Synthesis and Binding Properties of a Family of Potentially Chiral Spherands

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A new type of strongly binding and chiral spherand is reported, which is composed of a phenanthroline and four alkoxy benzene units incorporated in 18-membered rings whose binding free energies and ^{1}H NMR spectra suggest the systems to be preorganized for complexation.

This paper describes the first incorporation of a phenanthroline unit into a number of spherands, and the resulting effects on their structures and binding properties. With the help of Corey–Pauling–Koltun (CPK) molecular models, we designed the compounds to be highly preorganized, strong binders of alkali metal, ammonium and alkylammonium ions, to be chiral but possessing C_2 axes, and to be potentially useful as chiral catalysts for reactions involving carbanide ion pairs.[1]

Earlier papers reported that while prototypical spherand **1** was the strongest binder of Li^+ and Na^+ known at the time,[2] chiral spherand **2** of D_3 symmetry was a relatively weak binder of these ions.[3] The EtO groups of chiral C_2 system **3** can pass through the centre of its 18-membered ring at working temperatures, and therefore its enantiomers are subject to racemization.[4] Here we report the results of an investigation of hosts **5** and **6** to establish synthetic feasibility, to determine their configurations, and to assess their configurational stabilities. Model examination of **4** and **5** provided the conclusion that configurationally pure material would probably racemize at working temperatures by sequential passage of all of the RO groups through the centre of the macroring, but that **6** should be enantiomerically stable. We chose **5** over **4** to study since in CPK models, one Me group of the four present in **4** can turn inward to fill its cavity, whereas an Et group of **5** turned inward appears to be a higher energy conformation than one with all Et groups turned outward. Systems enantiomerically stable in the latter conformation, such as **6**, possess C_2 symmetry, and appear in models to be good candidates for use as asymmetric catalysts.

Spherands **5** and **6** were synthesized by the reaction sequences, **7**$^5 \rightarrow$ **8**† $\rightarrow$ **9**† $\rightarrow$ **10**† $\rightarrow$ **11**,**11** + **12**$^6 \rightarrow$ **13**† $\rightarrow$ **14** $\rightarrow$ **15**† $\rightarrow$ **16**† $\rightarrow$ **5**,† and **16** $\rightarrow$ **17**† $\rightarrow$ **6**† + **18**.‡ Compound **18** is the *meso*-form of **6**, characterized most convincingly by its crystal structure (see below). The ^{1}H NMR spectra of **5** and **5**·NaBr in $(CD_3)_2SO$, 360 Hz, clearly show the CH_2Me

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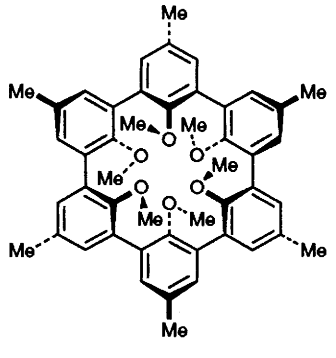
† These new compounds gave elemental analyses within 0.30% of theory, and the expected ^{1}H NMR and mass (m/z, M + H^+) spectra.

‡ Diol **7**^{5} was monoethylated with 1.1 equiv. of K_2CO_3 and excess of Et_2SO_4 in acetone at 25 °C (22 h) to give **8**† (95%) as a colourless oil, which was brominated with Br_2 in $CHCl_3$ at 25 °C to provide **9**† (78%) as prisms, m.p. 97–98 °C. This phenol was ethylated with excess of K_2CO_3 and Et_2SO_4 in acetone (25 °C, 26 h) to give **10**† (96%) as a colourless oil. This bromide with BuLi in tetrahydrofuran at −78 °C (10 min) gave the corresponding lithiate. This material was treated with $(MeO)_3B$ at −78 °C; the boronic ester was allowed to warm to 25 °C and was hydrolysed with H_3O^+–Et_2O to the boronic acid **11** (75%) and 25% of reduced material. Without separation, the mixture was submitted to a Suzuki[7] coupling with **12**^{6} [Ar, Na_2CO_3, $Pd(PPh_3)_4$, MeC_6H_5, H_2O at reflux] to give after alumina gel chromatography (80% cyclohexane 20% CH_2Cl_2) **13**† (90%) as a white foam. This product was deethylated by refluxing it in 48% aqueous HBr and AcOH for 48 h to give tetraphenol **14** (*ca.* 100%), m.p. > 300 °C, whose elemental analysis was unsatisfactory but whose ^{1}H NMR and mass spectra were as expected. Bromination of **14** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone[8] gave **15**† (77%) as an orange powder, m.p. > 300 °C (decomposition). This material when ethylated with NaH, Et_2SO_4, tetrahydrofuran under Ar at 25 °C for 24 h gave **16**† (83% after filter chromatography on alumina gel–Et_2O)



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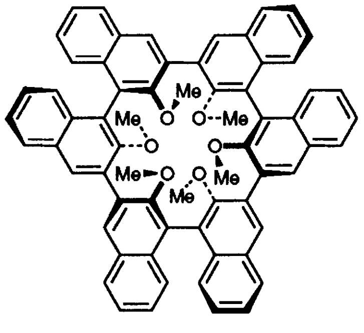

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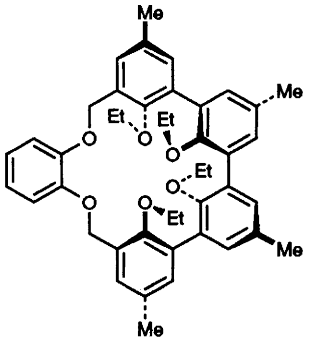

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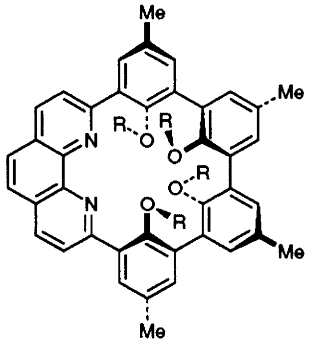
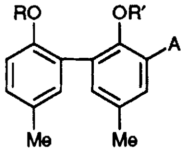
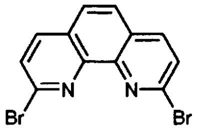


4; R = Me
5; R = Et
6; R = Bu^i



7; R = R′ = A = H
8; R = Et, R′ = A = H
9; R = Et, R′ = H, A = Br
10; R = R′ = Et, A = Br
11; R = R′ = Et, A = B(OH)$_2$



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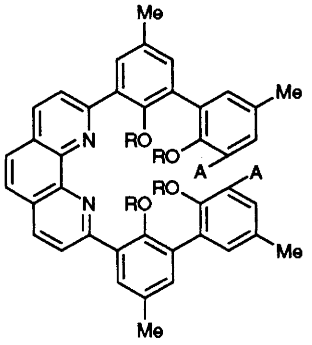

13; R = Et, A = H
14; R = A = H
15; R = H, A = Br
16; R = Et, A = Br
17; R = Bu^t, A = Br

protons to be diastereotopic, being split into four distinct multiplets lying between δ 3 and 4, (the same protons of noncyclic **13** and **16** were enantiotopic). This spectrum shows that **5** possesses C_2 symmetry and that its OEt groups possess the up–down–up–down arrangement formulated in **5**. The ^{1}H NMR spectra of **6** and **6**·NaBr in $(CD_3)_2CO$ also indicated these compounds to possess C_2 symmetry. Further splitting of its protons was observed in the ^{1}H NMR spectrum of **6**·Na (+)-camphorsulfonate, whose chiral counterion produces diastereomeric complexes, which results in the doubling of at least four of its aromatic proton signals.

A stereoview of the crystal structure of **18** (R = 0.08) is formulated in **21**. The conformational structures **19** and **20** are consistent with very preliminary crystal structures, respectively, of **5** and **5**·NaBr (not given here), as well as with their ^{1}H NMR spectra and conclusions drawn from inspection of their CPK molecular models.

These results taken as a whole provide the following structural conclusions. (*i*) The host of **5**·NaBr and free **5** are sufficiently similar to indicate **5** to be fully preorganized for binding, and are members of the spherand–spheraplex family of compounds. (*ii*) Both **19** and **20** possess a down–up–down–up arrangement of their OEt groups, and belong to the chiral C_2 point group. (*iii*) The arrangement of ligands about the Na^+ in **20** cannot assume an ideal octahedral geometry, as evident from model examination. (*iv*) Host **18** possesses an up–down–down–up arrangement of Me_2CHCH_2O groups as shown in **21**. Host **18** is preorganized to not bind cations, and is a diastereoisomer of **6**. The latter undoubtedly possesses the down–up–down–up arrangement, as indicated by its ^{1}H NMR spectrum.

The free energies for binding ($-\Delta G°$, kcal mol^{-1}; 1 cal = 4.184 J) by **5** of the alkali metals and NH_4, $MeNH_3$ and Me_3CNH_3 picrates (Pic) were determined at 25 °C in $CDCl_3$ saturated with D_2O by the extraction of the salts from D_2O by the host at 10^{-3} l mol^{-1} in $CDCl_3$.[11] The respective values of $-\Delta G°$ were as follows: Li^+, 15.8; Na^+, 15.7; K^+, 15.0; Rb^+, 13.6; Cs^+, 13.7; NH_4^+, 14.3; $MeNH_3^+$, 13.4; $Me_3CNH_3^+$, 11.5 kcal mol^{-1}. Thus **5** is a remarkably strong general binder of all of these ions, the range spanning from 15.8 for Li^+ to 11.5 kcal mol^{-1} for $Me_3CNH_3^+$, the smaller Li^+, Na^+, and K^+ being the more strongly complexed, but by small amounts.

These results show reduced binding and loss of specificity when the phenanthroline group is substituted for two alkoxyaryl units in prototypical spherand, **1**, which binds only LiPic

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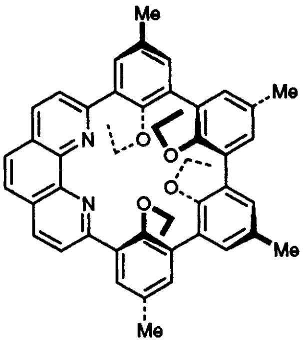
as a white foam. Similarly, tetraphenol **15** was isobutylated with Bu^{i}I–NaH–Me_2NCHO to give **17**† (62%) as a white foam. Ring closure of dibromide **16** was accomplished under dry conditions under Ar by lithiation at −78 °C in tetrahydrofuran, and by cannulating the lithiate (20 min) into a dry, refluxing MeC_6H_5 solution of tris(pentanedionato)iron(III) (high dilution). The mixture was refluxed for 1 h, cooled, stirred with aqueous HCl, evaporated under vacuum, and the residual solids were extracted with CH_2Cl_2. The resulting extracts were evaporated, and the residue was submitted to reverse phase chromatography on coated silica gel[9] with 6% (v/v) NaBr in 60:40 (v/v) acetone–H_2O as the mobile phase. During this chromatographic step, **5**·Li^+ underwent cation exchange to give **5**·Na^+. The fractions containing product were evaporated and the dried material was extracted into CH_2Cl_2. The combined extracts were filtered and the filtrate was evaporated and dried to give **5**·NaBr (14%) as a foam, whose ^{1}H NMR and mass spectra were as expected. This complex suspended in MeOH and deionized water was heated to reflux and the MeOH allowed to evaporate. The water was decanted, and the procedure repeated three times. The residual solid was dried at 110 °C for 6 h to give **5**† (86%) as a powder. Application of the same ring-closing and decomplexing procedure[10] to dibromide **17** gave **6**† (0.4%) as a powder, and a trace of isomeric host **18** as a crystalline solid.

The crystal structure of **18**·$2Me_2CO$ (crystallized from acetone–water, determined at 25 °C) belongs to the monoclinic space group C_2/c: a = 24.507(3), b = 25.582(4), c = 18.356(3) Å, β = 116.683(4)°, Z = 8; 3313 reflections with $I > 3\sigma(I)$; $2\theta_{max}$ = 100°; Cu-Kα radiation; R = 0.08, R_w = 0.12, GOF = 3.48. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



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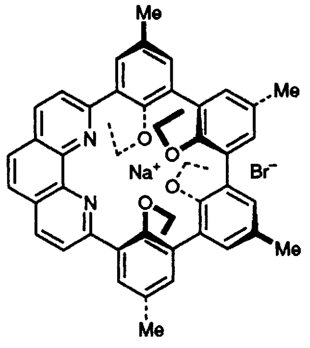

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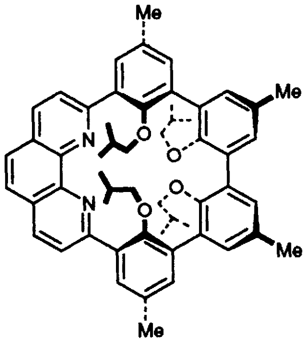

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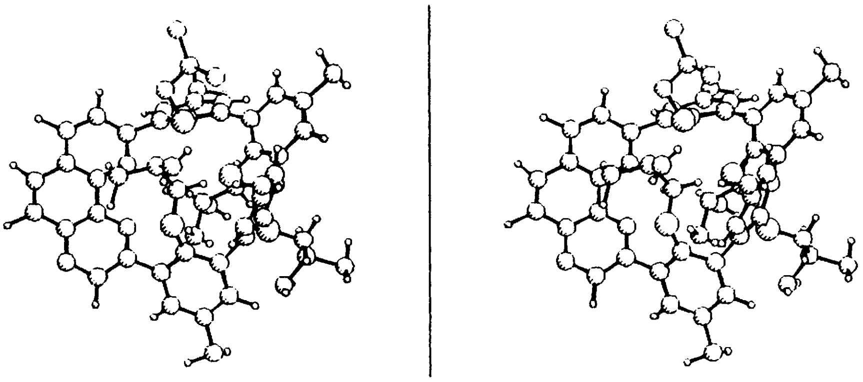

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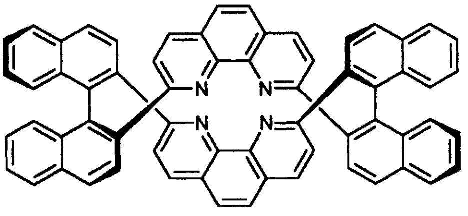

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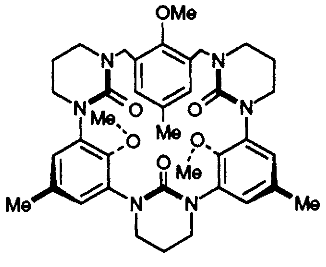

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and NaPic, but with $-\Delta G°$ values of >23 and 19.3, kcal mol^{-1}, respectively.[12] Host **1** is not only preorganized for binding, but also its ligating sites are shielded from solvation, which is not true in **5**. The planar phenanthroline ring spreads the ends of the quateraryl moiety, which provides the system with great flexibility regarding the placement of solvent molecules and of its ligating oxygens, and determination of its cavity size. What is surprising is that **5** binds Li$^+$ so well, since in CPK models, only two nitrogens and two of the alkoxy oxygens can simultaneously ligate the metal. The most similarly shaped analogue of **5** is **3**, which binds Li$^+$ with only 7 kcal mol^{-1} ($-\Delta G°$).[4] The $-\Delta G°$ values for **5** binding Li$^+$, Na$^+$ and K$^+$ resemble those observed for **22**[13] which contains two phenanthroline units, and provides the respective values of 15.4, 15.5 and 14.4 kcal mol^{-1}. In overall binding ability, **5** resembles hemispherand **23**[14] whose $-\Delta G°$ values (kcal mol^{-1}) are: Li$^+$, 12.1; Na$^+$, 15.4; K$^+$, 15.6; Rb$^+$, 14.2; Cs$^+$, 13.1; NH_4^+, 14.4; $MeNH_3^+$, 14.4; and $Me_3CNH_3^+$, 13.2. The low yield in the synthesis of **6**, whose enantiomers are undoubtedly stable to racemization, unfortunately makes it a poor candidate for asymmetric induction studies.

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