without further purification. The activity measured for H_2ase depended on the assay method used[15] but was approximately 5–6 U mg^{-1} (1 U = 1 μmol of F_0 or 2 μmol of MV^{2+} reduced/min) before immobilization; the immobilization yield was ~40% and the activity of the resulting swollen gel ~3–10 U mL^{-1} for H_2ase and ~1 U mL^{-1} for F_0NR. The gel-immobilized H_2ase (suspended in 50 mM Tris, pH 7.5) showed no loss in activity over 2 weeks when stored under H_2 at 25 °C in the presence of 2 mM MV and 2-mercaptoethanol or under Ar at 5 °C.

A preparation of D-lactate illustrates the operation of the MV-mediated redox cycle. In a 2-L, three-necked, round-bottomed flask was placed 1 L of solution containing pyruvate (400 mmol), NAD (0.2 mmol), MV^{2+} (2 mmol), DTT (3 mmol), and 300 U each of immobilized H_2ase (40 mL of gel, assay based on 2 mM MV^{2+}, pH 8.0), LipDH (8 mL of gel), and D-LDH (0.5 mL of gel).[16] The suspension was deoxygenated with a stream of Ar for 30 min and evacuated to 0.01 torr (*boiling*). Dihydrogen (1.2 atm) was introduced and the pH controlled at 7.8 using a pH-stat by adding oxygen-free 2 N KOH solution. An additional 500 U of LipDH was added every 2 days.[17] The reaction was completed in 12 days. The suspension was flushed with Ar to remove H_2, the gel was allowed to settle, and the solution was decanted and treated with 20 g of activated charcoal to remove MV and NAD(H). D-Lactate was isolated from this solution as its zinc salt (340 mmol of D-lactate, 10 mmol of L-lactate, 85% yield, 94% ee) as described previously.[5] Turnover numbers (TN) and quantities of enzymes recovered are summarized in Table I.

The operation of the redox system mediated by F_0 is illustrated by a preparation of *threo*-D_s(+)-isocitrate. In the same apparatus was placed 1 L of deoxygenated solution (0.1 M Tris, pH 7.8) containing α-ketoglutarate and $NaHCO_3$ (200 mmol each), $MnCl_2$ (5 mmol), DTT (3 mmol), NADP (0.1 mmol), and F_0 (0.08 mmol). PAN-immobilized H_2ase (500 U based on F_0, pH 7.5), F_0NR (~100 U),[15] and ICDH (100 U) were added, and the mixture was maintained at pH 7.8 under 1.2 atm of 4:1 mixture of H_2 and CO_2 for 12 days. Unreacted α-ketoglutarate was destroyed by using NH_4Cl (100 mmol) and glutamate dehydrogenase (100 U) and *threo*-D_s(+)-isocitric acid isolated as its barium salt (43 g, 96% purity, 100 mmol, 50% yield) as described previously.[5]

These procedures demonstrate the usefulness of the H_2ase from *M. thermoautotrophicum* as the basis for catalytic procedures for reducing nicotinamide cofactors by H_2 in situ. The thermodynamics of the overall reactions strongly favor reduction (for NAD + H_2 → NADH + H^+, $\Delta E_0' = 0.1$ V, $\Delta G_0' = -4.6$ kcal/mol, $K_{eq}' = 2400$, pH 7.0, 1 atm of H_2).[18] This H_2ase has a high specific activity;[9] it (and F_0NR if required) can be obtained in large quantities from a nonpathogenic organism using a simple isolation and can be used in crude form; it is stable and is not irreversibly inactivated by O_2; it accepts as substrates a number of cofactors and redox dyes (F_0, MV^{2+}, benzyl viologen, diquat, FAD, FMN, others) and can thus be utilized in a variety of ways. In addition, the other coupling enzymes required are either commercially available or readily prepared. The disadvantages of these systems are that the *M. thermoautotrophicum* fermentation is not trivial, yeast LipDH is unstable under the reaction conditions, H_2ase, FdR, F_0NR, and F_0 must be prepared, F_0NR is specific for NADP, and LipDH is specific for NAD.

In summary, this work demonstrates the practicality of organic synthetic procedures based on NAD(P)H-requiring enzymes, in which H_2/H_2ase is the ultimate reducing agent. The H_2ase used here seems the most attractive presently available for H_2 activation.[19] Of the two configurations tested for NAD → NADH, the most practical seems to be H_2/H_2ase/MV^{n+}/LipDH/NAD, although the problem of the instability of LipDH remains to be solved. Evaluation of the merits of this system for reduced nicotinamide cofactor regeneration, relative to others presently available or being developed (formate/formate dehydrogenase,[3,4] glucose 6-phosphate/G-6-P dehydrogenase,[5] various electrochemical procedures[2,20]) will almost certainly vary with the characteristics of the contemplated synthesis, and especially with its scale. H_2ase-based systems are of greatest interest in large-scale work, where the cost of the reagents is critical. In laboratory-scale work, where convenience is more important, the most attractive procedures are (in our experience) those based on glucose-6-PDH or formate dehydrogenase; the procedure described here is too complex for small-scale work.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM 26543 to G.M.W.; GM 28358 to W.O.J.) and the Monsanto Company. L.D. held a NIH Postdoctoral Fellowship (GM 06600). We thank Dr. W. T. Ashton of Merck, Sharpe, and Dohme for the generous gift of F_0. The starter culture of *M. thermoautotrophicum* was a gift from Professor J. G. Zeikus (Bacteriology, University of Wisconsin). Our colleague F. Jacobson helped in the fermentations. The molecular and catalytic properties of purified H_2/F_0 and F_0/NADP oxireductases will be reported subsequently (F. Jacobson, C. Walsh, L. Daniels, and W. H. Orme-Johnson, in preparation).

Supplementary Material Available: Details of the *M. thermoautotrophicum* fermentation (2 pages). Ordering information is given on any masthead page.

(15) Activities and assay conditions (32 °C, 1 atm H_2): 68.2 U mg^{-1} (pH 9.0, 2 mM MV^{2+}), 5.5 U mg^{-1} (pH 8.0, 0.1 mM MV^{2+}, and 6.0 U mg^{-1} (pH 7.5, 50 μM F_0). Reactions were followed by using the absorbance of the coupling agents: ε (F_0, at the isobectic point at 400 nm, pH 7.5) = 25 mM^{-1} cm^{-1}; ε [NAD(P)H, 340 nm] = 6.22 mM^{-1} cm^{-1}; ε (MV^+, 560 nm, pH 8.0) = 8.0 mM^{-1} cm^{-1}.

(16) The K_m values of substrates and cofactors are MV^{2+} for H_2ase, 0.45 mM (pH = 9); F_0 for H_2ase, 34 μM (pH 7.5). Jacobson, F.; Daniels, L.; Fox, J.; Orme-Johnson, W. H.; and Walsh, C., unpublished. NAD for LipDH, 0.14 mM; NAD and NADP for FdR, 3.8 mM and 10 μM (Shin, M. *Methods Enzymol.* **1971**, *28*, 440–447).

(17) LipDH from yeast lost activity rapidly under these conditions. Preliminary observations indicate that LipDH from pig heart is more stable.

(18) Segel, I. H. "Biochemical Calculations", 2nd ed.; Wiley: New York, 1975; pp 414–415.

(19) The H_2ase from this species has high specific activity and stability. The organism was grown strictly anaerobically under H_2. Another organism *Alcaligenes eutrophus* must be grown under mixtures of H_2 and O_2, a procedure which presents safety hazards. *Desulfovibrio* species also contain high levels of H_2ase, but production of H_2S by the bacteria make growth of the organism unattractive. Several clostridial species contain H_2ase, but most are irreversibly deactivated by O_2 and thus difficult to handle.

(20) Shaked, Z.; Barber, J. J.; Whitesides, G. M. *J. Org. Chem.*, submitted. DiCosimo, R.; Wang, C.-H.; Daniels, L.; Whitesides, G. M. *Ibid.*, submitted.

Augmented and Diminished Spherands and Scales of Binding[1]

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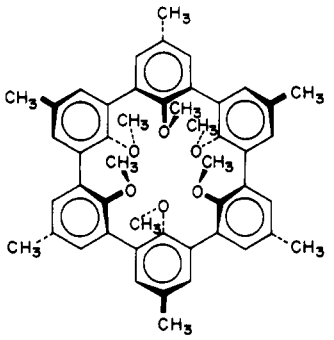
We report the syntheses of three new spherands, the crystal structures of lithium salt complexes of two highly strained, bridged spherands, and a comparison of the binding abilities toward Li^+ and Na^+ of spherands **1–5** (Chart I), standard cryptands and crowns, and an open-chain model compound.

Treatment of 2,6-bis(3-bromo-2-hydroxy-5-methylphenyl)-4-methylanisole[2] with $(TsOCH_2CH_2)_2O$–KOH[3] gave **6**[4,5] (74%).

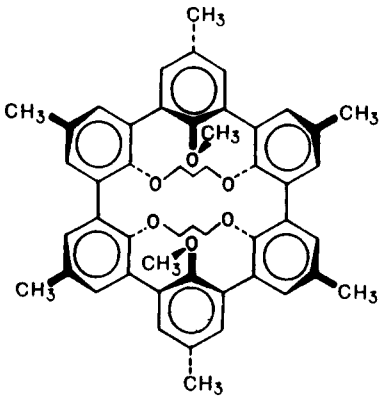
(1) Support for the syntheses and complexation measurements by the Division of Basic Sciences of the Department of Energy, Contract AT(04-3)34, P.A. 218 is gratefully acknowledged by D. J. Cram, G. S. Lein, T. Kaneda, and R. C. Helgeson. Support for the X-ray crystal structure determinations by the National Science Foundation Grants GP-28248, 77-18748, and 80-22526 is gratefully acknowledged by K. N. Trueblood, C. B. Knobler, and E. Maverick.

0002-7863/81/1503-6228$01.25/0

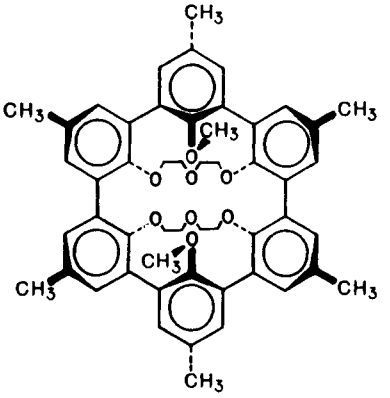
Chart I



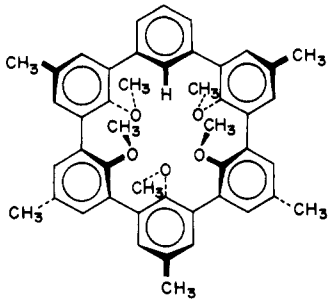
1, $(CH_3C_6H_2OCH_3)_6$



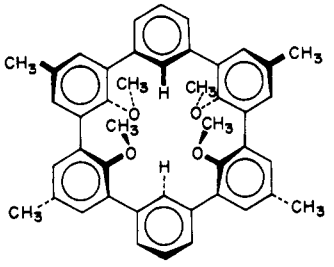
2, $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$



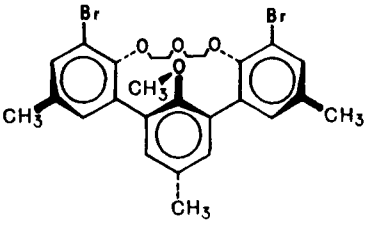
3, $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$



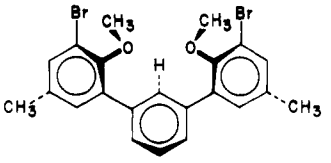
4, $(CH_3C_6H_2OCH_3)_5(C_6H_4)$



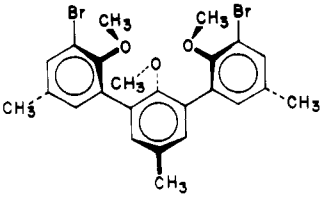
5, $(CH_3C_6H_2OCH_3)_4(C_6H_4)_2$



6



7



8

This dibromide was dilithiated with butyllithium, the product was oxidized with $Fe(AcAc)_3$, and the resulting spherand complex was anion exchanged to give **3**·LiCl[4-6] (6%). When heated at 100 °C in 4:1 (v/v) water–pyridine, **3**·LiCl gave **3**[4-6] (66%), the decomplexation being driven by crystallization of **3** from the medium. Dilithiation with *sec*-butyllithium of a 3.9:1 molar mixture of **7**[4,7] and **8**,[8] respectively, in THF at −78 °C, followed by addition of the resulting mixture to a refluxing benzene solution of $Fe(AcAc)_3$, gave after appropriate manipulations,[9] **1**[8] (9%), **4**[4,5] (6%), and **5**[4,5] (12%). Spherands **1**[8] and **2**[2] have been previously reported.

Only two stereoisomeric structures are sterically possible for spherand **2**[2] or spherand **3**. Crystal structures of lithium salt complexes of **2** and **3** reported here show that for each of these spherands the two bridges are on one side with the two methoxyls on the opposite side of the macroring. Molecular models (CPK) of **2** and **3** can be assembled only by shaving ~15% from the sides of the four oxygens that contact one another in pairs at the bridge termini. Unmodified molecular models of much less strained stereoisomers of **2** and **3** can be assembled in which all pseudoortho oxygens are anti to one another as in **1** and whose two bridges are anti to one another as well. On the basis of such model comparison, we mistakenly assigned the less strained structure

(2) Cram, D. J.; Kaneda, T.; Lein, G. M.; Helgeson, R. C. *J. Chem. Soc., Chem. Commun.* **1979**, 948–950.

(3) The reaction was carried out in THF at reflux by a procedure modeled after procedure II in: Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930–1946.

(4) Compound gave C and H analyses within 0.30% of theory. Mass and ^1H NMR (200 MHz, Brüker) spectra were as expected.

(5) Melting points (uncorrected) were as follows (°C): **3**·LiCl, >360 dec; **3**, 306–310 dec; **4**, 324–326; **5**, >360.

(6) Procedures resembled those used in the preparation of **2**·LiCl and **2**.[2]

(7) We are indebted to Dr. K. E. Koenig, who synthesized **7** as follows. A Grignard reagent prepared from 2-bromo-4-methylanisole was coupled with 1,3-dibromobenzene in a reaction catalyzed by $Cl_2Ni[P(C_6H_5)_3]_2$ (Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969) to give 1,3-bis(2-methoxy-5-methylphenyl)benzene as an oil (71%), which was demethylated with BBr_3–CH_2Cl_2 to produce 1,3-bis(2-hydroxy-5-methylphenyl)benzene as an oil (90%). This compound was dibrominated (Br_2–$CHCl_3$) to give 1,3-bis(2-hydroxy-3-bromo-5-methylphenyl)benzene (90%), which was methylated with CH_3I–K_2CO_3–acetone to produce **7** (90%), mp 140–141 °C.[4]

(8) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 6752–6754.

(9) To a solution of 9.0 g of **7** and 2.5 g of **8** in 150 mL of THF at −78 °C was added 50 mL of *sec*-butyllithium (1.4 M cyclohexane dispersion). The mixture was stirred 10 min and cannulated into 1.8 L of refluxing benzene containing 32 g of $Fe(AcAc)_3$. The mixture was refluxed for 1 h, cooled to 25 °C, and stirred with 500 mL of 4 N aqueous HCl solution containing 10 g of $FeCl_3·6H_2O$ for 4 h. The organic phase was evaporated from the mixture, and the tan solid that separated was dried and triturated with 75 mL of Et_2O. The mixture was filtered, the ether was evaporated, and the residue chromatographed on 100 g of silica gel (CH_2Cl_2–Et_2O) to give 130 mg of **4**. The ether-insoluble material, 1.4 g, was stirred with 150 mL of CH_2Cl_2 (8 h) to give 0.7 g of **5**, which was filtered. The filtrate was twice extracted with 0.2 N LiCl solution saturated with EDTA and then evaporated; the residue was recrystallized from toluene (100 mL) to give 165 mg (9%) of **1**·LiCl. The filtrate was chromatographed on silica gel (75 g) to give 0.20 g of additional **5** and 0.13 g of **4**. The combined samples of **5** were recrystallized from $CHCl_3$–C_6H_6 to give 0.72 g (12%) of pure **5**, mp >360 °C. The combined samples of **4** were recrystallized from CH_2Cl_2–EtOH to give 190 mg (6%) of pure **4**, mp 324–326 °C.

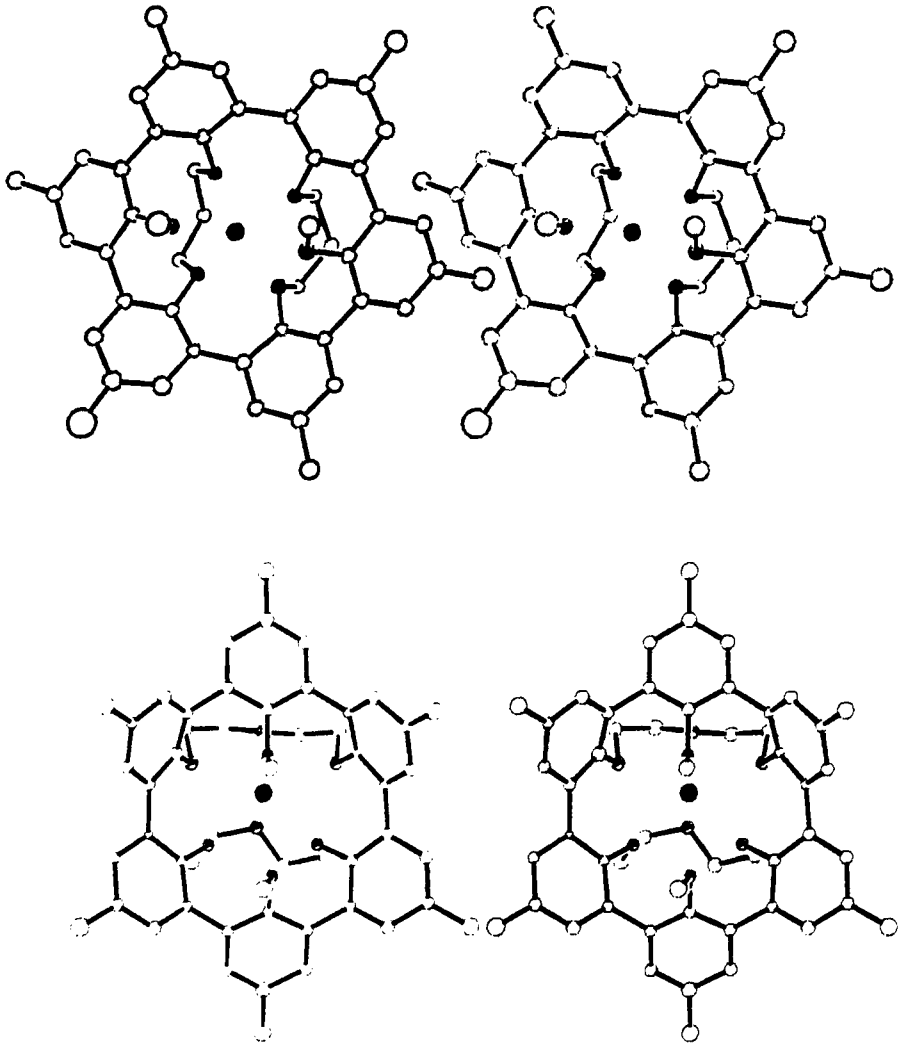


Figure 1. Stereodrawing of **2a** and **3a**.

to **2** and its complexes.[2] In predicting structures of complexes assembled from their individually stable host–guest components, CPK molecular models serve well because binding energies are insufficient to deform bonds greatly and compress atoms. However, the ring-closing step in the syntheses of **2** and **3** involved what probably is a lithium ion-templated coupling of two aryl radicals with the release of enough energy to pay high molecular deformation costs. In models of the all-anti structure for **2**·Li^+, only five oxygens can simultaneously contact a sphere of 1.3-Å diameter, and in the all-anti structure for **3**·Li^+, only six oxygens can contact a sphere of 1.5-Å diameter.

The crystal structures of **2**·$LiFeCl_4$ and **3**·LiCl were determined at 115 K from diffractometer measurements.[10] The resulting structures **2a** and **3a** have been refined to R values of 0.064 and 0.070, respectively. The structures of **2a** and **3a** cations in their crystals almost contain mirror planes bisecting their lithiums and CH_3O groups. The effect of the bridges in each of the two structures is essentially to "squeeze out" of ligating range one of the methoxyl oxygens to provide long lithium-to-oxygen distances of 2.88 and 3.48 Å in **2a** and **3a**, respectively. The Li^+ of **2a** is ligated by the remaining five oxygens to give a Li^+ diameter of 1.27 Å, while in **3a**, ligation by the remaining seven oxygens gives a Li^+ diameter of 1.71 Å.[11] These average diameters are calculated from Li-to-O distances that range from 2.004 to 2.085 Å in **2a** and from 2.03 to 2.42 Å in **3a**. These diameters compare with that of 1.48 Å for Li^+ in **1**·LiCl, which contains six octahedrally arranged oxygens.[12] Average Li^+ diameters calculated from crystal structures of other selected compounds are as follows: four-coordinate, tetrahedral, 1.12 Å; five-coordinate, 1.36 Å; six-coordinate, octahedral, 1.50 Å.[13] To our knowledge, no seven-coordinate lithium complex has been reported previously.

The ligand systems of **2a** and **3a** are severely strained. All six of the pseudoortho and one of the pseudometa O-to-O distances in **2a** are less than the normal van der Waals distance of 2.80 Å, averaging 2.64 Å (range, 2.50–2.73 Å). In **3a**, the two bridge-terminating, pseudoortho O-to-O distances, the shortest of the four CH_3O to pseudoortho $ArOCH_2$, and the four near O-to-O distances in the two $OCH_2CH_2OCH_2CH_2O$ bridges average 2.67 Å (range, 2.57–2.79 Å). The six O's of **2a** are bent out of the best planes of their attached aryls by an average of 0.20 Å (range, 0.08–0.33 Å) and the corresponding O's in **3a** by an average of 0.25 Å (range, 0.04–0.39 Å). The 12 C's of attached aryls are displaced from the best planes of their reference aryls in **2a** by

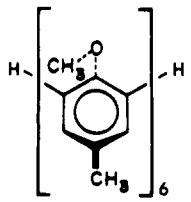
(10) Data were collected with Mo Kα radiation on a Syntex P$\bar{1}$ diffractometer. Crystals of **2**·$LiFeCl_4$,[2] $C_{50}H_{48}O_6$·$LiFeCl_4$, belong to space group $P2_1/c$, with a = 12.251 (3) Å, 22.582 (7) Å, 17.236 (4) Å, β = 101.33 (3)°, and Z = 4. Crystals of **3**·LiCl, $C_{52}H_{52}O_8$·LiCl, belong to space group P$\bar{1}$ with a = 12.773 (3) Å, b = 14.125 (3) Å, c = 15.147 (4) Å, α = 79.99 (2)°, β = 67.50 (2)°, γ = 67.72 (2)°, and Z = 2. Each structure was determined by direct methods and refined by full-matrix least squares. Neither structure is yet fully refined, some disordered solvent being present, especially in **3a**.

(11) These lithium diameters are calculated by averaging the shortest Li-to-O distances (five in **2a** and seven in **3a**), subtracting 1.40 Å [taken as the radius of an O atom (Pauling, L. C. "The Nature of the Chemical Bond", 3rd ed., Cornell University Press: Ithaca, NY, 1960; p 260)], and multiplying by two.

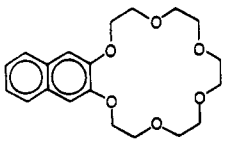
(12) Trueblood, K. N.; Knobler, C. B.; Maverick, E.; Helgeson, R. C.; Brown, S. B.; Cram, D. J. *J. Am. Chem. Soc.*, in press.

(13) Hermansson, K.; Thomas, J. O.; Olovsson, I. *Acta Crystallogr. Sect. B* **1977**, *B53*, 2857–2861.

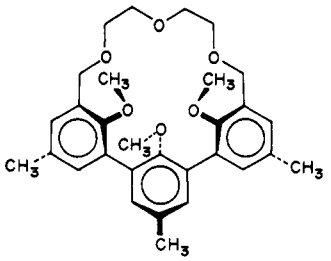
Chart II



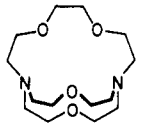
9, $H(CH_3C_6H_2OCH_3)_6H$



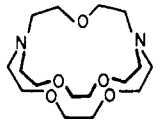
10, $Nap(OEOEO)_2E$



11, $(CH_3C_6H_2OCH_3)_3(CH_2OCH_2)_3$



12, $N(EOE)_2(EOEOE)N$



13, $N(EOE)(EOEOE)_2N$

an average of 0.29 Å (range, 0.01–0.43 Å) and in **3a** by an average of 0.33 Å (range, 0.10–0.55 Å). The six aryls are folded about their O–Ar–CH_3 axes by an average of 8° (range, 4–10°) in **2a** and by 8° (range, 2–13°) in **3a**. The aryl–aryl best plane dihedral angles range in **2a** from 28–51°, averaging 43°, and in **3a** from 22–55°, averaging 45°. Many of these features are visible in the stereodrawing of **2a** and **3a** (Figure 1). Crystal structures of free spherands **2** and **3** are not yet available. The configurational structures drawn for **4** and **5** are consistent with their ^1H NMR spectra and with analogies based on the structure of **1**. An equally reasonable structure for **5** involves a tetrahedral arrangement of the four oxygens, rather than the square-planar arrangement drawn.

Reactions followed by ^1H NMR spectra showed that hosts **1–4** in $CDCl_3$–2% $(CD_3)_2SO$ (v/v) complexed $LiClO_4$ and $NaClO_4$ instantaneously and completely but rejected $KClO_4$, $RbClO_4$, $CsClO_4$, $Mg(ClO_4)_2$, $Ca(ClO_4)_2$, and $La(ClO_4)_3$. Host **5** does not complex either $LiClO_4$ or $NaClO_4$ detectably under the same conditions. Extractions of D_2O solutions of Li^+ and Na^+ salts by $CDCl_3$ solutions of **1–4** led to slow complexation of Li^+ and Na^+ but not of the other ions.

Values of $-\Delta G°$ for complex formation between lithium or sodium picrates and the spherands were determined for purposes of correlating binding free energies with structure. The extraction method involved $CDCl_3$ saturated with D_2O at 25 °C as standard conditions.[14] The $-\Delta G°$ value for open-chain model compound **9**[4,5,15] was determined, and those for crown **10** and hemispherand **11** were available (Chart II).[16] The scale was extended to spherands of medium binding power by lowering the initial salt concentration in the D_2O phase.[17] Thus standard free energies ranging from 6 to 14 kcal mol^{-1} were measured directly. Free energy values for the best simple cryptand binder of Li^+ (**12**)[18] and Na^+ (**13**)[18] and for the medium spherand binders were obtained in the same medium by determining the equilibrium amounts of complexes and hosts obtained by distributing a guest between a host of known and one of unknown binding power.[19] The $-\Delta G°$ values for **1–3** were calculated from measured (^1H NMR methods) complexation (range, 7.5×10^4–1.2×10^6 mol^{-1} s^{-1}) and decomplexation rate constants (range, 2.2×10^{-4}–$<1.6 \times 10^{-12}$ s^{-1}) in the same medium.[20]

The hosts provided the following increasing order of $-\Delta G°$ values (kcal mol^{-1}) for binding LiPic: $H(CH_3C_6H_2OCH_3)_6H$ (**9**), <6; $(CH_3C_6H_2OCH_3)_4(C_6H_4)_2$ (**5**), <6; $Nap(OEOEO)_2E$ (**10**), ~6; $(CH_3C_6H_2OCH_3)_3(CH_2OCH_2)_3$ (**11**), 7.2; $(CH_3C_6H_2OCH_3)_5(C_6H_4)$ (**4**), 10.4; $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$ (**3**), 15.9; $N(EOE)_2(EOEOE)N$ (**12**), 16.6; $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$ (**2**), 16.8; $(CH_3C_6H_2OCH_3)_6$ (**1**), >22. This scale covers >16 kcal mol^{-1} (>10^{11} in K_a), with $H(CH_3C_6H_2OCH_3)_6H$ (**9**) as the weakest and $(CH_3C_6H_2OCH_3)_6$ (**1**) as the strongest binder of Li^+. These two hosts differ constitutionally only in the sense that open-chain compound **9** contains two hydrogens in place of one Ar–Ar bond in macrocycle **1**. Only two conformations of **9** out of 1024 possible can bind Li^+ octahedrally,[21] whereas **1**

(14) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.

(15) We warmly thank M. deGrandpre for determining the $-\Delta G°$ values for $H(CH_3C_6H_2OCH_3)_6H$ (**9**). The substance was prepared by oxidative coupling of $H(CH_3C_6H_2OH)_3H$ with $FeCl_3 \cdot 6H_2O$ in 3:1 (v/v) $CH_3C{\equiv}N$–H_2O at 25 °C for 7 days to give (17%) $H(CH_3C_6H_2OH)_6H$, mp 310–314 °C.[4] Methylation of this hexaphenol with $(CH_3)_2SO_4$–KOH in 10:1 THF–H_2O gave (70%) **9**, as a glass, purified by molecular distillation, 125–130 °C (glass transition temperature).[4]

(16) Koenig, K. E.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566.

(17) The initial concentrations of LiPic and NaPic in the D_2O phase and host in the $CDCl_3$ phase were 0.00100 M instead of the 0.0150 M normally used. Use of each set of concentrations in determining $-\Delta G°$ values for standard lipophilic crown hosts gave the same results. The procedure when applied to the spherands had to be modified because of the slow rates of extractions of LiPic and NaPic into the $CDCl_3$–host solution. The two solutions were rapidly mixed with a Teflon bar in a sealed flask until equilibrium was reached as shown by an absence of change in picrate absorbance (380 nm) of the $CDCl_3$ layer (18–216 h, depending on the rate of stirring).

(18) Lehn, J.-M. *Struct. Bonding (Berlin)* **1973**, *16*, 1–69.

(19) Crystalline complexes [2.2.1]cryptand·NaPic[4] and [2.1.1]cryptand·LiPic[4] were prepared by established methods. Thoroughly D_2O-washed $CDCl_3$ was equilibrated with fresh D_2O at 25 °C, and the layers were separated after centrifugation. Solutions (5 mL) of complexes (0.00175 M) were prepared to which were added 50 μL of a 0.05 M solution of purified Et_3N in D_2O-saturated $CDCl_3$. In the case of equilibration of NaPic between [2.2.1]-cryptand and **2**, enough **2** was added to provide 1:1, 3:1, and 5:1 molar amounts of cryptand to spherand in three NMR tubes, which were sealed at −78 °C. The ^1H NMR (Brüker, 200 MHz) spectra of these solutions ceased to change after 2 and up to 4 weeks. Relative concentrations of the cryptand complex and the spherand were determined by integration of the picrate peak (δ 8.819) vs. the most downfield ArH peaks (ArH complexed, δ 7.828; ArH noncomplexed, δ 7.601). A 5-s pulse delay was required for picrate relaxation. From the $-\Delta G°$ value for **2** (13.6 kcal mol^{-1}) and the equilibration results, $-\Delta G°$ values for [2.2.1]cryptand binding NaPic from the three tubes were 16.28, 16.32, and 16.17 kcal mol^{-1}, respectively. The same results were obtained in the absence or presence of Et_3N, which was added normally to neutralize any acid produced when cryptands were involved. The same equilibrium point was reached when **2**·NaPic was equilibrated with [2.2.1]-cryptand. The same procedure was applied to the equilibration of LiPic between [2.1.1]cryptand and **2** with 1:1, 1:2, and 2:1 ratios in the three tubes. The chemical shifts for ArH were as follows: Pic^-, δ 8.780; **2**·Li^+, δ 7.785, **2**, δ 7.601. The spherand complex was 0.3 ± 0.1 kcal mol^{-1} more stable than the cryptand complex.

(20) The decomplexation kinetics were followed by measuring the rate at three temperatures of transfer of metal ion from complexed spherand to OCD_3 group-labeled spherand in $CDCl_3$ (saturated with D_2O at 25 °C). The transfer was followed by ^1H NMR spectral changes through several half-lives and the pseudo-first-order rate constants were extrapolated to 25 °C. As expected, the entropies of activation for decomplexation of the spherands were all negative. The complexation kinetics were followed by measuring with ^1H NMR spectroscopy the rates of transfer of metal ions from hemispherand to spherand at 25 °C in the same medium. The latter measurements were possible only because the rates of complexation of hemispherand were much faster than those of the spherand, and the rates of decomplexation of spherand complexes were much slower than that of the hemispherand complex.

possesses only a single conformation, which is ideally organized for octahedral binding. Diminished spherand $(CH_3C_6H_2OCH_3)_4(C_6H_4)_2$ (**5**), with only four oxygens, also gave $-\Delta G° < 6$ kcal mol^{-1}. Standard crown Nap(OEOEO)$_2$E (**10**) and hemispherand $(CH_3C_6H_2OCH_3)_3(CH_2OCH_2)_3$ (**11**) with values of ~6 and 7.2 kcal mol^{-1}, respectively, lack conformations that provide direct cooperative binding by more than three or four oxygens of ions as small as Li^+. Diminished spherand $(CH_3C_6H_2OCH_3)_5(C_6H_4)$ (**4**) as a molecular model possesses an enforced cavity lined with five oxygens and one aryl hydrogen. Spheres of diameters of 1.3–1.5 Å can be inserted and fit snugly into this cavity without apparent increase in strain. The aryl hydrogen must adapt to larger spheres with strain-inducing molecular deformations. The $-\Delta G°$ value for **4** is 10.4 kcal mol^{-1}, >11 kcal mol^{-1} less than that of the ideally organized spherand $(CH_3C_6H_2OCH_3)_6$ (**1**). Although the cavity of augmented spherand $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$ (**3**) provides seven oxygens that contact Li^+ in structure **3a**, the binding energy of only 15.9 kcal mol^{-1} indicates that the organization of O's in the free host is far from ideal. Shaved molecular models of **3** provide an elongated cavity into which only spheres of 1.7–2.0 Å can be inserted snugly. To bind seven O's simultaneously, Li^+ may have to decrease the near oxygen–oxygen distances. The increase in compression energy is paid for by a decrease in binding energy. Cryptand N(EOE)$_2$(EOEOE)N (**12**) gives $-\Delta G° = 16.6$, and bridged spherand $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$ (**2**), gives $-\Delta G° = 16.8$ kcal mol^{-1} for binding Li^+. Host **12** is the strongest Li^+ binder among the simple cryptands and contains six heteroatom binding sites. In the crystal structure of **12**·LiI, all unshared electron pairs are turned inward,[22] but in CPK models of **12** itself, one or two methylenes can turn inward and nearby oxygens can turn outward to provide strain-free conformations, as in the crystal structure of the [2.2.2]cryptand analogue.[23] These conformations must be frozen out during capsular complexation. Shaved models of $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$ (**2**) and the crystal structure **2a** both indicate that only five oxygens can simultaneously contact an inserted sphere of the ~1.3-Å diameter of Li^+. Interestingly, the five binding oxygens of **2** provide a slightly higher $-\Delta G°$ value than the seven binding oxygens of **3**. Shaved models of **2** suggest a cavity diameter more complementary to the diameter of Li^+ than do models of **3**. The binding free energy of >22 kcal mol^{-1} that $(CH_3C_6H_2OCH_3)_6$ (**1**) shows toward Li^+ correlates with the nearly ideal organization of the six binding sites prior to complexation.

These same hosts provide a somewhat different increasing order of $-\Delta G°$ values (kcal mol^{-1}) for binding NaPic: H$(CH_3C_6H_2OCH_3)_6$H (**9**), <6; $(CH_3C_6H_2OCH_3)_4(C_6H_4)_2$ (**5**), <6; $(CH_3C_6H_2OCH_3)_5(C_6H_4)$ (**4**), 6.6; Nap(OEOEO)$_2$E (**10**), 8; $(CH_3C_6H_2OCH_3)_3(CH_2OCH_2)_3$ (**11**), 12.5; $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$ (**2**), 13.6; N(EOE)(EOEOE)$_2$N (**13**), 16.3; $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$ (**3**), 18.7; $(CH_3C_6H_2OCH_3)_6$ (**1**), 19.2. The scale covers a range of values >13 kcal mol^{-1} (>10^9 in K_a) with H$(CH_3C_6H_2OCH_3)_6$H (**9**) at the bottom and $(CH_3C_6H_2OCH_3)_6$ at the top. The larger diameter for Na^+ as compared to Li^+ has the following effects. Diminished spherand $(CH_3C_6H_2OCH_3)_5(C_6H_4)$ (**4**), bridged spherand $(CH_3C_6H_2O)_6(CH_3)_2(CH_2CH_2CH_2)_2$ (**2**), and parent spherand $(CH_3C_6H_2OCH_3)_6$ exhibit $-\Delta G°$ values for Na^+ at least 3.2 kcal mol^{-1} less than for Li^+, but their order remains the same. Conversely, crowns Nap(OEOEO)$_2$E (**10**), hemispherand $(CH_3C_6H_2OCH_3)_3(CH_2OCH_2)_3$ (**11**), and augmented spherand $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$ (**3**) bind Na^+ better than Li^+ by 2–5.3 kcal mol^{-1}; the binding order is the same. The best of the simple cryptands for binding Na^+, N(EOE)(EOEOE)$_2$N (**13**), gave a $-\Delta G°$ value of 16.3 kcal mol^{-1}, 2.9 kcal mol^{-1} less than the value for $(CH_3C_6H_2OCH_3)_6$ (**1**) and 2.4 kcal mol^{-1} less than that for $(CH_3C_6H_2O)_6(CH_3)_2(EOE)_2$ (**3**). The results show that when the host–guest relationships are the most complementary in any given host class, the order for binding LiPic and NaPic in $CDCl_3$ saturated with D_2O at 25 °C is spherands > cryptands > hemispherands > crowns > open-chain polyethers.

.The striking generalization that correlates host structure with binding power is *the larger the number of host ligating sites organized for binding during synthesis rather than during complexation, the greater the standard free energy change that accompanies complex formation.* Although the spherands owe their superior binding power mainly to preorganization, compensation for electron–electron repulsion by inserting a positive charge into their enforced cavities also probably contributes in some systems. The severe compression of the oxygens in bridged spherands **2** and **3** in particular may involve the latter effect.

(21) This compound is constitutionally like ended. It contains 5 potentially chiral elements associated with Ar–Ar rotations and 6 associated with CH_3–Ar rotations, 11 in all. The number of stereoisomers (conformers in this case) for a constitutionally like-ended system containing an odd number of potentially chiral elements is 2^{n-1} [Mislow, K. "Introduction to Stereochemistry"; W. H. Benjamin: New York, 1965; p 88].

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α-Disulfoxide and Sulfinic Anhydride in the Peroxy Acid Oxidation of 2-Methyl-2-propyl 2-Methyl-2-propanethiosulfinate

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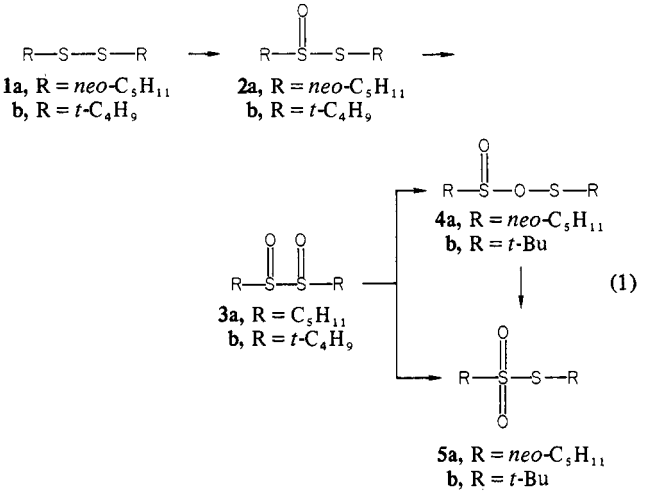
α-Disulfoxides **3** and sulfenyl sulfinates **4** have been postulated as intermediates in the peroxy acid oxidation of disulfides **1** or thiosulfinates **2** to thiosulfonates **5**. However, neither **3** nor **4** has been observed or isolated.[1-9]



Although it is generally accepted that disulfides **1** and thiosulfinates **2** are oxidized by peracids to thiosulfonates **5**, we have observed[2] that thiosulfonate **5a** is only a minor product in the low temperature *m*-chloroperoxybenzoic acid (MCPBA) oxidation of 2,2-dimethylpropyl 2,2-dimethylpropanethiosulfinate (**2a**). Although it has been reported that 2-methyl-2-propyl disulfide (**1b**) is oxidized to 2-methyl-2-propyl 2-methyl-2-propanethiosulfinate (**2b**, 93%) with peracetic acid,[10,11] other reports claim that **1b** is

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