50 mL) and stirred at rt under a nitrogen atmosphere. After 5 days, the solvent was removed under vacuum, and an aqueous NH_4Cl solution (100 mL, 1 M) was added to the purple solid. The mixture was extracted continuously with CH_2Cl_2 for 2 days. During this time, the aqueous solution changed from deep purple to colorless. The aqueous solution was then concentrated and subjected to a column chromatography (SiO_2: MeOH/H_2O/saturated aqueous NH_4Cl solution, 6:3:1). The tetracationic cyclophane-containing fractions were combined, and the solvent was removed in vacuo. The residue was dissolved in H_2O, and a saturated aqueous solution of NH_4PF_6 was added until no further precipitation was observed. After filtration, the white solid was washed with H_2O (50 mL) and Et_2O (50mL) to give **1**·4PF$_6$ (682 mg, 0.62 mmol, 62%), mp >275 °C, (lit. >275 °C). ^{1}H-NMR (400.1 MHz, CD_3CN) δ 5.74 (s, 8H), 7.52 (s, 8H), 8.14−8.18 (m, 8H), 8.84−8.88 (m, 8H); ^{13}C-NMR (100.6 MHz, CD_3CN) δ 65.7, 128.3, 131.4, 137.0, 146.2, 150.4.

Method B. 1,4-Bis(bromomethyl)benzene (**3**) (26.4 mg, 0.1 mmol), 1,1′-[1,4-phenylenebis(methylene)]bis(4,4′-bipyridinium) bis(hexafluorophosphate) (**2**·2PF$_6$) (70.6 mg, 0.1 mmol), and 1,5-bis(2-(2-methoxyethoxy)ethoxy)naphthalene (**5**) (109.2 mg, 0.3 mmol) were dissolved in dry DMF (10 mL). The reaction mixture was transferred to a high-pressure-reaction Teflon tube, which was then compressed (12 kbars) at room temperature for 3 days. After decompression of the reaction vessel, the solvent was evaporated off under vacuum, and an aqueous NH_4Cl solution (25 mL, 1 M) was added to the purple solid. Decomplexation was effected by continuous extraction of this mixture with CH_2Cl_2 as described under method A. The aqueous solution was then concentrated to give a white solid. Treatment of this crude solid, as described for the crude product in method A, afforded pure **1**·4PF$_6$ (89 mg, 0.081 mmol, 81%).

X-ray Crystallography. Crystal data for [**1**·4PF$_6$·(**5**)$_2$·2MeCN]: $C_{76}H_{82}N_4O_{12}$·4PF$_6$·2MeCN, M = 1911.49, monoclinic, a = 24.017(1), b = 13.360(1), c = 28.578(3) Å, β = 109.21(1)°, V = 8659.0(1) Å^3, space group $C2/c$, Z = 4, D_c = 1.466 g cm^{-3}, μ = 1.821 mm^{-1}, $F(000)$ = 3952. 5408 Independent reflections (3.8 < θ < 55°) were collected with graphite monochromated Cu K$_\alpha$ radiation using ω scans. Of these, 4562 had $|F_o| > 4\sigma|F_o|$ and were considered observed. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods and all non-hydrogen atoms were refined anisotropically using full-matrix least squares based on F^2. The positions of the hydrogen atoms were idealized (C−H = 0.96 Å), assigned isotropic U(H) = 1.2 U_{eq}(C), [U(H) = 1.5 U_{eq}-(C) for methyl groups], and allowed to ride on their parent atoms. Final R-factors are R_1 = 0.0731 and wR_2 = 0.1958 for 569 refined parameters. Computations were carried out using SHELXTL, version 5.03. Further details of the structure determination are available, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U. K.

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(25) The binding studies performed in MeCN revealed the formation of complexes [host]−[guest]$_n$ with n > 1 at molar concentrations higher than 10^{-3} M. The template-directed syntheses of the tetracationic cyclophane **1**·4PF$_6$ were performed at relatively high concentrations (C > 10^{-3} M) of the templating agent **5** in DMF. Thus, the high yields observed in these template-directed syntheses might also be aided and abetted by the formation of host−guest complexes with 1:n stoichiometries.