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Spherands vs. Nonspherands containing Two Methoxycyclohexane Units

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The superb complexing ability and preorganized cavity of the spherand $(\text{MeC}_6\text{H}_2\text{OMe})_6$ is destroyed by the substitution of two methoxycyclohexane units for two pseudo-*para* methoxytoluene units of the spherand.

The powerful binding of Li^+ and Na^+ by the spherand $(1)^{1-4}$ has been attributed to the organization of the electron-lined cavity in (1) during synthesis rather than during complexation.⁵ Although not quite isosteric with methoxytoluene, one or more methoxycyclohexane units organized as in $(2a-c)$ can be substituted for methoxytoluenes in Corey-Pauling-Koltun (CPK) molecular models of (1) without destroying the roughly octahedral arrangement of the oxygens. Accordingly, the macrocycle (2) was synthesized[†] and examined.

An X-ray crystal structure of $(2)^\ddagger$ proved it to be $(2d)$,

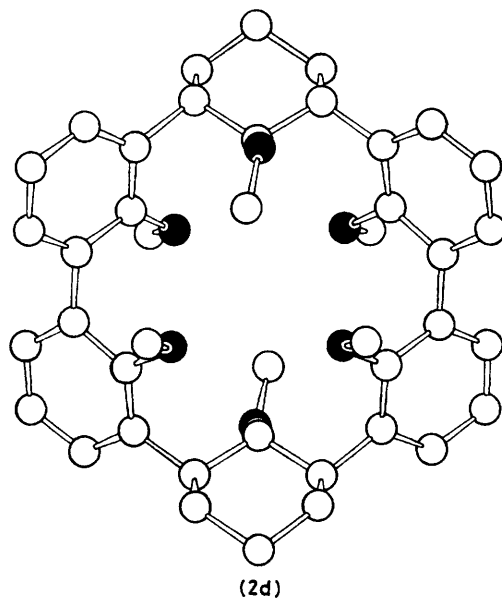
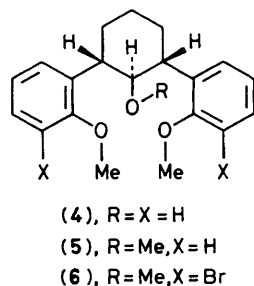
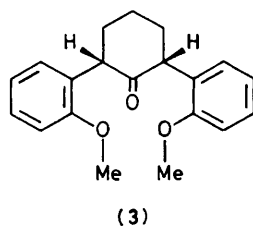
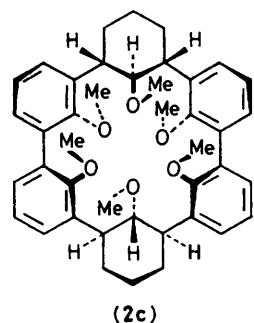
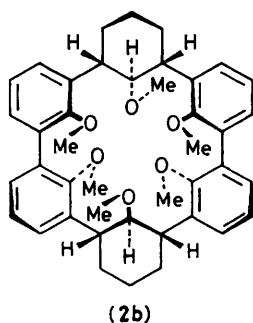
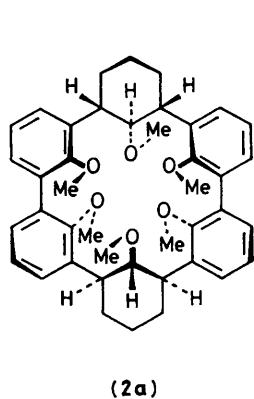
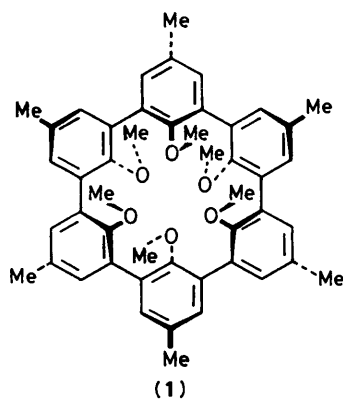
[†] All new compounds gave C and H analyses within 0.30% of calculated values, appropriate molecular ions in their mass spectra, and expected ^1H n.m.r. spectra. Treatment of *o*- $\text{MeOC}_6\text{H}_4\text{CH}_2\text{Br}^5$ with $\text{Ni}(\text{CO})_4^6$ in dimethylformamide (DMF) at 60°C gave (*o*- $\text{MeOC}_6\text{H}_4\text{CH}_2$)₂CO (93%, oil), which with $\text{Br}[\text{CH}_2]_3\text{Br}$ in $\text{Bu}^+\text{OH}-\text{Bu}^+\text{OK}$ under reflux⁷ gave (3) (40%, m.p. $152-153^\circ\text{C}$). Reduction of (3) with LiAlH_4 in tetrahydrofuran (THF) at -78°C gave (4) (96%, m.p. $116-117^\circ\text{C}$) as a single diastereoisomer, methylation of which with $\text{MeI}-\text{NaH}-\text{DMF}$ at 25°C gave (5) (100%, oil). Metallation of (5) with BuLi -tetramethylethylenediamine in diethyl ether at 25°C followed by bromination of the organolithium product at -78°C with cyanogen bromide gave (6) (chromatographic purification, 36%, m.p. $158-160^\circ\text{C}$). The configurations of $(3)-(6)$ were established from their ^1H and ^{13}C n.m.r. spectra. The dibromide (6) in THF was metallated with BuLi at -78°C , and the resulting solution was cannulated into a refluxing suspension of ferric triacetylacetonide in THF. The isolation procedure used for the lithium complexes of (1) when applied to those of (2) gave complexes that resisted purification but which gave a strong lithium flame test. Consequently, $(2)\cdot\text{LiCl}$ was heated in $\text{H}_2\text{O}-\text{MeOH}$ (3:1, v/v) at 120°C for five days. Compound (2) precipitated and was recrystallized from $\text{CHCl}_3-\text{MeOCH}_2-\text{CH}_2\text{OMe}$ (1.6%, m.p. $>300^\circ\text{C}$).

[‡] Crystal data: $(2d)$, $\text{C}_{42}\text{H}_{48}\text{O}_6$, $M = 648.8$, triclinic, $P1$, $a = 8.974(2)$, $b = 10.855(3)$, $c = 10.959(3)\text{Å}$, $\alpha = 77.47(2)$, $\beta = 76.56(2)$, $\gamma = 115.03(2)^\circ$, $U = 878.6(4)\text{Å}^3$, $\mu = 0.45\text{cm}^{-1}$, $Z = 1$, $\lambda = 0.7107\text{Å}$, crystal dimensions *ca.* (0.3 mm)³, $R = 0.10$ for 1685 reflections with $F \geq 3\sigma(F)$. The molecule has a centre of symmetry (at 0, 0, $\frac{1}{2}$).

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

which differs from $(2c)$ only in the sense that the two methyls of the methoxycyclohexyl units are turned inward, filling the cavity. The compound in CDCl_3 gave the following 200 MHz ^1H n.m.r. spectrum; δ 1.70–1.95 (m, 12H, $[\text{CH}_2]_3$), 2.50 (m, 4H, ArCH), 2.85 (s, 6H, CHOCH_3), 2.99 (s, 12H, ArOCH_3), 5.13 (t, 2H, J 9.7 Hz, CHO), 7.03–7.10 (m, 4H, ArH), and 7.19–7.30 (m, 8H, ArH). In ^1H n.m.r. spectrum-monitored experiments, a solution of equivalent amounts of NaBPh_4 and (2) in 98% $\text{CDCl}_3-2\%$ $(\text{CD}_3)_2\text{SO}$ (v/v) at 25°C showed no evidence of complexation after 30 min. However, at 50°C , (2) became completely complexed in 5 min, as shown by the movement of the CHOCH_3 singlet to δ 2.67, the ArOCH_3 singlet to 3.04, and the CHO triplet to 5.44. When this solution was vigorously agitated with deionized water, the CDCl_3 layer reproduced the spectrum of noncomplexed (2) . A solution of two equivalents of LiClO_4 to one of (2) in 98% $\text{CDCl}_3-2\%$ $(\text{CD}_3)_2\text{SO}$ (v/v) when heated at 60°C for 22 h produced a spectrum which did not change further with time. The spectrum (at 25°C) indicated (2) was *ca.* 45% complexed, and that at least two different complexes were formed, which provided five additional CH_3O singlets at δ 2.83, 3.08, 3.10, 3.23, and 3.38, and three additional CHO triplets (J *ca.* 10 Hz) at 5.35, 5.70, and 5.93.

These results are interpreted as follows. A very stable $(2a)\cdot\text{Li}^+$ complex was initially produced in a lithium ion-templated dimerization of two diradicals derived by oxidation of the dilithium salt of (6) . Molecular models (CPK) indicate that of the three possible complexes, $(2a)\cdot\text{Li}^+$, $(2b)\cdot\text{Li}^+$, and $(2c)\cdot\text{Li}^+$, only in $(2a)\cdot\text{Li}^+$ can all six oxygens simultaneously contact a sphere of 1.5 Å diameter. This complex resisted attempts at its purification, and showed a positive lithium flame test. When heated at 120°C for 5 days in $\text{MeOH}-\text{H}_2\text{O}$, the compound decomplexed, a process aided by the insolubility of the free ligand in the medium used. At this high temperature the $(2a)$ produced initially underwent ring inversion of all six methoxy groups to give $(2d)$. Examination of molecular models suggest that $(2d)$ should be more stable than either $(2a)$ or $(2c)$ because of the absence in $(2d)$ of oxygen-oxygen repulsions, a cavity, and any increase in strain over that of $(2a)$ or $(2c)$. The conformational flexibility



of the two cyclohexane rings facilitates the ring inversions. Only when heated to 50–60 °C did (2d) possess enough thermal energy to rotate its methoxycyclohexane methyl groups outward to give (2c), which was fully trapped by Na⁺ (when present) to give (2c)·Na⁺, and partially trapped by Li⁺ (when present) to give two different Li⁺ complexes.

In models of (2c)·Na⁺, all six oxygens can simultaneously contact a sphere of 1.9 Å diameter to give a single complex. In models of (2c)·Li⁺, only the four ArO and one of the CHO oxygens can simultaneously contact a sphere of 1.5 Å diameter. However, by an uninhibited reorganization, this complex can equilibrate with an equivalent complex in which the two CHO oxygens have switched roles. This complex accounts for two of the additional OCH₃ singlets and for one of the additional CHO triplet signals in the ¹H n.m.r. spectrum of the LiClO₄-(2) mixture. The remaining three CH₃O singlets and two triplet CHO signals are attributed to a modified (2c)·Li⁺ complex, in which one CHOCH₃ methyl still turns inward, as in (2d). Models of such a complex indicate five oxygen-to-sphere contacts, and the steric barrier to rotations of the CHOCH₃ methyl groups between 'in' and 'out' positions appears high enough to make equilibration

between the two equivalent complexes slow on the n.m.r. time scale.

Molecular model examinations suggest (1)·Li⁺ = ca. (2a)·Li⁺ ≫ (2b)·Li⁺ ≫ (2c)·Li⁺ in stability. The chief destabilizing feature in models of (2b)·Li⁺ and (2c)·Li⁺ is the compression of the MeOCH hydrogen and the oxygens of the two flanking methoxycyclohexane groups, which inhibits full co-operation of all six oxygens in binding Li⁺. The steric barrier to (2d) going to (2a)·Li⁺ in the presence of Li⁺ was too high to be climbed at 60 °C, even if such a process was thermodynamically feasible. The existence of an inward-turned methyl of a methoxy unit has now been observed in a potential hemispherand,⁸ an eight aryl spherand,⁹ and in (2d).

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