A Spherand containing an Enforced Cavity that selectively binds Lithium and Sodium Ions

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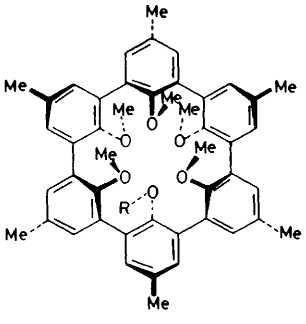
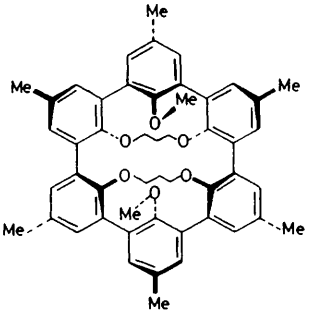
Summary A new type of ligand system is reported which by means of a rigid support structure, focuses the twenty-four electrons of six attached oxygens on an enforced cavity; the system complexes Li^+ and Na^+, but rejects other alkali or alkaline earth ions, solvents, and parts of its own support structure.

ELSEWHERE we have reported the design and synthesis of the spherands (**1**) and (**2**) and a survey of the complexing properties of (**1**).[1] Spherand (**1**) strongly binds Li^+ and Na^+ and scavenges these ions from other alkali or alkaline earth ions. Here we report the synthesis and a survey of the complexing properties of spherand (**3**). This system possesses the same cyclohexa-*m*-phenylene framework as (**1**) and (**2**), which holds six oxygen atoms with their twenty-four electrons arranged in a nearly perfect octahedron. Host (**3**) is made more rigid by two trimethylene bridges that cap the two sets of pseudo *meta* oxygen atoms. Two methyl groups cap the remaining pseudo *para* oxygen atoms. In Corey–Pauling–Koltun space-filling models the only structure for (**3**) that can be assembled contains a roughly spherical cavity lined with twenty-four electrons of the six octahedrally arranged oxygen atoms, which are pressed into contact with one another by the rigid support structure. One bridge and one methyl group protrude from one side of the macrocycle, and the second bridge and methyl group protrude from the other side to give a structure with C_{2h} symmetry. Graded spheres of diameters 1·3—1·9 Å can be pushed into the cavity, but the cavity is too small to be filled by any part of the support structure or by solvent. Thus unlike the crowns or cryptands,[2] this free ligand system contains an organized cavity before complexation. The term spherand[1] names the family of ligand systems that owes much of its binding properties to the release, upon complexation, of electron–electron repulsion between heteroatoms forced by their rigid attached framework into lining a cavity with electrons.

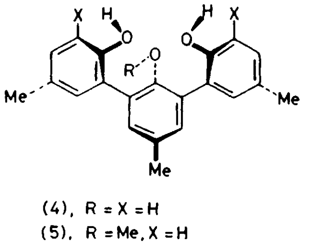


(1) R = Me
(2) R = H

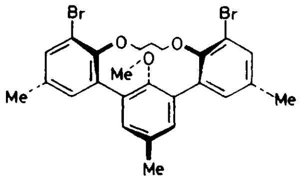


(3)

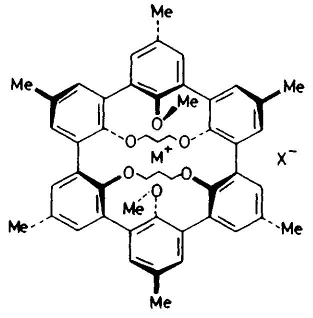
The spherand (**3**) was synthesized in seven steps from *p*-cresol in 1·2% overall yield. Oxidation of *p*-cresol gave the triphenol (**4**)[3] (20—40%) which with K_2CO_3 (1 equiv.) and excess of MeI in acetone (25 °C, 26 h) gave the centrally methylated compound (**5**)† (72%). Bromination of (**5**) at −78 °C in $CHCl_3$ gave (**6**)† (88%), m.p. 175—177 °C. Ring closure of (**6**) with $Br[CH_2]_3Br$, K_2CO_3, and KI in acetone at reflux (10 h in the dark) gave (**7**)† (44%), m.p. 186—188 °C. In a new reaction, the dibromide (**7**) was dimetallated with BuLi at −78 °C in tetrahydrofuran (THF), and the new organometallic was added to $Fe(acac)_3$ (3 equiv.) (acacH = pentane-1,4-dione) in C_6H_6 at reflux (1 h) to give a solution which was washed with aqueous $HFeCl_4$. The lithiospherium tetrachloroferrate produced was recrystallized from AcOH–CH_2Cl_2 to give (**8**)† (13%) as yellow needles, solid to 300 °C but with slow decomposition at higher temperatures. A CH_2Cl_2 solution of this salt was washed with an aqueous solution of LiCl containing ethylenediaminetetra-acetic acid (EDTA) to give lithiospherium chloride (**9**)† (91%), slow decomposition without melting, 110—400 °C. When heated at 100 °C in 4 : 1 (v/v) H_2O–pyridine (1 h), (**9**) decomplexed to give (**3**)† (83%), which crystallized during the reaction, m.p. *ca.* 360 °C (decomp.). The decomplexation did not occur at temperatures lower than *ca.* 80 °C, and appears to be driven by the crystallization of the free host from a medium in which it is insoluble.



(4), R = X = H
(5), R = Me, X = H
(6), R = Me, X = Br



(7)



(8), M = Li, X = FeCl4
(9), M = Li, X = Cl

The respective 200 MHz, ^1H n.m.r. spectra ($CDCl_3$) of (**3**) and (**9**) are consistent with their assigned C_{2h} structures: (**3**), δ 0·45—0·65 (2H, m, $\mathrm{CH_2C}H_2\mathrm{CH_2}$), 1·6—1·8 (2H, m, $\mathrm{CH_2C}H_2\mathrm{CH_2}$), 2·41 (12H, s, $\mathrm{CH_2OC_6H_2C}H_3$), 2·44 (6H, s, $\mathrm{MeOC_6H_2C}H_3$), 2·80 (6H, s, OMe), 3·15—3·35 (4H, m, OCH_2), 4·26 (4H, br t, OCH_2), 7·21 (4H, s, $\mathrm{C_6}H_2\mathrm{OCH_2}$), 7·24 (4H, s, $\mathrm{C_6}H_2\mathrm{OMe}$), and 7·60 (4H, s, $\mathrm{C_6}H_2\mathrm{OCH_2}$); (**9**), δ 0·85—1·05 (2H, m, $\mathrm{CH_2C}H_2\mathrm{CH_2}$), 1·9—2·1 (2H, m, $\mathrm{CH_2C}H_2\mathrm{CH_2}$), 2·49 (12H, s, $\mathrm{CH_2OC_6H_2C}H_3$), 2·51 (6H, s, $\mathrm{MeOC_6H_2C}H_3$), 2·89 (6H, s, OMe), 3·25—3·45 (4H, m, OCH_2), 4·48 (4H, br t, OCH_2), 7·35 (4H, s, $\mathrm{C_6}H_2\mathrm{OCH_2}$), 7·40 (4H, s, $\mathrm{C_6}H_2\mathrm{OMe}$), and 7·79 (4H, s, $\mathrm{C_6}H_2\mathrm{OCH_2}$).

Solutions (500 μl) of (**3**) in $CDCl_3$ (0·0015 M) were mixed with 10 μl of $(CD_3)_2SO$ solutions that were *ca.* 0·04 M in $LiClO_4 \cdot 3H_2O$, $NaClO_4 \cdot H_2O$, $KClO_4$, $RbClO_4$, $CsClO_4$, $Mg(ClO_4)_2$, or $CaBr_2$ to give homogeneous solutions of potential complexing partners in molar ratios of *ca.* 1·9 : 1 host to potential guest. The 200 MHz ^1H n.m.r. spectra were taken within 5 min to 3 h of mixing at *ca.* 30 °C (for $CaBr_2$, up to 7 days elapsed). All solutions gave identical signals for the free host. Only when Li^+ and Na^+ were present did additional signals appear for the complexes. Their intensities compared with those of the free host suggested that most or all of the guest present was complexed. The chemical shifts of the ArH, $ArCH_3$, and $ArOCH_3$ protons for the Li^+ and Na^+ complexes were distinguishably different, although the δ values were within 0·03 p.p.m. of one another. A solution of (**3**) (500 μl) in

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† C, H, and Cl (when present) analyses were within 0·30% of theory, and ^1H n.m.r. and mass spectra were consistent with the structural assignments.

$CDCl_3$ (0·0015 M) was mixed with 22 μl of a $(CD_3)_2SO$ solution that was *ca.* 0·04 M in $LiClO_4\cdot3H_2O$ to give a solution whose host/guest ratio was *ca.* 0·9, and in whose ^1H n.m.r. spectrum only lithiospherium perchlorate was visible. The addition of 10 μl of a $(CD_3)_2SO$ solution that was *ca.* 0·04 M in $NaClO_4\cdot H_2O$ did not change its ^1H n.m.r. spectrum in seven days. Thus Na^+ did not replace Li^+ in the complex. An identical experiment was run in which the $LiClO_4$ and $NaClO_4$ solutions were interchanged. The initially obtained ^1H n.m.r. spectrum showed the presence of only sodiospherium perchlorate. Within 1 h of addition of the $LiClO_4$ solution, both the Li^+ and Na^+ complexes were present, and after 72 h their respective ratio was *ca.* 1/2 (^1H n.m.r. spectroscopy). Thus all the Li^+ ions present replaced Na^+ in the complex. Repetition of the same two experiments with spherand (**1**) in place of (**3**) showed no displacement of Li^+ by Na^+ or of Na^+ by Li^+ in the corresponding complexes.

When violently shaken for 24 h with 1·0 ml of 0·0028 M solutions of (**3**) in $CDCl_3$ at 30 °C, 3—6 M aqueous solutions (1—3 ml) of LiBr, NaBr, KBr, $MgBr_2$, $CaBr_2$, or $SrBr_2$ gave ^1H n.m.r. spectra for the $CDCl_3$ layer which showed that host was completely complexed in the Li^+ and Na^+ experiments, and 5, 10, 5, and 32% complexed in the K^+, Mg^{2+}, Ca^{2+}, and Sr^{2+} experiments, respectively. The ^1H n.m.r. spectra of the lithiospherium and sodiospherium complexes were easily identifiable in the first two experiments. The spectra of the complexes formed in the other experiments were identical with that of the sodiospherium bromide.

These experiments demonstrate three points. (i) A very rigid compound, such as the spherand (**3**), can be prepared, which is composed of aryloxy ether units whose oxygen atoms in the free ligand line an enforced cavity which cannot be filled either with parts of the host or solvent. (ii) This host in $CDCl_3$–$(CD_3)_2SO$ strongly binds and lipophilizes Li^+ and Na^+ salts but not K^+, Rb^+, Cs^+, Mg^{2+}, or Ca^{2+} salts. (iii) In $CDCl_3$–$(CD_3)_2SO$ at 35 °C, Li^+ replaces Na^+ in the sodiospherium perchlorate, but Na^+ fails to replace Li^+ in lithiospherium perchlorate. No cation exchange in either direction was observed for the spherium perchlorates of (**1**).

A 2,6-substituted anisole unit used to replace a CH_2OCH_2 unit in 18-crown-6 greatly depresses the host's selectivity and binding ability for any of the cations tried.[4] Thus the powerful binding and structural recognition properties of these spherands must arise from the high energy and enforced dimensions of a cavity lined with electron pairs, which cannot be filled with anything other than small spheres. We conclude that spherands can be tailored to control both the kinetics and thermodynamics of complexation of many of the ions of the periodic table. Syntheses of spherands and hemispherands composed of methoxycyclohexane, pyridine oxide, cyclic urea, cyclic ketone, and cyclic amide units are under active investigation.

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