

A Strongly Binding, Helically Chiral Ligand System

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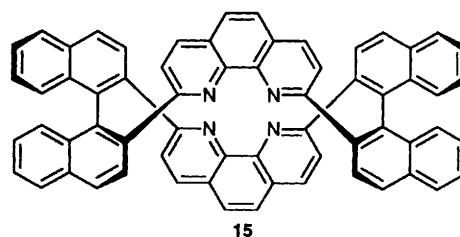
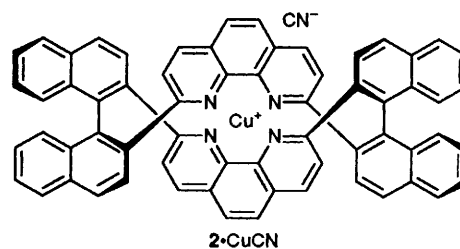
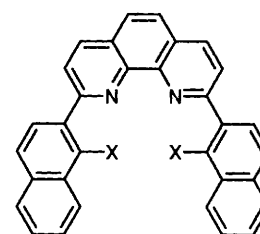
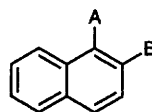
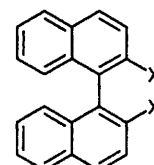
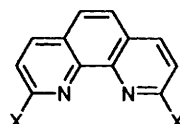
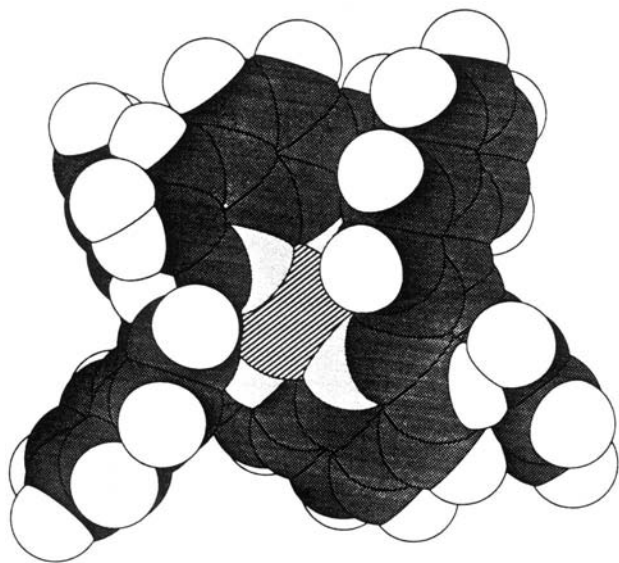
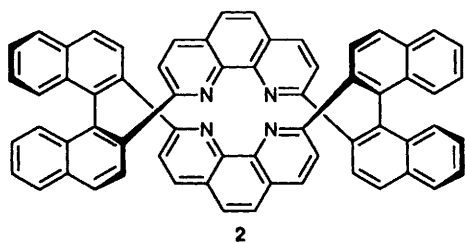
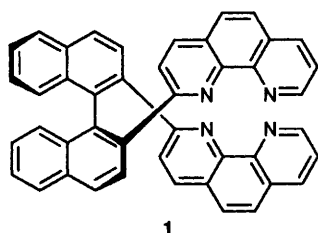
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The syntheses, characterization and binding properties are described for two helically chiral ligand systems containing two phenanthroline units whose nitrogens are roughly tetrahedrally arranged in one system and potentially arrangeable that way in a second.

Here we describe the synthesis, characterization and strong cation-binding properties of **1** and **2**, each of which contains two phenanthroline (**4**) units bonded to one another through one or two 1,1'-binaphthyl units, respectively. Macrocycle **2** is unique in the following ways. (i) It is a 20-membered macrocycle composed entirely of aromatic atoms. (ii) It is a chiral system possessing D_2 symmetry, whose six aromatic residues describe an enforced helical structure. (iii) Its four nitrogen atoms possess a nearly tetrahedral arrangement, which in Corey–Pauling–Koltun (CPK) molecular models appears to be complementarily arranged to bind many of the smaller metal ions (see CPK model drawing **3** ligating a metal cation). (iv) The area surrounding the central ligating hole is divided into two identical chiral cavities of molecular dimensions so that occupation of either one by a counterion provides

the same structure. Compound **1** is identical to **2** except that one binaphthyl group is replaced with two hydrogens. While **2** is fully preorganized for binding suitable cations, **1** is partially preorganized in the sense that the two phenanthrolines are connected, and it possesses one conformation out of four in which the two phenanthrolines can act in concert. We wished to determine the difference in binding free energies associated with full vs. partial preorganization for binding,¹ and ultimately to test the properties of **2** as a chiral catalyst.^{2,3}

The method of Sauvage was employed to prepare **1**.⁴ Binaphthol **6** was converted to dibromide **7** by treating the bis-trimethylsilyl ether of **6** as a melt with PBr_3 at $310^\circ C$ to give **7** in 37% yield.⁵ This dibromide in tetrahydrofuran at $-78^\circ C$ was treated with Me_3CLi (100 min) and the dilithiate produced was added to **5** in tetrahydrofuran at $25^\circ C$ (2 days). The crude product was aromatized by mixing with activated MnO_2 at $25^\circ C$ in a CH_2Cl_2 mixture for 24 h, and **1** was isolated by reverse phase high-pressure liquid chromatography (silica



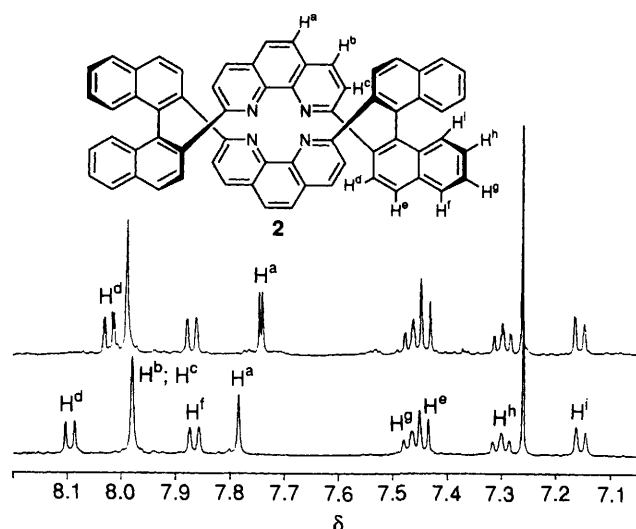


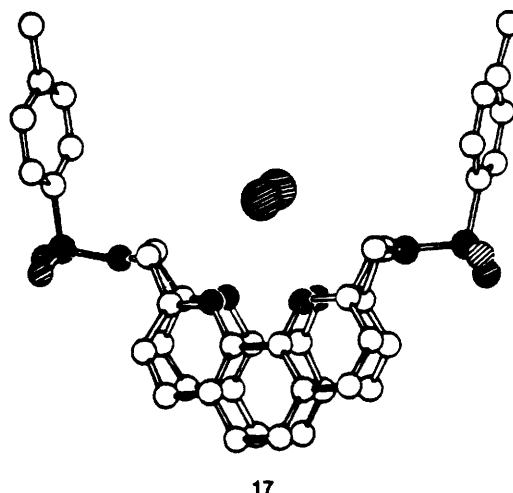
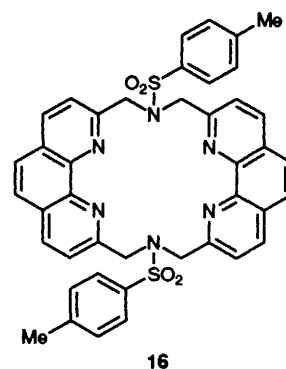
Fig. 1 The ^1H NMR (500 MHz, CDCl_3) spectra of 2-sodium (+)-camphorsulfonate (top) and free **2** (bottom)

gel, NaBr–MeOH mobile phase) and crystallization from methanol as a dihydrate, 5%, m.p. 360–362 °C (decomposition).

Host **2** was synthesized by the reaction sequences:† $8^6 \rightarrow 9 \rightarrow 10 \rightarrow 11 \rightarrow 12$; $12 + 5 \rightarrow 13 \rightarrow 14$;‡ and $2 \text{ } 14 \rightarrow 2$. The final and critical ring closure leading to **2** utilized the venerable Ullman coupling¹³ carried out in refluxing biphenyl-copper bronze at 255 °C (Wood's metal bath) for 20 min (time of complete consumption of **14**). The product mixture was dissolved in CH_2Cl_2 , and the solution extracted with aqueous NaCN, which decomplexed byproducts but not $2 \cdot \text{CuCN}$. The organic layer was mixed with pentane to precipitate product, which was purified by crystallization from MeOH, $2 \cdot \text{CuCN} \cdot 4\text{H}_2\text{O}^+$ (41%). This complex was converted to $2 \cdot \text{NaCN}$ by heating it at reflux in 12:1 (v:v) solution of MeCN–10% aqueous NaCN, allowing 60% of the mixture to evaporate, and recrystallizing the $2 \cdot \text{NaCN}$ (yellow solid that separated) from methanol. This material was dissolved in 5:1 MeOH–deionized water, the solution was heated to reflux, and the volume was reduced to about a third. The solid that

† All new compounds gave elemental analyses within 0.35% of theory, and the expected ^1H NMR and MS ($m/z \text{ M} + \text{H}^+$) spectra.

‡ Bromo aldehyde **8**⁶ in dry tetrahydrofuran was added to a dry solution of $\text{LiN}(\text{CH}_2\text{CH}_2)_2\text{O}^7$ in tetrahydrofuran under Ar at –78 °C followed by Bu^nLi , and finally Me_3SiCl to give **9**[†] (85%) as an oil. This aldehyde in aqueous MeCN– NaHPO_4 was oxidized with H_2O_2 (30%)– $\text{NaClO}_2 \cdot \text{H}_2\text{O}$ to give acid **10**[†] (70%) as colourless prisms, m.p. 147–150 °C. Application of the Barton reaction⁸ to acid **10** using acid-free BrCCl_3 , 4-*N,N*-dimethylaminopyridine, dicyclohexylcarbodiimide, azoisobutyronitrile, *N*-hydroxypyridine-2-thione⁹ and dry benzene at reflux under Ar gave (after chromatography on pentane-silica gel) bromo-compound **11**[†] (71%) as an oil. Lithiation of **11** with Bu^nLi in tetrahydrofuran at –78 °C and treatment of the product with $\text{B}(\text{OME})_3$ gave after H_3O^+ hydrolysis of the boronic diester, boronic acid **12** (60%), characterized only by mass and ^1H NMR spectra. This compound was immediately submitted to a Suzuki¹⁰ coupling reaction with dibromide **5**¹¹ in a mixture of aqueous toluene–EtOH– Na_2CO_3 – $\text{Pd}(\text{PPh}_3)_4$ refluxed for 4 h under Ar to give **13**[†] (99%) after filter chromatography (1:2 CH_2Cl_2 –pentane, Al_2O_3) and crystallization from cyclohexane, m.p. 244–253 °C. Treatment of **13** in CH_2Cl_2 – CCl_4 with ICl at 25 °C for 30 min¹² gave the diiodide **14**[†] (71%) as a white solid, m.p. >320 °C (decomp.). These reactions were all amenable to a 20–200 g scale.



separated was subjected to the same treatment to give free host. This material was dissolved in CH_2Cl_2 and filtered into pentane. The resulting precipitate was $1 \cdot \text{H}_2\text{O}^+$ (79% from $1 \cdot \text{CuCN} \cdot 4\text{H}_2\text{O}$), isolated as a tan solid.

The byproducts of the cyclization were examined, but the *meso*-isomer of **2** (drawing **15**) was not detected. Although CPK models of **15** appear to be strain-free, the two phenanthroline units are far enough from being coplanar to prevent them from ligating the same metal ion at the same time. The absence of **15**, coupled with the high yield of $2 \cdot \text{CuCN}$ obtained without employing high dilution, strongly suggests that the cyclization was templated by Cu^+ , as was the formation of certain biphenyls *via* a modified Ullman reaction.¹⁴

Confirmation that **2** is a racemate is shown by the changes in δ and the doubling of the H^d and H^a protons in the ^1H NMR spectrum of its sodium (+)-camphorsulfonate complex *vs.* that of free **1** shown in Fig. 1. The proton spectral assignments were made based on decoupling experiments and CPK molecular model examination.

The association constants ($K_a \text{ l mol}^{-1}$) and free energies ($-\Delta G^\circ \text{ kcal mol}^{-1}$; $1 \text{ cal} = 4.184 \text{ J}$) for **1** and **2** binding the first three of the alkali metal ions in CDCl_3 at 25 °C were determined by the picrate salt extraction method in the absence and presence of host at 0.02 l mol^{-1} for **1** and 0.001 l mol^{-1} for **2**.¹⁵ The respective $-\Delta G^\circ$ values are as follows: for **1**, LiPic, 7.7; NaPic, 6.2; KPic, 6.4; for **2**, LiPic, 15.4; NaPic, 15.5; KPic, 14.4 kcal mol^{-1} . Thus, neither **1** nor **2** shows much discrimination between binding Li^+ , Na^+ or K^+ . However, the increased preorganization of **2** over that of **1** causes increases in binding values that range from 7.7 to 9.3 kcal mol^{-1} in $-\Delta G^\circ$, which reflect a 5–7 power of 10 increase in K_a values. The powerful binding properties of **2** recall that of Bell's torands, in which six pyridines are incorporated in an 18-membered ring.¹⁶

Compound **1** possesses the four conformations *syn-syn*, *syn-anti*, *anti-syn* and *anti-anti*, of which only the *syn-syn*

allows the four nitrogens simultaneously to ligate a metal cation. The free energy cost of freezing out three out of four conformations of **1** is hardly enough to account for the dramatic difference of *ca.* 8.5 kcal mol⁻¹ between the binding power of **1** and **2**. We believe that much of this large difference is due to the greater steric inhibition of hydration in CDCl₃ saturated with D₂O of **2** compared to **1**. In CPK models of the conformers of **1**, two molecules of water can beautifully bridge by hydrogen bonding the two nitrogens of each phenanthroline, whereas in those of **2** there is space available for only one hydrogen of one water.

In this connection, the elemental analysis of **2** showed the presence of one molecule of water after drying at 190 °C at 10⁻⁵ Torr for 36 h, whereas **1** showed the presence of two molecules. By analogy with this interpretation, **16**, which contains two phenanthroline moieties incorporated into an 18-membered ring, provides the crystal structure **17**, in which one molecule of water bridges by hydrogen bonding the two nitrogens of each phenanthroline unit.¹⁷ Attempts to obtain crystals suitable for crystal structure determination of **2** failed.

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