The residue was shaken with a mixture of 40 mL of 5% aqueous NaCl solution and 30 mL of $CHCl_3$. The organic layer was washed with 50 mL of deionized water. Toluene (20 mL) was added to the undried $CHCl_3$ solution, and the $CHCl_3$ was evaporated under reduced pressure to provide fine white crystals of **1**·NaCl which was dried to give **18** mg (95%) of product, mp 300–370 °C dec: MS (230 °C inlet), M^+ for $A(AA)_2Ah$ at 706 (base peak), M^+ for $A(AA)_2A^-Na^+$ at 728; ^1H NMR, see Table III. Anal. Calcd for $C_{48}H_{48}O_6$·NaCl: C, 73.98; H, 6.21; Cl, 4.55. Found: C, 73.74; H, 6.22; Cl, 4.36.

Attempted Conversion of $A(AA)_2Ah$ (6) to $A(AA)_2A$·KCl (1·KCl). Procedure E was applied to 20 mg of **6** in an experiment in which reagent grade KOH was substituted for the NaOH of procedure E. During the isolation, reagent grade KCl in deionized water was substituted for the NaCl solution of procedure E. The products obtained were 9.7 mg (44%) of $A(AA)_2A$·NaCl, 4.5 mg (22%) of $A(AA)_2Ah$, and 4.5 mg (20%) of $A(AA)_2A$. No $A(AA)_2A$·KCl was detected (^1H NMR, MS) among the products of this reaction.

Registry No. **1**·LiCl, 72446-98-1; **1**·LiBr, 72447-00-8; **1**·$LiClO_4$, 72446-99-2; **1**·$LiFeCl_4$, 72446-97-0; **1**·NaCl, 72447-01-9; **1**·NaBr, 72447-02-0; **1**·$NaSO_4CH_3$, 79111-13-0; **2**, 95839-28-4; **2**·$LiClO_4$, 95740-51-5; **2**·$NaClO_4$, 95740-53-7; **3**, 95839-29-5; **4**, 95782-47-1; **4**·LiCl, 73229-56-8; **4**·LiBr, 95763-28-3; **4**·$LiFeCl_4$, 73229-55-7; **4**·NaCl, 95763-29-4; **4**·NaBr, 95763-30-7; **5**, 95782-50-6; **5**·LiCl, 80128-40-1; **5**·LiBr, 95763-31-8; **5**·NaCl, 95763-32-9; **5**·NaBr, 95784-15-9; **6**, 72526-87-5; **7**, 51699-89-9; **8**, 79115-30-3; **9**, 71128-89-7; **10**, 71128-90-0; **11**, 95839-30-8; **12**, 95763-26-1; **13**, 95740-46-8; **14**, 95740-47-9; **15**, 73229-34-2; **16**, 73229-35-3; **17**, 95839-31-9; **18**, 95740-48-0; **19**, 73499-38-4; **20**, 73229-36-4; **21**, 73499-39-5; **22**, 73493-77-3; BrAhAhAhBr, 72542-40-6; H(A)6H, 80108-98-1; $Br(CH_2)_3Br$, 109-64-8; TsOEOEOTs, 7460-82-4; HAhPAhH, 80109-03-1; $Fe(acac)_3$, 14024-18-1; 2-bromo-5-methylanisole, 95740-49-1; 1,3-dibromobenzene, 108-36-1.

Supplementary Material Available: General experimental indicating solvent and reagent handling and equipment used; description of crystal structure data collection; purity of salts used and the extraction procedures; association constants and free energies of binding by $H(AA)_2P$ (**2**) of lithium and sodium picrates; and table of data (4 pages). Ordering information is given on any current masthead page.

Host–Guest Complexation. 36. Spherand and Lithium and Sodium Ion Complexation Rates and Equilibria[1,2]

Donald J. Cram* and George M. Lein

Contribution from the Department of Chemistry and Biochemistry, University of California at Los Angeles, Los Angeles, California 90024. *Received September 14, 1984*

Abstract: Thermodynamiic and kinetic parameters for complexation by three spherands of lithium and sodium picrates in $CDCl_3$ are reported. The hosts are composed of the following units (Chart I) bonded to one another in 18-membered-ring systems: 2,6-disubstituted 4-methylanisyl (A); 2,6-disubstituted 4-methylanisyl deuterated in the methoxy group (Ad); 2,6-disubstituted 4-methylphenol (Ah); 2,6-disubstituted 4-methyl-1-allyloxybenzene (Aa); 2,6-disubstituted 4-methylphenyloxy (B); 1,3-phenylene (P); 1,2-cyclohexano (Cy); ethylene (E); methylene (M); oxygen (O); and nitrogen (N). The orders of the letters in the line formulas indicate the orders of attachment of the units in the cyclic or bicyclic hosts. In the polycyclic hosts, transannular B units serve as the bridgeheads linked through their oxygens to M_3 or EOE units to transannular B units, at their 2-positions to A units, and at their 6-positions to either other B units (spherands) or to M units (hemispherands). In the cryptands, the nitrogen atoms act as bridgeheads. Chart II identifies the letters with the structures of the units and the structures and compound numbers with the line formulas. The hemispherands listed were useful in proving low, known concentrations of guests, while the chorand listed was used for dissolving sodium and lithium picrates in $CDCl_3$. The K_a and $-\Delta G°$ values for $[B(A)(M_3)B]_2$ (**2**) binding sodium picrate were determined at 25 °C in $CDCl_3$ saturated with D_2O by the direct picrate extraction method. The K_a values for $A(AA)_2A$ (**1**) and $[B(A)(EOE)B]_2$ (**3**) binding sodium picrate and for all three spherands binding lithium picrate could not be measured directly. Accordingly, values were obtained kinetically. Decomplexation rates for $Ad(AdAd)_2Ad$ (**1d**), $[B(Ad)(M_3)B]_2$ (**2d**), and $[B(Ad)(EOE)B]_2$ (**3d**) were prepared. With ^1H NMR techniques at three temperatures in $CDCl_3$ saturated at 25 °C with D_2O, the rate constants were determined for Li^+ or Na^+ transferring from nondeuterated to deuterated hosts. Because the reaction rate was comparable to rates of demethylation of the complex at high temperatures, only a maximum value could be placed on the rate constant for **1**·Li^+ + **1d** → **1** + **1d**·Li^+. Values for $\Delta H^‡$ and $\Delta S^‡$ for decomplexation were calculated, and decomplexation rate constants were extrapolated to 25 °C. Rate constants for $A(AA)_2A$ (**1**), $[B(A)(M_3)B]_2$ (**2**) and $[B(A)(EOE)B]_2$ (**3**) complexing sodium picrate were determined at 25 °C by following the ^1H NMR changes as guest was transferred from B[A][EOE][$(MOE)_2O$]B·NaPic (**6**·NaPic) to each of the three spherands. The complexation rate for complexing NaPic is much higher for **6** than for **1**, **2**, or **3**. The role of **6**·NaPic was to provide a preequilibrium concentration of NaPic low enough to bring the complexation rate of the spherands onto the human time scale. The complexation rate constant of **1** with LiPic was determined by competition experiments between NaPic and LiPic, which were delivered in $CDCl_3$ solutions via $Cy(OEOEO)_2Cy$·NaPic (**8**·NaPic) and **8**·LiPic. The rate constants for **2** and **3** complexing LiPic were determined by competition experiments between **1** and **2** and between **1** and **3** for LiPic. The complexation and decomplexation rate constants were used to calculate association (equilibrium) constants and free energies of complexation. The $-\Delta G°$ values (kcal mol^{-1}) for the various complexing partners are as follows: $A(AA)_2A$ (**1**) with LiPic, >23, and with NaPic, 19.2; $[B(A)(M_3)B]_2$ (**2**) with LiPic, 16.8, and with NaPic, 13.3; $[B(A)(EOE)_2B]_2$ (**3**) with LiPic, 15.9, and with NaPic, 18.7. The decomplexation rate constants of the spherand complexes vary by a factor of $>10^8$, whereas the complexation rate constants vary by a maximum factor of 16. Cryptand complex $N(EOE)_2(EOEOE)N$·LiPic (**9**·LiPic) was equilibrated in $CDCl_3$ at 25 °C with **2**, and the $-\Delta G°$ value for formation of **9**·LiPic was calculated to be 16.7 kcal mol^{-1}. Equilibration of $N(EOE)(EOEOE)_2N$·NaPic (**10**·NaPic) with **2** gave $-\Delta G°$ = 17.7 kcal mol^{-1} for formation of **10**·NaPic. The results show that when 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 > chorands > open-chain polyethers.

In the companion paper of this series[3] are described the syntheses of spherands **1**–**5** and the crystals structures of **1**, **1**·LiCl, **1**·$NaSO_4CH_3$, **2**·$LiFeCl_4$, and **3**·LiCl. Qualitative binding studies of **1**–**4** established that they complexed only Li^+ and Na^+ de-

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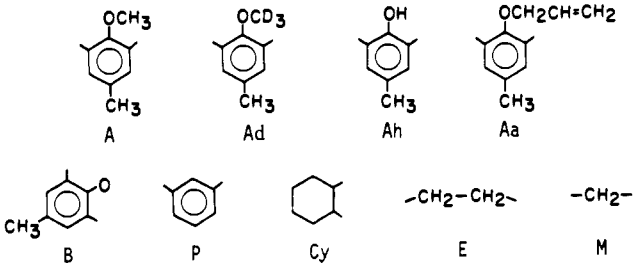
Chart I



tectably and that the binding free energies of **1** and **3** particularly were too high to be obtained by the picrate salt extraction method. This paper reports the results of quantitative binding studies that involve hosts **1–11**. The values of the following parameters in $CDCl_3$ saturated at 25 °C with D_2O are reported: the decomplexation rate constants for the LiPic and NaPic complexes of **1–3** at three temperatures and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for decomplexation; the complexation rate constants for the same hosts and guests; the association (equilibrium) constants and free energies of binding for the same hosts and guests; and the association (equilibrium) constants of [2.1.1]cryptand (**9**) for LiPic and of [2.2.1]cryptand (**10**) for NaPic. Correlations of structures of spherands, cryptands, hemispherands, chorands, and podands (e.g., **11**) are then made in terms of the principles of complentarity and preorganization.

We have found it useful to use line formulas in which capital letters identify the component units of the macrocycles. Their orders of appearance in the line formulas indicate their bonding patterns. Chart I identifies the letters with the structures of these units. Chart II provides the structural formulas of hosts **1–11** and their associated line formulas.

Results

Syntheses. Hosts $A(AA)_2A$ (**1**),[3] $[B(A)(M_3)B]_2$ (**2**),[3] $[B(A)(EOE)B]_2$ (**3**),[3] $A(AA)_2P$ (**4**),[3] $A(AA)_2Ah$ (**5**),[3] $H(A)_6H$ (**11**),[3] B[A][EOE][$(MOE)_2O$]B (**6**),[4] and B[Aa][EOE]-[$(MOE)_2O$]B (**7**)[4] were available from earlier investigations, whereas $Cy(OEOEO)_2Cy$ (**8**) (commercial mixture of isomers), $N(EOE)_2(EOEOE)N$ (**9**), and $N(EOE)(EOEOE)_2N$ (**10**) were purchased. Hosts deuterated in their methoxy groups, Ad-$(AdAd)_2Ad$ (**1d**), $[B(Ad)(M_3)B]_2$ (**2d**), and $[B(Ad)(EOE)B]_2$ (**3d**), were prepared by substituting $(CD_3)_2SO_4$ or CD_3I for the $(CH_3)_2SO_4$ or CH_3I used in synthesizing **1**, **2**, and **3**.[3] Crystalline complexes **1**·NaPic, **2**·NaPic, and **3**·NaPic were prepared by adding a solution of excess salt in CH_3CN to a CH_2Cl_2 solution of spherand and purifying the complexes that formed. Crystalline complexes $N[EOE]_2[EOEOE]N$·LiPic (**9**·LiPic), $N[EOE]$-$[EOEOE]_2N$·NaPic (**10**·NaPic), $N(EOEOE)_3N$·KPic, N-$[EOE]_2[EOEOE]N$·LiBr·H_2O, and $N[EOE][EOEOE]_2N$·NaBr were prepared by adding an excess of salt to a solution of cryptand in methanol and purifying the complexes that formed.

Guest Specificity in Complexation by Spherands. In previous work, spherands $A(AA)_2A$ (**1**), $[B(A)(M_3)B]_2$ (**2**), $[B(A)$-$(EOE)B]_2$ (**3**), and $A(AA)_2P$ (**4**) in 2% $(CD_3)_2SO$–98% $CDCl_3$ (v:v) were found to complex detectably only Li^+ and Na^+ salts. Salts of K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, and La^{3+}, when present in these solutions, failed to modify the ^1H NMR spectra of **1–4**, whereas Li^+ and Na^+ salts altered these spectra significantly. In the present work, further attempts were made to complex $KClO_4$, $RbClO_4$, and $CsClO_4$ by heating 2 equiv of these guests with host **1** in 2% $(CD_3)_2SO$–98% $CDCl_3$ (v:v) at 112 °C for 16 h in a sealed tube. No complex formation was detected. In an attempt to complex $HClO_4$, a solution of 1 equiv of 0.04 M $HClO_4$ in CD_3CN was added to a 0.002 M solution of **1** in $CDCl_3$. The ^1H NMR spectrum of monophenol $A(AA)_2Ah$ (**5**) immediately appeared in place of that of $A(AA)_2A$ (**1**). When 0.5 equiv of $HClO_4$ was used, 0.5 equiv of **5** was produced and 0.5 equiv of **1** remained. Substitution of picric acid or CF_3CO_2H for $HClO_4$ failed to demethylate **1**. Thus complexation of spherands **1–4** appears to be limited to Li^+ and Na^+ ions.

Table I. Selected ^1H NMR Chemical Shifts (δ, Singlets) of Spherands and Their Complexes in $CDCl_3$

compound	Ar-CH_3	O-CH_3	Ar-H
$A(AA)_2A$ (**1**)	2.404 (18 H)	2.848 (18 H)	7.166 (12 H)
1·LiPic	2.500 (18 H)	3.035 (18 H)	7.341 (12 H)
1·NaPic	2.480 (18 H)	2.944 (18 H)	7.317 (12 H)
$[B(A)(M_3)B]_2$	2.407 (12 H)	2.800 (6 H)	7.206 (4 H), 7.236
(**2**)	2.439 (6 H)		(4 H), 7.602 (4 H)
2·LiPic	2.486 (12 H)	2.884 (6 H)	7.352 (4 H), 7.406
	2.518 (6 H)		(4 H), 7.784 (4 H)
2·NaPic	2.482 (12 H)	2.870 (6 H)	7.351 (4 H), 7.405
	2.513 (6 H)		(4 H), 7.823 (4 H)
$[B(A)(EOE)B]_2$	2.346 (12 H)	2.293 (6 H)	7.029 (4 H), 7.267
(**3**)	2.470 (6 H)		(4 H), 7.330 (4 H)
3·LiPic	2.396 (12 H)	2.276 (6 H)	7.061 (4 H), 7.239
	2.526 (6 H)		(4 H), 7.563 (4 H)
3·NaPic	2.393 (12 H)	2.282 (6 H)	7.046 (4 H), 7.402
	2.523 (6 H)		(4 H), 7.638 (4 H)

Comparison of the ^1H NMR Spectra of Spherands and Their Complexes. Table I records selected 200-MHz ^1H NMR chemical shifts of $A(AA)_2A$ (**1**), $[B(A)(M_3)B]_2$ (**2**), $[B(A)(EOE)B]_2$ (**3**), and their LiPic and NaPic complexes in $CDCl_3$. Addition of 1–2% $(CD_3)_2SO$ by volume to the solutions of the spherands or their complexes changed the δ values very little (±0.005 ppm). Addition of a $(CD_3)_2SO$ solution of 1 equiv of LiPic or NaPic to $CDCl_3$ solutions of **1–3** changed their spectra completely to those of their complexes. Additional guest had no effect on the spectra. The chemical shifts of the lithium and sodium complexes of **1–3** in 2% $(CD_3)_2SO$–98% $CDCl_3$ (v:v) were found to be independent of counterion when Cl^-, Br^-, ClO_4^-, and Pic^- were examined.

Host–Guest Exchange Experiments. A solution of 1 equiv of sodium or lithium salt in $(CD_3)_2SO$ was added to a solution of spherand in $CDCl_3$, and the ^1H NMR spectrum of the resulting solution was taken to ensure that no free host remained. A solution of a second spherand in $CDCl_3$ (1 equiv) was then added. The ^1H NMR spectra of the resulting mixtures indicated that only in one experiment did exchange of the cations between spherands occur at room temperature. The sodium complexes of $[B(A)(M_3)B]_2$ (**2**) lost their guests to $A(AA)_2A$ (**1**) at rates dependent on the counterions. Exchange was 50% complete in 30 min with Pic^-, but it required 150 min with ClO_4^- or Br^-. The exchange was monitored by measuring the relative peak heights of the most downfield Ar-H of **2** and its complexes. If a small excess of **1** was present, the reaction, **2**·NaPic + **1** → **2** + **1**·NaPic, went to completion. No attempts were made to transfer Na^+ from **2**·Na^+ to **3** to form **3**·Na^+, but the kinetic results described in a later section suggest this reaction would also have gone to completion. Attempts to exchange Na^+ out of **1**·Na^+ or **3**·Na^+ or Li^+ out of any of the three complexes failed.

Experiments also were conducted to substitute one guest for another in various complexes. A solution of 1.2 equiv of salt solution in $(CD_3)_2SO$ was added to a spherand solution in $CDCl_3$. The ^1H NMR spectrum was taken to confirm that no free spherand remained. A solution in $(CD_3)_2SO$ of 1.2 equiv of the salt of a second metal ion was then added. The larger amount of $(CD_3)_2SO$ present caused the chemical shifts to move downfield ~0.02 ppm from those reported in pure $CDCl_3$ in Table I. Again, only one exchange was observed. The addition of lithium salts to sodium complexes of $[B(A)(M_3)B]_2$ (**2**) caused slow formation

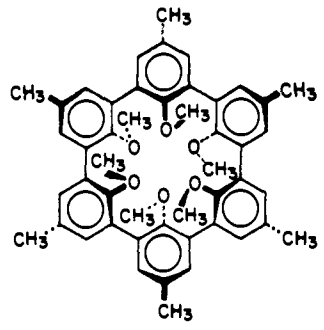
(1) We gratefully acknowledge support for this research from the Division of Basic Sciences of the Department of Energy.

(2) Some of these results have appeared as communications: (a) Lein, G. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.*, **1982**, 301–304. (b) Cram, D. J.; Lein, G. M.; Kaneda, T.; Helgeson, R. C.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6228–6232. (c) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 6752–6754.

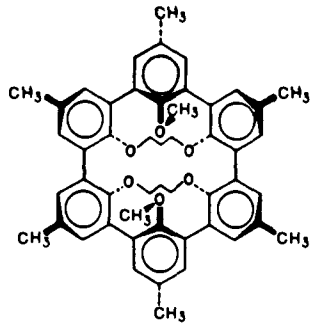
(3) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.*, preceding paper in this issue.

(4) Lein, G. M.; Cram, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 448–455.

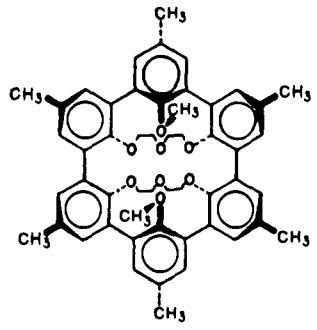
Chart II



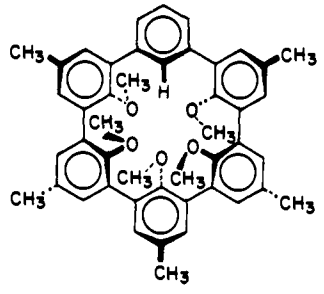
1, $A(AA)_2A$



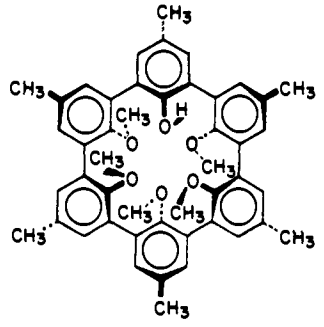
2, $[B(A)(M_3)B]_2$



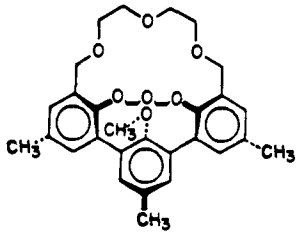
3, $[B(A)(EOE)B]_2$



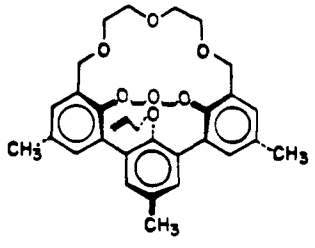
4, $A(AA)_2P$



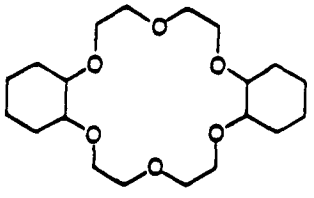
5, $A(AA)_2Ah$



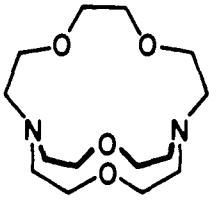
6, $B[A][EOE][(MOE)_2O]B$



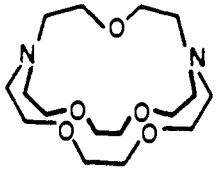
7, $B[Aa][EOE][(MOE)_2O]B$



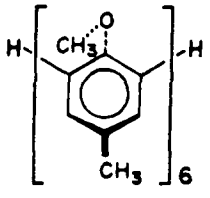
8, $Cy(OEOEO)_2Cy$



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



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



11, $H(A)_6H$

of the lithium complex of **2**. With LiPic, the exchange was complete in <168 h. Other attempts at such ion-for-ion exchange failed.

Competition Experiments in Complexation. In the first set of experiments, equal volumes of stock solutions of $A(AA)_2A$ (**1**) and $[B(A)(M_3)B]_2$ (**2**) in $CDCl_3$ were mixed, and to this mixture containing 1 equiv of each host was added less than 1 equiv of either lithium or sodium salt solutions in $(CD_3)_2SO$. A ^1H NMR spectrum was taken immediately. Peak heights were used to estimate the relative amounts of each host and complex present. These data allowed estimation of the ratio of rate constants for complexation by the two spherands of each metal ion (see future section for kinetic treatment). The average values of two determinations of k_1^2/k_1^1 (complexation rate constant ratio) obtained were as follows: $(k_1^2/k_1^1)^{LiClO_4} \equiv (k_1^2/k_1^1)^{LiPic} = 2.0$; $(k^2/k^1)^{LiBr} = 1.8$; $(k^2/k^1)^{NaClO_4} = 1.1$; $(k^2/k^1)^{NaPic} = 0.7$; $(k^2/k^1)^{NaBr} = 1.0$. The values involving the sodium salts represent only lower limits, since small amounts of Na^+ exchange thermodynamically favoring

Table II. Association Constants (K_a) and Free Energies of Complexation ($-\Delta G°$) for $[B(A)(M_3)B]_2$ Binding Sodium Picrate in $CDCl_3$ at 25 °C

run	phase	K_a (M^{-1})	$-\Delta G°$ (kcal mol^{-1})
1	$CDCl_3$	7.6×10^9	13.5
1	H_2O	1.0×10^{10}	13.6
2	$CDCl_3$	7.5×10^9	13.5
2	H_2O	9.8×10^9	13.6
3	$CDCl_3$	9.0×10^9	13.6
3	H_2O	1.1×10^{10}	13.7

1·NaX probably occurred before the spectral determinations were completed.

In the second set of competition experiments, equivalent amounts of lithium and sodium salts in $(CD_3)_2SO$ were mixed. To solutions of $A(AA)_2A$ (**1**) or $[B(A)(M_3)B]_2$ (**2**) in $CDCl_3$ were added 1.1 equiv of each salt in the above solution. Analysis of the peak heights in the ^1H NMR spectrum allowed estimation of the relative rates of complexation of the two metal ions by each host (see future section for kinetic treatment). The average values of two determinations of $(k_1^{Na}/k_1^{Li})^X_{host}$ are as follows: $(k_1^{Na}/k_1^{Li})_1^{ClO_4} = (k_1^{Na}/k_1^{Li})_1^{Br} = 15$; $(k_1^{Na}/k_1^{Li})_1^{Pic} = 20$; $(k_1^{Na}/k_1^{Li})_2^{ClO_4} = 2.6$; $(k_1^{Na}/k_1^{Li})_2^{Pic} = 4.1$; $(k^{Na}/k^{Li})_2^{Br} = 2.5$. The values involving host **2** are only approximate due to the reaction **2**·Na^+ + Li^+ → **2**·Li^+ + Na^+ proceeding partially before the spectral determinations were complete.

Association (Equilibrium) Constant and Free Energy of Complexation of Sodium Picrate by $[B(A)(M_3)B]_2$ (2). The values were determined by a modification of the picrate extraction method[6a,b] with extended times of mixing in quartz-Teflon equipment. Equilibrium was reached in times between 18 and 200 h, depending on the rate of stirring. Table II records the K_a and $-\Delta G°$ values.

Attempts to apply the same technique to $A(AA)_2A$ (**1**) or $[B(A)(EOE)B]_2$ (**3**) complexing NaPic demonstrated that after about 30 days of stirring, 95% of the NaPic had reached the organic layer and was still proceeding. Thus the binding was too strong for determinations by this method. Attempts to apply the same techniques to **1**–**3** complexing LiPic failed because the rates of extraction were too slow to allow establishment of equilibrium in reasonable lengths of time.

Decomplexation Rate Constants for Spherand Complexes. In the absence of a direct method for determining values of the association (equilibrium) constants (K_a of eq 1) for most host–guest combinations, we turned to the indirect method of calculating K_a from measured values of the complexation and decomplexation rate constants (k_1 and k_{-1}, respectively) for host (H), guest (G), and complex (HG) of eq 1.

For determination of the decomplexation rate constants (k_{-1}), transfers of Li^+ or Na^+ from unlabeled to deuterium-labeled spherands were followed by ^1H NMR techniques on a Bruker WP-200 instrument in $CDCl_3$ saturated at 25 °C with D_2O as solvent. We assumed the absence within experimental error of any hydrogen–deuterium isotope effect on the complexation–decomplexation rates and observed none on the equilibria reached with $[B(A)(M_3)B]_2$ (**2**) and $[B(Ad)(M_3)B]_2$ (**2d**) or with $[B(A)(EOE)B]_2$ (**3**) and $[B(Ad)(EOE)B]_2$ (**3d**). Because of the higher temperatures required for decomplexation of $A(AA)_2A$ (**1**)·Mpic, equilibria between **1** and $Ad(AdAd)_2Ad$ (**1d**) and their LiPic or NaPic complexes could not be reached due to competing demethylation reactions. With **1**·LiPic, the decomplexation rate was so slow that only an upper limit could be put on its k_{-1} value. The disappearance of the $CH_3O\cdots M^+$ proton resonance was followed through two to five half-lives in at least triplicate runs at each of three temperatures for each host–guest combination.

Table III. Decomplexation Rate Constants (k_{-1}) for Picrate Salt Complexes of Spherands **1**–**3** in $CDCl_3$ Saturated at 25 °C with D_2O

host	guest	temp (°C)	k_{-1} (s^{-1})	$\pm\sigma^a$	$\Delta H^‡$ (kcal mol^{-1})	$-T\Delta S^{‡b}$ (kcal mol^{-1})
1	Na^+	69.8	1.0×10^{-6}	0.3		
1	Na^+	84.8	5.6×10^{-6}	0.5	25	4
1	Na^+	99.8	2.1×10^{-5}	0.5		
2	Na^+	25.0	2.2×10^{-4}	0.1		
2	Na^+	40.0	6.0×10^{-4}	0.4	9	14
2	Na^+	50.0	7.2×10^{-4}	0.2		
2	Li^+	65.1	7.5×10^{-6}	0.1		
2	Li^+	79.6	2.6×10^{-5}	0.1	18	9
2	Li^+	94.8	6.9×10^{-5}	0.8		
3	Na^+	95.3	4.2×10^{-6}	0.3		
3	Na^+	110.2	1.0×10^{-5}	0.2	23	6
3	Na^+	125.2	4.9×10^{-5}	0.8		
3	Li^+	54.5	2.1×10^{-5}	0.4		
3	Li^+	69.9	9.3×10^{-5}	0.3	22	4
3	Li^+	85.4	4.2×10^{-4}	0.9		
1[c]	Na^+	25.0	3.4×10^{-9}			
1[c]	Li^+	25.0	$<10^{-12}$			
2[c]	Li^+	25.0	1.9×10^{-7}			
3[c]	Na^+	25.0	1.6×10^{-9}			
3[c]	Li^+	25.0	6.7×10^{-7}			

[a] Mean standard deviation of three runs. This error is larger than the least-squares polts within runs. [b] 25 °C. [c] Extrapolated to 25 °C.

First-order rate constants for k_{-1} (s^{-1}) were calculated from the least-squares slope of the plot of $-(\ln \{[HG]_i[H^*]_i - ([HG]_i + [H^*]_i)[H]\} \div \{[HG]_i + [H^*]_i\})$ vs. time which provided $k_{-1}/[H^*]_i$ values according to eq 4 (derived by integration of eq 3). The terms in eq 2–4 are defined as follows: $[H^*]$ and $[H^*G]$ are respectively the initial concentrations of deuterated host and complex; $[H^*]_i$ and $[HG]_i$ are respectively the initial concentrations of deuterated host and nondeuterated complex; $[H]$ is the concentration at time t of nondeuterated host; k_1 is the second-order complexation rate constant; and k_{-1} is the first-order decomplexation rate constant. The least-squares fits gave correlation coefficients of 0.99 to 0.95. First-order rate constants (k_{-1}) derived from these plots are reported in Table III. Values of $\Delta H^‡$ and $\Delta S^‡$ were calculated from Eyring plots[5] and are reported in Table III, along with values for k_{-1} extrapolated to 25 °C.

$$H + G \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HG \qquad K_a = k_1/k_{-1} \tag{1}$$

$$H^* + G \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^*G \tag{2}$$

$$d[H]/dt = k_{-1}[HG] - k_1[H][G] \tag{3}$$

$$\frac{-(\ln \{[HG]_i[H^*]_i - ([HG]_i + [H^*]_i)[H]\}}{[HG]_i + [H^*]_i} + \frac{\ln ([HG]_i[H^*]_i)}{[HG]_i + [H^*]_i} = \frac{k_{-1}t}{[H^*]_i} \tag{4}$$

The value of $<10^{-12}$ s^{-1} for k_{-1} for **1**·LiPic decomplexing is derived from the maximum value that could have been observed at 125 °C, which was extrapolated to 25 °C with the same $\Delta S^‡$ value observed for decomplexation of **1**·NaPic (Table III). The fact that $\Delta S^‡$ was the same within experimental error for **1**·NaPic, **3**·NaPic, and **3**·LiPic suggests our reasoning by analogy is sound.

Implicit in our kinetic treatment is the assumption that the transfer of Li^+ and Na^+ from HG to H*G occurs by a dissociative mechanism rather than by the bimolecular mechanism, HG + H* ⇄ H*G + H. Bimolecular mechanisms have been found to compete with dissociative mechanisms under special circumstances.[7] Evidence for the absence of a bimolecular component for the dissociations of complexes of **1** to **3** are as follows. (1) Crystal X-ray analysis,[3] molecular model examination, and molecular mechanical calculations[17] all indicate that these anisyl-based spherand hosts possess a single, sterically enforced conformation in which the unshared electron pairs line a hollow cavity. The oxygens are covered by a skin of six aryl and six methyl groups. In a bimolecular transition state for guest transfers in

(5) Gordon, A. J.; Ford, R. A. "The Chemists Companion"; John Wiley: New York, NY, 1972; pp 135–136.

(6) (a) 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. (b) Koenig, K.; Lein, G. M.; Stückler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553–3566. (c) These values are more accurate than those reported earlier (ref 6b).

Table IV. Complexation Rate Constants (k_1) at 25 °C for Spherands and Picrate Salts in $CDCl_3$ Saturated with D_2O

host	guest	k_1 (M^{-1} s^{-1})	no. of runs averaged	cc[a] range
1[b]	NaPic	4.1 (± 0.6) × 10^5	3	0.999–0.992
2[b]	NaPic	1.2 (± 0.0) × 10^6	3	0.993–0.987
3[b]	NaPic	8.6 (± 0.3) × 10^4	3	0.988–0.962
1[c]	LiPic	7.5 (± 0.3) × 10^4	4	
2[d]	LiPic	3.8 (± 0.6) × 10^5	3	
3[d]	LiPic	3.0 (± 0.5) × 10^5	3	

[a] Correlation coefficient. [b] Direct measurement. [c] Determined from competition experiments between NaPic and LiPic released from complexes of **8** and captured by **1**. Values for **2** and **3** are 6.3 × 10^5 and 3.4 × 10^5 M^{-1}, respectively. [d] Determined from competition experiments of **2** and **1** or **3** and **1** capturing LiPic released from **8**·LiPic.

our systems, the metal cation, for steric reasons, would have to be surrounded by six methyls (or two methylenes and two methyls) and would be distant from the oxygens of either host. Systems in which bimolecular exchange components have been observed (chorands, cryptands, and monensin) are conformationally flexible, and oxygens of two different hosts can simultaneously coordinate the same metal cation.[7] (2) Values of k_{-1} (monomolecular) for $[B(A)(M_3)B]_2$·NaPic (**2**·NaPic) calculated from the kinetics of exchange (Table II) are within experimental error of the k_{-1} value calculated from the K_a and k_1 values measured in entirely different experiments (see future sections). (3) Unrefined kinetic exchange experiments of guest from **2**·Na^+ into **1** at varying concentrations indicated the absence of detectable bimolecular components.

Complexation Rate Constants for Spherands. Complexation rate constants (k_1 of eq 1) for $A(AA)_2A$ (**1**), $[B(A)(M_3)B]_2$ (**2**), and $[B(A)(EOE)B]_2$ (**3**) with NaPic were determined in $CDCl_3$ saturated with D_2O at 25 °C by following the ^1H NMR changes as NaPic was transferred from B[A][EOE][$(MOE)_2O$]B·NaPic (**6**·NaPic) into each of the three spherands. Whereas transfer from **6**·NaPic to **1**, **2**, or **3** took >37 min, equilibration of NaPic between hemispherands **6**·NaPic and B[Aa][EOE][$(MOE)_2O$]B (**7**) was complete in <2 min. The complexation rates for forming **6**·NaPic or **7**·NaPic are much faster than those for forming **1**·NaPic, **2**·NaPic, or **3**·NaPic. Thus the role of **6**·NaPic in our hemispherand-to-spherand transfer experiments was to provide a preequilibrium concentration of NaPic low enough to bring the rate of Na^+ transfer into the spherands onto the human time scale. Table IV reports the averaged values of k_1 obtained in triplicate runs with 15–20 kinetic points obtained during 1.5–4 half-lives.

Second-order rate constants, k_1 (M^{-1} s^{-1}), for **1** and **3** complexing NaPic were calculated from the least-squares slopes of the linear plots of ln (b + [S]) − ({([C]$_i$ + [S]$_i$)/b} ln {[S] ÷ (b + [S])}) vs. time, which provided k_1/K' values according to eq 5–9. The terms in eq 5–9 are defined as follows: C, CG, G, S,

$$C + G \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} CG \qquad K' = k_1'/k_{-1}' \tag{5}$$

$$S + G \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SG \qquad K = k_1/k_{-1} \tag{6}$$

$$-d[S]/dt = k_1[S][G] - k_{-1}[SG] \tag{7}$$

$$b = [CG]_i - [S]_i \tag{8}$$

$$\left\{\ln (b + [S]) - \frac{[C]_i + [S]_i}{b} \ln \frac{S]}{b + [S]}\right\} - \left\{\ln b - \frac{[C]_i + [S]_i}{b}\right\} = \frac{k_1 t}{K'} \tag{9}$$

and SG refer respectively to uncomplexed **6**, **6**·NaPic, NaPic, free spherand, and complexed spherand; the [ ]$_i$ terms refer to the initial concentrations of the species in solution and the [ ] term to concentrations at times t; K' is K_a for **6** binding NaPic in $CDCl_3$ saturated with D_2O at 25 °C, which is 2.4 × 10^9 M^{-1}.[4] The assumptions made in deriving eq 9 are the following: the rate of complexation by **6** of NaPic is much faster than by the spherands (see above); and the decomplexation rate of the spherands, k_{-1}[SG] of eq 7, is negligible compared to the complexation rate, k_1[S][G] of eq 7. The data from Table III indicate the second assumption to be valid for spherands **1** and **3** complexing NaPic, but not for **2**.

For calculation of k_1 for spherand **2**, eq 10 was used. The parameters a, b, and c are defined in eq 11–13, $f(0)$ is a constant equal to the bracketed term when [S] = [S]$_i$, and K = 9.1 × 10^9 M^{-1} (Table II, averaged K_a).

$$\left\{\frac{1}{2c} \ln (a + b[S] + c[S]^2) - \frac{([C]_i + [S]_i + b/2c)}{\sqrt{-(4ac - b^2)}} \times \ln \frac{2c[S] + b - \sqrt{-(4ac - b^2)}}{2c[S] + b + \sqrt{-(4ac - b^2)}}\right\} - f(0) = k_1 t \tag{10}$$

$$a = -\frac{[S]_i[C]_i + [S]_i^2}{K} \tag{11}$$

$$b = \frac{[CG]_i - [S]_i}{K'} - \frac{2[S]_i + [C]_i}{K} \tag{12}$$

$$c = \frac{1}{K'} + \frac{1}{K} \tag{13}$$

The complexation rate constant (k_1) of **1** with LiPic at 25 °C was determined by competition experiments between NaPic and LiPic to give the ratio of rate constants from which that for LiPic was calculated. Solutions of known ratios of NaPic-to-LiPic complexes of $Cy(OEOEO)_2Cy$ (**8**, commercial mixture of isomers) in $CDCl_3$ (saturated at 25 °C with D_2O) were mixed with solutions of **1**, and the relative amounts of **1**, **1**·NaPic, **1**·LiPic, and total picrate were determined by ^1H NMR measurements. Control experiments showed that once formed the complexes of **1** did not undergo exchange under the reaction conditions. Four runs were made in which the concentrations of NaPic to LiPic varied from 3:1 to 5:1. The ratio of the rate constants for complexation, $(k_1^{Na}/k_1^{Li})^1$, obtained was 5.5 ± 0.2. From this ratio and the determined value for k_1^{Na} (Table IV), k_1^{Li} was calculated (Table IV).

The ratios for $(k_1^{Na}/k_1^{Li})^1$ were calculated from eq 14. Definitions are as follows: K_a^{Na} and K_a^{Li} are the respective association (equilibrium) constants for forming **8**·NaPic and **8**·LiPic; [CNa] and [CLi] are the respective final concentrations; and [CNa]$_i$ and [CLi]$_i$ are the respective initial concentrations of **8**·NaPic and **8**·LiPic. The average value of the association constants for **8**, K_a^{Na} = 1.7 × 10^6 M^{-1}, was obtained from three determinations (±0.13) by the published extraction method,[6a,b] and that of K_a^{Li} = 5.1 × 10^4 M^{-1} was obtained from three determinations (±0.10) by a modified method in which 0.050 M **8** in $CDCl_3$ and 0.015 M LiPic in D_2O were substituted for the usual concentrations.[6]

$$\frac{k_1^{Na}}{k_1^{Li}} = \frac{K_a^{Na}}{K_a^{Li}} \frac{\ln ([CNa]/[CNa]_i)}{\ln ([CLi]/[CLi]_i)} \tag{14}$$

Application of the same method to spherands **2** and **3** provided much more approximate values of k_1^{Li} (footnote *c* of Table IV) because of ^1H NMR analytical difficulties. More accurate values were obtained through competition experiments between **1** and **2** and between **1** and **3** complexing LiPic in $CDCl_3$ saturated with D_2O at 25 °C (^1H NMR analytical technique). A solution of **8**·LiPic was added to a solution of a mixture of **1** and **2** or **1** and **3**. Control experiments demonstrated that once formed the complexes did not undergo exchange in the times used for the mixing and the measurements. The ratios of rate constants, $(k_1^2/k_1^1)^{Li}$ = 5.0 ± 0.7 and $(k_1^3/k_1^1)^{Li}$ = 4.0 ± 0.5, are the averages

(7) (a) Cox, B. G.; Garcia-Rosas, J.; Schneider, H. *J. Am. Chem. Soc.* **1982**, *104*, 2434–2437. (b) McLain, S. J. *Ibid.* **1983**, *105*, 6355–6357. Cox, B. G.; Truong, Ng van; Rzeszotarska, J.; Schneider, H. *Ibid.* **1984**, *106*, 5965–5969.

Table V. Association (Equilibrium) Constants (K_a) and Free Energies of Binding ($-\Delta G°$) in $CDCl_3$ (Saturated with D_2O) at 25 °C

host	guest	K_a (M^{-1})	$-\Delta G°$ (kcal mol^{-1})
$A(AA)_2A$ (**1**)	LiPic	$>7 \times 10^{16}$	>23
$A(AA)_2A$ (**1**)	NaPic	1.2×10^{14}	19.2
$[B(A)(M_3)B]_2$ (**2**)	LiPic	2.0×10^{12}	16.8
$[B(A)(M_3)B]_2$ (**2**)	NaPic	5.5×10^{9}	13.3
$[B(A)(EOE)B]_2$ (**3**)	LiPic	4.4×10^{11}	15.9
$[B(A)(EOE)]_2$ (**3**)	NaPic	5.4×10^{13}	18.7
$A(AA)_2P$ (**4**)[a]	LiPic	4.1×10^{7}	10.4
$A(AA)_2P$ (**4**)[a]	NaPic	6.8×10^{4}	6.6
B[A][EOE][$(MOE)_2O$]B (**6**)	LiPic	2.1×10^{5}	7.3
B[A][EOE][$(MOE)_2O$]B (**6**)	NaPic	2.4×10^{9}	12.8
$Cy(OEOEO)_2Cy$ (**8**)	LiPic	5.1×10^{4}	6.4
$Cy(OEOEO)_2Cy$ (**8**)	NaPic	1.7×10^{16}	8.5
$N(EOE)_2(EOEOE)N$ (**9**)	LiPic	1.7×10^{12}	16.7
$N(EOE)(EOEOE)_2N$ (**10**)	NaPic	9.0×10^{11}	16.3
$H(A)_6H$ (**11**)	LiPic	$<2.5 \times 10^{4}$	<6
$H(A)_6H$ (**11**)	NaPic	$<2.5 \times 10^{4}$	<6

[a] Reference 3.

of three determinations. These ratios coupled with the value of k_1 for **1** complexing Li^+ provided the values of k_1 for **2** and **3** complexing Li^+ that are reported in Table IV.

The above ratios were calculated from eq 15 in which k_1^1, k_1^2, and k_1^3 are the rate constants for complexation; $[S^1]$, $[S^2]$, and $[S^3]$ are the final concentrations of free spherands and $[S^1]_i$, $[S^2]_i$, and $[S^3]_i$ are the initial concentrations.

$$\frac{k_{Li}^2}{k_{Li}^1} = \frac{\ln ([S^2]/[S^2]_i)}{\ln ([S^1]/[S^1]_i)} \text{ or } \frac{k_{Li}^3}{k_{Li}^1} = \frac{\ln ([S^3]/[S^3]_i)}{\ln ([S^1]/[S^1]_i)} \quad (15)$$

Application of the same method with **8**·NaPic substituted for **8**·LiPic provided additional rate ratios useful as an independent check on the direct measurements of k_1 for the three spherands complexing NaPic. In experiments with NaPic and **2**, the ^1H NMR determinations had to be run as quickly as possible after mixing since Na^+ exchanges from **2**·Na^+ into **1** are fairly fast on the human time scale. The relative values of the rate constants for the three spherands complexing NaPic by direct measurement are $k_1^3:k_1^1:k_1^3$ 14.0:4.8:1 (Table IV) while the same ratio obtained from the relative rate experiments is 9.7:4.1:1. The low relative rate constant obtained for **2** in the competition experiment is probably due to some exchange of Na^+ from **2**·NaPic into **1** before the ^1H NMR measurements were completed.

Association (Equilibrium) Constants and Free Energies of Complexation. The association (equilibrium) constants (K_a) at 25 °C in $CDCl_3$ saturated with D_2O for spherands **1–3** with LiPic and NaPic were calculated from the respective k_1 and k_{-1} values of Tables III and IV and eq 1. From these K_a values, the free energies of binding ($-\Delta G°$) were calculated. Table V records the results, along with the values of K_a and $-\Delta G°$, which were measured directly for chorand $Cy(OEOEO)_2Cy$ (**8**) and hemispherand B[A][EOE][$(MOE)_2O$]B (**6**). Also listed are the maximum values for $H(A)_6H$ (**11**) binding LiPic and NaPic. Attempts to determine K_a values for **11** by the standard picrate extraction method[6] as applied to Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, $CH_3NH_3^+$, and $(CH_3)_3CNH_3^+$ were too low to be measured (<2.5×10^4 M^{-1}). The association constant and free energy of complexation for $[B(A)(M_3)B]_2$ (**2**) binding NaPic obtained by the kinetic and by the direct extraction methods are in good agreement with one another. Thus $K_a = 5.5 \times 10^9$ M^{-1} and $-\Delta G° = 13.3$ kcal mol^{-1} from kinetics, and $K_a = 9.1 \times 10^9$ M^{-1} and $-\Delta G° = 13.6$ kcal mol^{-1} by extraction. The error limits for $-\Delta G°$ listed in Table V are probably about ±1.0 kcal mol^{-1}.

Association Constants and Free Energies of Binding of Cryptands. The association (equilibrium) constants (K_a) and free energies of binding ($-\Delta G°$) were determined for cryptand complexes $N[EOE]_2[EOEOE]N$·LiPic (**9**·LiPic) and N[EOE]-$[EOEOE]_2N$·NaPic (**10**·NaPic) by equilibrating them in $CDCl_3$ saturated with D_2O at 25 °C with $[B(A)(M_3)B]_2$ (**2**) or [B-(A)(EOE)B]$_2$ (**3**) in the presence of Et_3N to neutralize any DCl arising from the $CDCl_3$. Table VI reports the results. In runs 11 and 12, equilibrium was approached from the opposite direction, with $[B(A)(M_3)B]_2$·NaPic acting as the initial complex with $N(EOE)(EOEOE)_2N$ (**10**) as the acceptor host. The reactions were conducted at 25 °C in sealed quartz ampules. Their ^1H NMR spectra were taken after 2, 3, 4, and 8 weeks at 25 °C, and equilibration was complete after 2 weeks. In runs in which **2**·NaPic was the initial complex (**8–10**) equilibrium was reached in 24 h.

$$C + G \overset{K_a^c}{\rightleftharpoons} CG \quad (16)$$

$$S + G \overset{K_a^s}{\rightleftharpoons} SG \quad (17)$$

$$K_a^s/K_a^c = [SG]_e[C]_e/[CG]_e[S]_e \quad (18)$$

The equilibria involved are indicated in eq 16–18 in which C, S, G, CG, and SG refer to free cryptand, free spherand, free guest, cryptand complex, and spherand complex, respectively. The subscripts to the concentration brackets, e and i, refer to equilibrium and initial concentrations, respectively. In runs 1–7 with **9**·LiPic as the starting complex and **2** or **3** as the acceptor host, $[CG]_i/[S]_i$ values varied between 0.69 and 5.0 to give K_a values that varied between 9.3×10^{11} and 2.9×10^{12} M^{-1} to give $(K_a)_{av} = 1.7 \pm 0.5 \times 10^{12}$ M^{-1} and $-\Delta G° = 16.7$ kcal mol^{-1}. Runs 8–10 were made with **10**·NaPic as the starting complex and **2** as the acceptor host, and $[CG]_i/[S]_i$ varied from 1.1 to 5.9. Runs **11** and **12** involved **2**·NaPic as the initial complex and **10** as the acceptor host. The K_a values for cryptand **10** binding NaPic were based on the K_a value for **2**·NaPic of 9.1×10^9 M^{-1} (Table II), and they varied from 7.3×10^{11} to 1.1×10^{12} to give $(K_a)_{av} = 9.0 \pm 0.9 \times 10^{11}$ M^{-1} and $-\Delta G° = 16.3$ kcal mol^{-1}. These average K_a values and their corresponding $-\Delta G°$ values are recorded in Table V.

Table VI. Association Constants (K_a) and Free Energies of Binding ($-\Delta G°$) in $CDCl_3$ of LiPic and NaPic with Cryptands $N(EOE)_2(EOEOE)N$ (**9**) and $N(EOE)(EOEOE)_2N$ (**10**) at 25 °C[a]

run no.	initial complex	acceptor host	$[CG]_i/[S]_i$	$[SG]_e/[S]_i$	K_a^s/K_a^c	K_a (M^{-1})	$-\Delta G°$ (kcal mol^{-1})
1[b]	**9**·LiPic	**2**	0.69	0.48	2.2	9.3×10^{11}	16.3
2[b]	**9**·LiPic	**2**	1.3	0.64	1.7	1.2×10^{12}	16.5
3[b]	**9**·LiPic	**2**	1.7	0.67	1.4	1.5×10^{12}	16.6
4[b]	**9**·LiPic	**3**	1.1	0.32	0.21	2.3×10^{12}	16.9
5[b]	**9**·LiPic	**3**	1.8	0.49	0.35	1.4×10^{12}	16.5
6[b]	**9**·LiPic	**3**	2.6	0.54	0.31	1.5×10^{12}	16.6
7[b]	**9**·LiPic	**3**	5.0	0.57	0.17	2.9×10^{12}	17.0
8[c]	**10**·NaPic	**2**	1.30	0.30	0.12	1.0×10^{13}	17.7
9[c]	**10**·NaPic	**2**	1.28	0.31	0.15	8.6×10^{12}	17.6
10[c]	**10**·NaPic	**2**	1.34	0.28	0.10	1.2×10^{13}	17.8
11[c,d]	**2**·NaPic	**10**			0.0085	1.1×10^{12}	16.4
12[c,d]	**2**·NaPic	**10**			0.010	8.8×10^{11}	16.3

[a] Solvent is D_2O-saturated $CDCl_3$ containing 5–10 equiv of Et_3N per equiv of cryptand. [b] K_a values for cryptand are based on K_a values for spherands **2** and **3** reported in Table V. [c] The K_a values for cryptand are based on the K_a value for **2**·NaPic of 9.1×10^9 (extraction method). [d] The $[C]_i/[SG]_i$ value was 1.0 in both runs 11 and 12, and the $[SG]_e/[SG]_i$ value was 0.07 in run 11 and 0.08 in run 12.

Discussion

Correlation of Structure with Free Energy of Complexation. The hosts of Table V provide the following increasing order of $-\Delta G°$ values (kcal mol^{-1}) for complexing LiPic: H(A)$_6$H (**11**), < 6; Cy(OEOEO)$_2$Cy (**8**), 6.4; B[A][EOE][(MOE)$_2$O]B (**6**), 7.3; A(AA)$_2$P (**4**), 10.4; [B(A)(EOE)B]$_2$ (**3**), 15.9; N(EOE)$_2$(EOEOE)N (**9**), 16.7; [B(A)(M$_3$)B]$_2$ (**2**), 16.8; A(AA)$_2$A (**1**), > 23. This scale covers >17 kcal mol^{-1} in binding free energies and >10^{12} M^{-1} in association constants, with H(A)$_6$H (**11**) the weakest and A(AA)$_2$A (**1**) the strongest binder of LiPic. Similarly, the hosts of Table V provide the following increasing order of $-\Delta G°$ values (kcal mol^{-1}) for complexing NaPic: H(A)$_6$H (**11**), <6; A(AA)$_2$P (**4**), 6.6; Cy(OEOEO)$_2$Cy (**8**), 8.5; B[A][EOE][(MOE)$_2$O]B (**6**), 12.8; [B(A)(M$_3$)B]$_2$ (**2**), 13.3; N(EOE)(EOEOE)$_2$N (**10**), 17.7; [B(A)(EOE)B]$_2$ (**3**), 18.7; A(AA)$_2$A (**1**), 19.2. This scale covers >13 kcal mol^{-1} in binding free energy acid >10^{10} M^{-1} in association constants, with H(A)$_6$H (**11**) the weakest and A(AA)$_6$A (**1**) the strongest binder of NaPic.

These two hosts differ constitutionally only in the sense that podand **11** contains two hydrogen atoms in place of one Ar–Ar bond in macrocycle **1**. The two hosts differ mainly in their conformational structures. Spherand **1** possesses a single conformation in which its six oxygens are octahedrally arranged with the orbitals of their unshared electron pairs lining a roughly spherical cavity whose diameter is in between that of the diameters of Li$^+$ and Na$^+$. These facts are established from the crystal structures of **1**, of **1**·Li$^+$, and of **1**·Na$^+$, the organic parts of which are nearly identical in organization. Podand **11** in principle can exist in 1024 conformations, only two of which can bind Li$^+$ octahedrally.[8]

The price in free energy for organizing spherand **1** into a single conformation complementary to Li$^+$ or Na$^+$ was paid during its synthesis. The price in free energy for organizing open-chain compound **11** into a binding conformation for Li$^+$ or Na$^+$ has to be paid out of the free energy of complexation. The orbitals containing the unshared electron pairs of the oxygens of **1** are in a microenvironment whose dielectric properties are between those of a vacuum and those of a hydrocarbon. No solvent can approach the oxygens, since they are completely surrounded by six methyls and six aryls, so they are unsolvated. In contrast, the oxygens of **11** are solvated and exist in a dielectric microenvironment between that of $CDCl_3$ saturated with water and that of hydrocarbon. During complexation, the binding sites of **11** must be desolvated, whereas those of **1** are not solvated before complexation. Thus **1** is said to be *preorganized* and **11** is not.

The large difference in binding free energies between **1** and **11** provides the prime example of the power of the self-evident principles of complementarity and preorganization. The principle of complentarity states that "in complexes of substantial stability, the binding sites of host and guest components must simultaneously contact and attract one another". The principle of preorganization states that "the more highly hosts and guests are organized for binding and low solvation *prior* to their complexation, the more stable will be their complexes".[10] We have defined host–guest complexes as two or more molecules or ions held together in unique structural relationships.[11] The structuring of host–guest complexes depends on cooperativity between many contacting sites which, because of their organization, are able to compete with solvent. As measured by its ability to hydrogen bond, the oxygen of the anisyl group is an intrinsically poor ligand.[12] Thus it is hardly surprising that **11** is such a poor ligand system. The principle of complementarity is illustrated by the strong complexing of A(AA)$_2$A of Li$^+$ and Na$^+$, whose respective cavity and ionic diameters match, and by the failure of A(AA)$_2$A to complex detectably H$^+$ or K$^+$, whose respective cavities and ionic diameters do not match. The principle of preorganization is illustrated by the fact that through almost perfectly enforced alignment of dipoles, enforced location of unshared electron pairs, and enforced shielding by hydrocarbon groups of the binding sites, a collection of six anisyl oxygens can be turned into the strongest Na$^+$ and Li$^+$ binders yet devised.

The positions of the other spherands in the binding scale reflect differing degrees of complementarity and preorganization. The crystal structure of augmented complex [B(A)(EOE)B]$_2$·Li$^+$ (**3**·Li$^+$) indicates that although seven oxygens ligate the Li$^+$, the O-to-Li$^+$ distances range from 2.03 to 2.42 Å (2.253 Å average), whereas those of A(AA)$_2$A·Li$^+$ are all 2.14 Å. The hole diameter in **3** itself appears in CPK molecular models to be nonideal for Li$^+$ and more complementary to Na$^+$. Thus unlike A(AA)$_2$A, which binds Li$^+$ better than Na$^+$ by ≳4 kcal mol^{-1}, [B(A)(EOE)B]$_2$ binds Na$^+$ better than Li$^+$ by 2.8 kcal mol^{-1}. Models also indicate that unlike A(AA)$_2$A, [B(A)(EOE)B]$_2$ possesses some degrees of conformational freedom in the two EOE bridges, although not enough for the CH_2 groups to turn inward to occupy the cavity. The fact that [B(A)(EOE)B]$_2$ (**3**) possesses up to eight oxygens potentially available for binding Na$^+$ does not completely compensate for the more ideal organization of A(AA)$_2$A, which binds Na$^+$ better than **3** by 0.5 kcal mol^{-1}.

The crystal structure of diminished spherand [B(A)(M$_3$)B]$_2$·Li$^+$ (**2**·Li$^+$) indicates, as do molecular models, that five oxygens are rigidly complementary to Li$^+$, but that the sixth is distant. Accordingly, the $-\Delta G°$ values for binding Li$^+$ and Na$^+$ decrease to 16.8 and 13.3 kcal mol^{-1}, respectively. The cavity diameter of **2** in **2**·Li is only 1.27 Å, considerably less than the Na$^+$ diameter of 1.75 Å in **1**·Na$^+$. It seems likely that considerably more strain must be introduced into **2** during complexation of Na$^+$, which accounts for its relatively low $-\Delta G°$ value. Molecular models of further diminished spherand A(AA)$_2$P (**4**) indicate it to be essentially like A(AA)$_2$A (**1**) with one CH_3O group missing. As with **1**, **4** binds Li$^+$ better than Na$^+$ (by 3.8 kcal mol^{-1}), but both ions are bound at the much reduced levels of 10.4 and 6.6 kcal mol^{-1}, respectively. This reduction in binding free energy is attributed not only to the loss of the sixth oxygen binding site but also to the loss of the shielding of the remaining oxygens by the missing methyl group from solvent.

Next to spherands **1** and **2**, the cryptands **9** and **10** were the best binders of LiPic and NaPic. Host N(EOE)$_2$(EOEOE)N (**9**), the best cryptand binder of Li$^+$ in CH_3OH[13], gave a $-\Delta G°$ value for forming **9**·LiPic in $CDCl_3$ saturated with D_2O of 16.7 kcal mol^{-1}. Cryptand N(EOE)(EOEOE)$_2$N (**10**), the best for Na$^+$ in CH_3OH,[13] gave a $-\Delta G°$ value for forming **10**·NaPic in $CDCl_3$ saturated with D_2O of 17.7 kcal mol^{-1}. Their CPK molecular models show their cavities are readily filled by inward-turned methylene groups and that there are no constraints which force the orbitals of the unshared electron pairs on the oxygens or nitrogens into conformations preorganized for binding. Furthermore, the unshared electron pairs are available for interactions with the solvent, and the C–O and C–N dipoles are in a microenvironment whose dielectric properties are between those of the medium and those of the macrocycle. Upon complexation, the guest must develop its own cavity by reorganizing both the host and its solvent shell. Contributing to the binding is the fact that aliphatic ethers and amines are better general ligands than anisyl units[12] and that, once formed by the guest, each cavity is beautifully organized for focusing the maximum number of electron pairs on the guest without generating strain in the bridges. Should the cryptands be as preorganized as spherands **1** or **3**, they would probably far outstrip **1** or **3** as complexing agents.

(8) Compound H(A)$_6$H (**11**) is like ended. It contains five potentially chiral elements associated with Ar–Ar rotations and six associated with CH_3O–Ar rotations, eleven 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]. Its two conformations, which provide an octahedral arrangement of oxygens complementary to Li$^+$, are enantiomers of one another.

(9) Trueblood, K. N.; Knobler, C. B.; Maverick, E.; Helgeson, R. C.; Brown, S. B.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5594–5596.

(10) Artz, S. P.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 2160–2170.

(11) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571.

(12) (a) Mitsky, J.; Jaris, L.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 3442–3445. (b) Atkins, H. W.; Gilkerson, W. R. *Ibid.* **1973**, *95*, 8551–8559.

Hemispherand B[A][EOE][$(MOE)_2O$]B (**6**) is half composed of three contiguous and self-organizing anisyl units, the other half being conformationally flexible MOE and EOE units. Molecular models indicate it to be about half preorganized, but its cavity is not very complementary to either Li^+ or Na^+ which accounts for its relatively low $-\Delta G°$ values of 7.3 and 12.8 kcal mol^{-1}. Molecular models suggest that in the absence of guest, methylene groups occupy the somewhat elongated cavity. For the cavity to become spherical and complementary to Na^+ or Li^+, considerable strain must be introduced into the aryls and their attached groups. Chorand Cy$(OEOEO)_2$Cy (**6**) in molecular models is still less preorganized and has correspondingly lower binding free energies for LiPic and NaPic of 6.4 and 8.5 kcal mol^{-1}, respectively.

These results show that when 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 > chorands > podands. 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 free energy changes that accompanies complex formation.*

Specificities for Spherands Binding Alkali Metal Ions. The orbitals of the unshared electron pairs of the oxygens converge on an empty cavity in the spherands in an arrangement enforced by the support structure. This unique feature provides little flexibility to the cavity size and shape and limits them to forming only capsular complexes. In contrast, the conformational adaptability of the chorands and hemispherands allows them to form either nesting or perching complexes depending on the size of the guest.[14] The lack of adaptability of the spherands suggests they should exhibit high ion specificity in complexation. Such specificity has been realized.

A companion paper[3] describes attempts through ^1H NMR spectral changes to detect complexation by $A(AA)_2A$ (**1**), [B$(A)(M_3)B]_2$ (**2**), $[B(A)(EOE)B]_2$ (**3**), and $A(AA)_2P$ (**4**) of the perchlorate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, or La^{3+} in 98% $CDCl_3$–2% $CDCl_3$ (v:v). Complexations of Li^+ and Na^+ were easily observed, but no complexation of the other ions could be detected. In extraction experiments with $CDCl_3$ solutions of **1–4** and concentrated D_2O solutions of salts containing the same metal ions, only Li^+ and Na^+ ions were extracted, even when present as low-level impurities in the other salts. Because of the importance to physiology of Li^+, Na^+, K^+, Ca^{2+}, and Mg^{2+}, it would be desirable to have $K_a^M/K_a^{M'}$ ratios for each spherand for each pair of metal ions (M and M'). However, the K_a values for these four spherands binding all metal ions except Li^+ or Na^+ are too low to be measured by our techniques. Our experiments amply demonstrate that $(K_a^{Li}/K_a^{M'})^{1-4}$ and $(K_a^{Na}/K_a^{M'})^{1-4}$ values for M' = K^+, Rb^+, Cs^+, Ca^{2+}, and Mg^{2+} are very high indeed. We guess that those for $A(AA)_2A$ are in excess of 10^{10}. In this section, we illustrate the application of preorganization–complementarity concepts to interpreting $(K_a^M/K_a^{M'})^{host}$ ratios that have been measured in $CDCl_3$–D_2O at 25 °C.

Values of (K_a^{Li}/K_a^{Na}) for the four spherands of this study are as follows: $A(AA)_2A$ (**1**), >500; $A(AA)_2B$ (**4**), 600; [B$(A)(M_3)B]_2$ (**2**), 360; $[B(A)(EOE)B]_2$ (**3**), 0.008. Of the hosts we have examined containing the cyclic urea unit, only **12** and **13** show a preference for Li^+ over Na^+: $(K_a^{Li}/K_a^{Na})^{12} \sim 30$ and $(K_a^{Li}/K_a^{Na})^{13} = 7$. Unlike the purely anisyl spherands, these hosts can form perching complexes, and **12**, with three cyclic urea units, shows little discrimination in binding the alkali metal ions.[15] None of the many chorands[6,14] or hemispherands[4,10] we have examined have shown (K_a^{Li}/K_a^{Na}) values substantially greater than unity, and they range to a low of about 10^{-4}.[10] For example, B[A]-[EOE][$(MOE)_2O$]B (**6**) gives $(K_a^{Li}/K_a^{Na}) = 0.00009$. Thus of the neutral, all-oxygen ligating systems, spherands **1**, **2**, and **4** appear unique in their high specificity for binding Li^+ better than Na^+ and spherands **1–4** in binding Na^+ and Li^+ better than any other ions. The smaller cryptands, $N(EOE)_2(EOEOE)N$ (**9**) and $N(EOE)(EOEOE)_2N$ (**10**), also show high specificity for Li^+ and Na^+.[13]

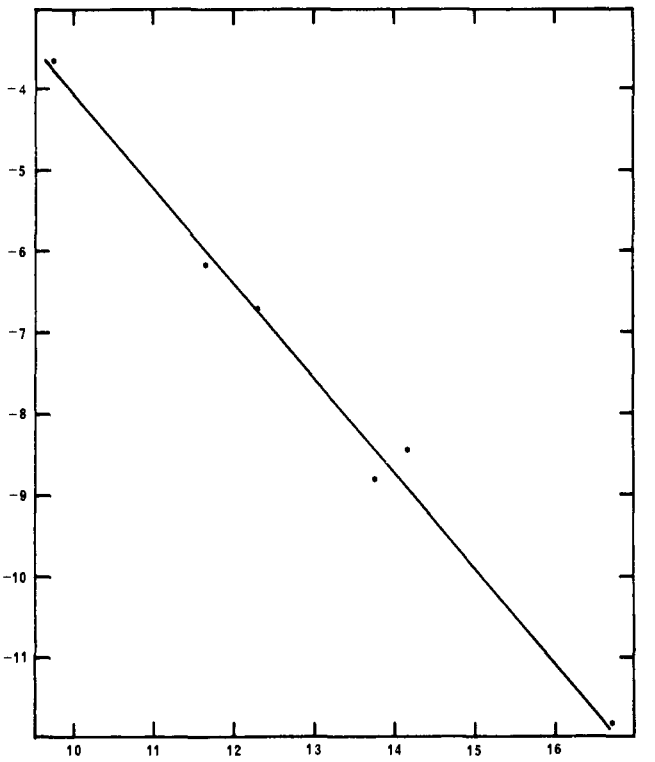
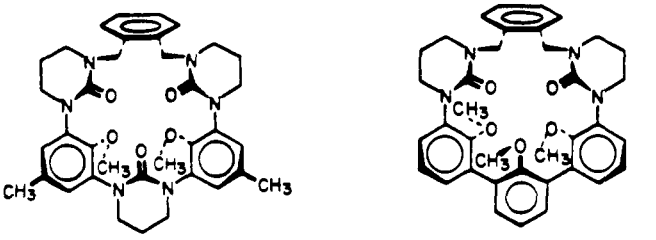


Figure 1. Plot of the logarithm of the dissociation rate constant (log k_{-1}, s^{-1}) against the logarithm of the association (equilibrium) constant (log K_a, M^{-1}) for spherands **1**, **2**, and **3** complexing LiPic and NaPic in $CDCl_3$–D_2O at 25 °C.



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Correlation of Structure with Complexation and Decomplexation Rates of the Spherands. The spherand complexation rate constants of Table IV range between 7.5 and 10^4 and 1.2×10^6 M^{-1} s^{-1}, or only by a factor of 16, whereas the decomplexation rate constants of Table III range from a high of 2.2×10^{-4} to a low of $<10^{-12}$ s^{-1}, or by a factor of $>10^8$. Thus the $>10^7$ M^{-1} variation in the association (equilibrium) constants seen in Table V is governed largely by the difference in the dissociation rate constants. Figure 1 provides a reasonly linear plot of log k_{-1} vs. log K_a.

This correlation strongly suggests that the transition states common to complexation and decomplexation lie very near to the host and guest reactants. Since the host is preorganized, its structure does not change much during or upon complexation. The crystal structures of $A(AA)_2A$ (**1**), **1**·Li^+, and **1**·Na^+ are very similar to one another.[3] Molecular models indicate $[B(A)(M_3)B]_2$ (**2**) and $[B(A)(EOE)B]_2$ (**3**) to be very rigidly preorganized before complexation as well. In all three hosts their cavities are lined with electrons surrounded first by oxygens and then by hydrocarbon. To reach these electrons, guests must pass through lipophilic sleeves of diameters too small to accommodate a metal ion plus ligands. Thus disengagement of ionic guests from their solvent ligands and reengagement of the ions with the electrons

(13) (a) Lehn, J.-M., *Struct. Bonding (Berlin)* **1973**, *16*, 1–69. (b) Lehn, J.-M.; Sauvage, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6700–6707.
(14) Cram, D. J.; Trueblood, K. N. *Top. Current Chem.* **1981**, *98*, 43–106.

of these spherands cannot happen simultaneously. The Li^+ and Na^+ ions in the transition states are largely surrounded by methyl or methylene groups. In reaching the transition states from the noncomplexed side, the cations must shed most of their coordinating ligands and enter the sleeves. This process does not structurally perturb the spherands much, so the rates of complexation are little affected by the structural differences between the spherands.

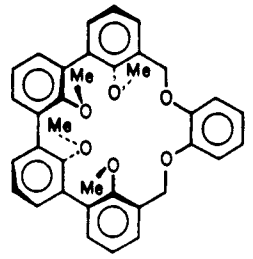
For decomplexation, the starting complexes differ structurally in the number of oxygen atoms ligated (**5–7**), in the compression of their oxygen atoms, and in deformations of their bond angles.[3] Thus the free energy differences in the complexes themselves seem to be mainly responsible for the $>10^8$ s^{-1} differences in decomplexation rate constants of the spherands. To decomplex, the ions must shed their nearly stationary ligands of the host and enter the hydrocarbon sleeves with minimum engagements of ligands in the solvent. The fact that the rates of complexation and decomplexation vary slightly with the character of the counterion indicates a small involvement of counterion in the transition state.

Next to the spherands, the cryptands are the most preorganized ligand systems. Cox et al.[16] have observed a roughly linear correlation between log K_a and log k_{-1} values which applies to $N(EOE(EOEOE)_2N$ (**10**) and $N[EOEOE]_2N$ binding a variety of ions in several solvents. As with the spherands, the association rate constants of the cryptands varied over a much smaller range than the dissociation rate constants[16] and showed no correlation with the association (equilibrium) constants. The association rate constants (k_1) of the two cryptands best preorganized for binding Li^+ and Na^+ (**9** and **10**) varied between about 10^4 and 10^7 M^{-1} s^{-1} for a variety of combinations of host, guest, and solvent, with most values lying in the same range as we observed for the spherands. The solvents involved in that study included H_2O, MeOH, EtOH, Me_2SO, DMF, $CH_3CH_2CONHCH_3$, and $(CH_2)_3O_2CO$.[16]

These cryptand–spherand comparisons taken together suggest that the association rate constants of the spherands will lie in this same range as solvent is changed from $CDCl_3$ (D_2O saturated) to those listed above, but that the values of the dissociation rate constants will increase somewhat as the solvents become better ligands for the metal ions. The values of the association (equilibrium) constants will decrease accordingly. However, we expect less solvent effect on K_a values for the spherands than for the cryptands, particularly in hydrogen-bonding solvents. Unlike the cryptands, the binding sites of the spherands are preorganized and essentially completely shielded from solvent by their hydrocarbon shells. Therefore, the spherands neither have to be reorganized nor desolvated during complexation, as do the cryptands. In this connection, it is interesting that the enthalpic and entropic contributions to the activation free energies for decomplexation of the five measurable spherand complexes reenforce rather than cancel one another.

Values for the association and dissociation rate constants for hemispherands **14–17** binding KPic in $CDCl_3$ saturated with D_2O at 25 °C have been estimated.[10] Those for k_1 range from 10^7 to 10^9 M^{-1} s^{-1}, comparable to the range observed for $N(EOEOE)_3N$ binding K^+ in a variety of solvents at 25 °C.[16] However, k_{-1} (s^{-1}) for **14–17** releasing complexed K^+ in $CDCl_3$–D_2O at 25 °C varied only by a factor of 7, from 27 s^{-1} for **15** to 4 s^{-1} for **17**. For these partially preorganized and solvated hosts binding the less strongly solvated K^+ ion (compared to Na^+ and Li^+), the association rate constants play a larger role in determining K_a values than do the dissociation rate constants, in contrast to the spherands and cryptands.

Experimental Results, Molecular Mechanical Calculations, and Predictions Based on CPK Molecular Model Examinations. Kollman et al.[17] have performed molecular mechanical calculations on the spherands binding Li^+, Na^+, and K^+ ions. They found that



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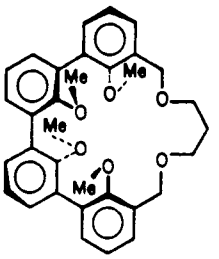

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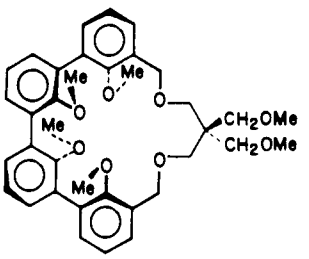

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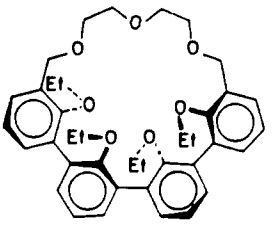

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the *p*-methyl groups of $A(AA)_2A$ (**1**) made little difference in their initial results, so these groups were omitted in their calculations on **1**, **2**, and **4**. A fundamental problem with such calculations as applied to host–guest complexation is that they apply to complexation phenomena under vacuum, whereas experimental results usually are obtained in solution. Hosts are collections of solvation sites covalently bonded together that are more or less organized to bind guests. Hosts must compete with solvent in binding guests, guests must compete with solvent in binding hosts, and the complexes themselves are solvated as well. That solvation plays an important role in host–guest complexation of cryptands is amply illustrated by Cox et al.,[18] who found that $-\Delta G°$ values (kcal mol^{-1}) for complexation of Li^+ by $N(EOE)_2[EOEOE]N$ (**9**) changed with solvent as follows: H_2O 7.5; EtOH, 11.5; $(CH_2)_3O_2CO$, 16.9; $(CH_3)_2SO$, 7.9. Complexation of Na^+ by $N(EOE)(EOEOE)_2N$ (**10**) changed likewise: H_2O, 7.4; EtOH, 13.9; $(CH_2)_3O_2CO$, 16.4; $(CH_3)_2SO$, 9.4. The spherands are unique in the sense that solvation of the hosts and their complexes should be similar to one another and of less importance (than in flexible hosts) since the binding sites of both species are deeply buried in hydrocarbon skins. This fact coupled with the freedom of the spherands from conformational ambiguity makes comparisons between calculated models, CPK molecular models, and experimental results particularly interesting.

The Kollman calculations[17] provided the following conclusions. (1) The calculated structures of **1**, **2**, and **4** and their Li^+ and Na^+ complexes are very close to the structures predicted from CPK molecular model examinations and those observed through X-ray analysis. Particularly impressive is the fact that all three approaches arrive at structures for **2**·Li^+, in which only five oxygens ligate the Li^+ ion. Both CPK molecular model examination[19] and the calculated structures[17] of *anti*-**2** (the two bridges on the opposite sides of the macroring face) predict that this (as yet unknown) isomer and its complexes will be more stable than the *syn*-**2** isomer and its complexes, which are in hand. The calculations predict *anti*-**2**-Li^+ will exhibit a higher $-\Delta G°$ value than **1**·Li^+.[17] (2) The calculations indicate **1** is an excellent binder of Li^+ and Na^+ because it has a nearly ideal "ion binding" conformation before complexation, and its $ArOCH_3$ binding groups are able to align their dipoles very effectively toward the cation in the complexes.[17] This compound was designed and synthesized as

(15) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **185**, *107*, 7150–7167.
(16) Cox, B. G.; Garcia-Ross, J.; Schneider, H. *J. Am. Chem. Soc.* **1981**, *103*, 1054–1059.
(17) Kollman, P.; Wipff, G.; Singh, U. C. *J. Am. Chem. Soc.*, in press.
(18) Cox, B. G.; Garcia-Rosas, J.; Schneider, H. *J. Am. Chem. Soc.* **1981**, *103*, 1384–1389.

a result of CPK molecular model examination which suggested its binding properties would provide an extreme test of the principles of preorganization and complementarity..[2,3,19] Experimentally, **1** is the best binder of Li^+ and Na^+ tested thus far. (3) The calculations indicate that **1** binds Na^+ ~40 kcal mol^{-1} (ΔE) better than K^+. Although CPK models of the capsular K^+ complex can be made, the dipoles of the $ArOCH_3$ are badly misaligned for binding a cation of this large a diameter. Experimentally, no K^+ binding could be detected. (4) The calculations indicate that unsolvated Li^+ and Na^+ have no intrinsic activation energy barriers to entering **1** but that K^+ has a substantial barrier. Examination of CPK models provides the same conclusions. Experimentally, the free energy of activation barrier for **1** complexing NaPic in $CDCl_3$ saturated with D_2O is 9.8 kcal mol^{-1}, which is presumably due mainly to the desolvation of the Na^+ and to separation of charge in going from NaPic to **1**·Na^+Pic^-. (5) The calculations provide a $\Delta(-\Delta G°)$ for **1** binding Li^+ and Na^+ vs. $A(AA)_2P$ (**4**) binding these ions of 14–17 kcal mol^{-1}, close to the 12–13 kcal mol^{-1} observed experimentally. Molecular model examination provided no guidance on this point. We look forward to the time when solvation of host, guest, and complex can be included in such calculations.

Experimental Section

General. Solvents were purified as in the companion paper,[3] and the same spectrometers, melting point, and drying methods were used as well. Treatment of glassware by method A refers to glassware that has been soaked in Chromerge for 14 h, rinsed with water, and soaked in 1:6 concentrated NH_4OH–H_2O for 1 h. It is then washed five times with low conductivity water and dried at 200 °C. Method A was used whenever spherands or cryptands came in contact with the glassware over a period of time. Treatment of glassware by method B refers to Chromerge-soaking and rinsing as above, followed by soaking in dilute aqueous $NaHCO_3$ for 1 h. The glassware was then washed five times with low conductivity water and dried at 200 °C. This method was applied only to volumetric flasks for CH_3CN solutions. The NMR tubes were new and were washed five times with CH_2Cl_2 and dried. The syringes were washed with CH_3CN and then washed five times with CH_2Cl_2 and dried. To avoid withdrawal of Na^+ from the glassware by the spherands or cryptands, quartz vessels were used when long periods of contact were involved. The $CDCl_3$ saturated with D_2O solutions were prepared by mixing 10–15 mL of D_2O and $CDCl_3$ (100%, Aldrich) in a clean 40-mL centrifuge tube which was sealed with a rubber septum. The phases were mixed on a vortex mixer for 3 min, and the $CDCl_3$ layer was removed with a syringe.

Derivations of the kinetic equations are available on microfilm from the Ph.D. thesis of George Max Lein, Jr., Host–Guest Chemistry: The Synthesis and Properties of Macrocycles Containing Convergent Aryl Oxygens, Appendices I–V, 1981, UCLA, Los Angeles, CA 90024.

Deuterated Spherands and the Reaction Intermediates Used in Their Syntheses. The systematic names, methods of syntheses, and full characterization of all of the nondeuterated spherands used here and their intermediates are given in the companion paper.[3] Unless noted otherwise, identical procedures were applied to preparing $Ad(AdAd)_2Ad$ (**1d**), $[B(Ad)(M_3)B]_2$ (**2d**), and $[B(Ad)(EOE)B]_2$ (**3d**), as were used for **1–3** except that CD_3I and $(CD_3)_2SO_4$ were substituted at the appropriate places for the CH_3I and $(CH_3)_2SO_4$ used in the former syntheses.[3] The yields and melting points obtained were comparable to those reported for the nondeuterated compounds. The deuterated compounds that were fully characterized (^1H NMR, MS, and C and O or C and Br analyses) are as follows: HAhAdAhH; BrAhAdAhBr; BrB(Ad)(M_3)BBr; BrB(Ad)(EOE)BBr; BrAdAdAdBr (this compound was prepared in 80% yield by treating BrAhAdAhBr with $(CD_3)_2SO_4$ and KOH in THF–H_2O; $Ad(AdAd)_2Ad$ (**1d**); $[B(Ad)(M_3)B]_2$ (**2d**); and $[B(Ad)(EOE)B]_2$ (**3d**)). All C and O or C and Br elemental analyses were within 0.30% of theory. All MS and ^1H NMR spectra were as expected based on the spectra of their protonated counterparts.[3]

Sodium and Lithium Picrate Complexes of the Spherands. The ^1H NMR spectral peaks of these complexes are recorded in Table I. The procedure is illustrated with the preparation of $[B(A)(M_3)B]_2$LiPic (**2**·LiPic). To a solution of 40.6 mg (0.0545) of **2** in 10 mL of CH_2Cl_2 was added a solution of 15.4 mg (0.065 mmol) of LiPic dissolved in 4 mL of CH_3CN. The solution was stirred for 5 min, the solvent was evaporated under reduced pressure, and the residue was dissolved in 20 mL of CH_2Cl_2. This solution was stirred for 1 h with 100 mL of low-conductivity water. The organic layer was removed by syringe, and the solvent was evaporated under reduced pressure and dried at ambient temperature under vacuum. The yellow residue was dissolved in 10 mL of CH_2Cl_2, and 50 mL of Et_2O was added. The solution was evaporated to a volume of 10 mL, and 50 mL of additional Et_2O was added. When the solution was allowed to evaporate to 10 mL, yellow crystals separated. Another 50 mL of Et_2O was added, and again the solvent was allowed to evaporate to 10 mL. The crystals were collected, washed with Et_2O and dried to give 51 mg (86–95%) of **2**·LiPic. Anal. Calcd for $C_{56}H_{50}LiN_3O_{13}$: C, 68.64; H, 5.14; N, 4.39. Found: C, 68.52; H, 5.19; N, 4.24.

Complex $[B(A)(EOE)B]_2$·LiPic (**3**·LiPic) was similarly prepared and was crystallized from a mixture of 10 mL of CH_2Cl_2 and 10 mL of $(CH_2)_6$. Anal. Calcd for $C_{58}H_{54}LiN_3O_{15}$: C, 66.92; H, 5.23; N, 4.04. Found: C, 67.05; H, 5.34; N, 4.03.

Complex $A(AA)_2A$·LiPic (**1**·LiPic) was similarly prepared and recrystallized from CH_2Cl_2–$(CH_2)_6$. Anal. Calcd for $C_{54}H_{50}LiN_3O_{13}$: C, 67.85; H, 5.27; N, 4.40. Found: C, 67.91; H, 5.19; N, 4.52.

Preparations of the NaPic complexes are illustrated with the preparation of **2**·NaPic. To a solution of 30.5 mg (0.041 mmol) of **2** in 10 mL of CH_2Cl_2 was added a solution of 13.5 mg (0.054 mmol) of NaPic in 2 mL of CH_3CN. The solvents were evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2. The solution was filtered to remove excess NaPic, the filtrate was evaporated under reduced pressure to 2 mL, and 4 mL of $(CH_2)_6$ was added. After 24 h, the yellow crystals that separated were collected, washed with $(CH_2)_6$, and dried to give 28.6 mg (70–77%) of **2**·NaPic. Anal. Calcd for $C_{56}H_{50}NaN_3O_{13}$: C, 67.53; H, 5.06. Found: C, 67.32; H, 4.92.

Complex $A(AA)_2A$·NaPic (**1**·NaPic) similarly prepared was crystallized from CH_2Cl_2–$(CH_2)_6$ (96%). Anal. Calcd for $C_{54}H_{50}N_3NaO_{13}$: C, 66.73; H, 5.19; N, 4.32. Found: C, 66.65; H, 5.19; N, 4.36.

Complex $[B(A)(EOE)B]_2$·NaPic (**3**·NaPic) was similarly prepared and crystallized (91–95%). Anal. Calcd for $C_{58}H_{54}N_3NaO_{15}$: C, 65.97; H, 5.15; N, 3.98. Found: C, 65.87; H, 5.27; N, 4.01.

Lithium 4,7,13,18-Tetraoxa-1,10-diazabicyclo[8.5.5]eicosane Picrate or $N(EOE)_2(EOEOE)N$·LiPic (9·LiPic). This procedure was applied to all of the cryptand complexes. To 10 mL of deoxygenated CH_3OH under N_2 was added 120 mg (0.42 mmol) of $N(EOE)_2(EOEOE)N$ (**9**) (E. Merck) and 110 mg (0.47 mmol) of LiPic. The mixture was stirred until homogeneous, and then crystals formed. The solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and filtered to remove the excess LiPic. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 3 mL of hot CH_3OH and cooled to −20 °C to give yellow needles which were collected, washed with CH_3OH, and dried to give 172 mg (78%) of **9**·LiPic, mp 164–165 °C. Anal. Calcd for $C_{20}H_{30}LiN_5O_{11}$: C, 45.89; H, 5.58. Found: C, 45.95; H, 5.61. ^1H NMR (200 MHz, $CDCl_3$) δ 2.525–2.644 (m, NCH_2, 4 H), 2.730 (t, NCH_2, J^3 = 5.1 Hz, 4 H), 2.862–2.981 (m, NCH_2, 4 H), 3.550 (t, OCH_2, J^3 = 5.1 Hz, 4H), 3.589–3.713 (m, OCH_2, 8 H), 3.668 (s, OCH_2, 4 H), 8.817 (s, ArH, 2 H).

Sodium 4,7,13,16,21-Pentaoxa-1,10-diazabicyclo[8.8.5]tricosane Picrate or $N(EOE)(EOEOE)_2N$·NaPic (10·NaPic). This compound, prepared from 113 mg (0.34 mmol) of **10** (E. Merck) and 94.3 mg (0.38 mmol) of NaPic, was recrystallized from 2 mL of THF and enough Et_2O to reach a cloud point at 25 °C. When cooled to −20 °C, orange needles separated which were collected, washed with Et_2O, and dried to give 50 mg (25%) of **10**·NaPic, mp 88–89 °C. Anal. Calcd for $C_{22}H_{34}N_5NaO_{12}$: C, 45.58; H, 5.87. Found: C, 45.67; H, 5.94. ^1H NMR (200 MHz, $CDCl_3$) δ 2.604–2.667 (m, NCH_2, 12 H), 3.521–3.573 (m, OCH_2, 12 H), 3.652 (s, OCH_2, 8 H), 8.816 (s, ArH, 2 H).

Potassium 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane Picrate or $N(EOEOE)_3N$·KPic. Application of the above procedure to 103 mg (0.27 mmol) of $N(EOEOE)_3N$ (E. Merck) and 86 mg (0.30 mmol) of KPic gave a residue which was recrystallized from 10 mL of THF and 10 mL of $(CH_2)_6$ (1 week of standing). The yellow crystals that separated were collected, washed with $(CH_2)_6$, and dried to give 156 mg (90%) of $N(EOEOE)_3N$·KPic, mp 120–121 °C. Anal. Calcd for $C_{24}H_{38}KN_5O_{13}$: C, 44.78; H, 5.95. Found: C, 44.71; H, 5.89. ^1H NMR (200 MHz, $CDCl_3$) δ 2.522–2.568 (m, NCH_2, 12 H), 3.510–3.556 (m, OCH_2, 12 H), 3.529 (s, OCH_2, 12 H), 8.825 (s, ArH, 2 H).

Sodium 4,7,13,16,21-Pentaoxa-1,10-diazabicyclo[8.8.5]tricosane Bromide or $N(EOE)(EOEOE)_2N$·NaBr (10·NaBr). The same procedure was applied to 110 mg (0.33 mmol) of **10** and 37.1 mg (0.36 mmol) of NaBr. The residue was crystallized from 1 mL of CH_2Cl_2 and 5 mL of THF to give white crystals (−20 °C), which were collected, washed with THF, and dried to yield 52 mg (36%) of **10**·NaBr, mp 86–145 °C dec. Anal. Calcd for $C_{16}H_{32}BrNaN_2O_5$: C, 44.14; H, 7.41. Found: C, 44.10; H, 7.52.

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

Lithium 4,7,13,18-Tetraoxa-1,10-diazobicyclo[8.5.5]eicosane Bromide Monohydrate or $N(EOE)_2(EOEOE)N\cdot LiBr\cdot H_2O$ ($9\cdot LiBr\cdot H_2O$). Application of the same procedure to 104 mg (0.36 mmol) of **9** and 35.7 mg (0.41 mmol) of LiBr gave a residue that was recrystallized from acetone at −20 °C to give white crystals that were collected, washed, and dried. Anal. Calcd for $C_{14}H_{30}BrLiN_2O_5$: C, 42.96; H, 7.69. Found: C, 42.92; H, 7.72.

Association (Equilibrium) Constant for $[B(A)(M_3)B]_2$ (2) Complexing NaPic. Aliquots (10 mL) of a 0.001 M solution of **2** in $CDCl_3$ and of a 0.000976 M solution of NaPic in low-conductivity water were stirred magnetically at 25 °C in a 50-mL quartz flask fitted with a Teflon stopper sealed with parafilm. Periodically, 100-μL aliquots of each phase were removed and diluted with 5 mL of CH_3CN, and the absorbance of the picrate ion at 380 nm was determined as in methods already described.[6] Table II records the results.

Decomplexation Rates for Spherand Complexes of LiPic and NaPic. Method 1 was applied to $[B(A)(M_3)B]_2\cdot NaPic$ (**2**·NaPic), transferring its NaPic to $[B(Ad)(M_3)B]_2$ (**2d**). Method 2 was applied to $A(AA)_2A\cdot NaPic$ (**1**·NaPic), transferring its NaPic to $Ad(AdAd)_2Ad$ (**1d**), and to **2**·LiPic, transferring its LiPic to **2d**. Method 3 was applied to $[B(A)(EOE)B]_2\cdot NaPic$ (**3**·NaPic) and to **3**·LiPic, transferring their picrate salts to $[B(Ad)(EOE)B]_2$ (**3d**). Attempts made to apply method 2 to **1**·LiPic and **1d** led to temperatures at which dimethylation and decomplexation rates were comparable.

Method 1. Solutions (5 mL each) in $CDCl_3$ (D_2O saturated at 25 °C) were prepared that were respectively 0.002 M in **2**·NaPic and 0.002 M in **2d**. Aliquots (250 μL) of each solution were added to an NMR tube, mixed, and placed in the probe of a Bruker WP-200 equilibrated to the desired temperature. The tube was allowed to come to temperature (5–10 min), and ^1H NMR spectra were run at intervals (20–25 points over 3 to 3.5 half-lives) and stored on a disk using the programming capabilities of the Bruker WP-200 instrument. Since 20 scans were used, the time used for any given point was taken at the midpoint of the total accumulation time (82 s). An infinity point was taken by running an ^1H NMR spectrum after 5–10 half-lives, after which a 50-μL aliquot was removed and diluted to 5 mL with spectral grade CH_3CN. An absorbance reading was taken at 380 nm on this solution to determine the initial concentration of **2**·NaPic. For integrals of the ^1H NMR peaks, the desired pairs of resonances were expanded to full scale before integration. A Laurential line broadening factor of 0.1 was used.

Method 2. Solutions (10 mL each) of 0.002 M of unlabeled spherand complex and of 0.002 M labeled spherand were prepared in $CDCl_3$ (D_2O saturated at 25 °C). In all cases, the three runs made at a given temperature were carried out simultaneously, using the same stock solutions. A run made with **2**·LiPic and **2d** is illustrative. Aliquots (3 mL) of the solutions of **2**·LiPic and of **2d** were measured out by syringe and mixed. A 50-μL aliquot was removed and diluted to 5 mL with spectral grade CH_3CN for determination of the **2**·LiPic concentration. The remainder was transferred in 350-μL aliquots into 6-in. tubes (14–15 of them) prepared from Corning 8-mm outer diameter special wall 1.5-mm tubing which had restricted necks 1.5–2.0 in. from the top to facilitate sealing. Long narrow syringe needles were used in this transfer, and care was taken to prevent contact between the solution and the tube near the restricted neck. The tubes were sealed at atmospheric pressure at −78 °C, warmed to 25 °C, and placed in a constant temperature oil bath containing a standardized Beckmann thermometer. The tubes were given 10 min to equilibrate to bath temperature. A tube was removed for a zero point and cooled with cold water and then to −78 °C. Other tubes were removed at desired intervals, the last one after 5–10 half-lives. After completion of the run, the frozen tubes were warmed to 25 °C, and the ^1H NMR spectra of their contents were taken. Integrals of useful peaks were taken as in method 1. A second and third run were made simultaneously, with solution volumes of 4 mL of **2**·LiPic to 2 mL of **2d** and of 2 mL of **2**·LiPic to 4 mL of **2d**.

Method 3. This method is identical with method 2, except that shift reagent had to be added to differentiate between the ^1H NMR peaks of **3** and **3**·NaPic, or **3** and **3**·LiPic. Accordingly, after transfer of each aliquot to the NMR tube, a 35- to 45-μL aliquot of a 0.05 M solution in $CDCl_3$ of $Pr(fod)_3$ (Aldrich) was added. The optimum amount of the shift reagent for each run was determined by adding 35, 40, and 45 μL of the shift reagent solution to tube 12 of the run and determining the ^1H NMR spectrum after each amount.

The values of $[HG]_i$, $[H^*]_i$, and [H] of eq 4 were calculated from the picrate absorbance at 380 nm (ε 16 900) and the ratios of the integrals in the ^1H NMR spectra. The values of $[HG]_i$ was calculated from the picrate absorbance. The value of $[H^*]_i$ was calculated from the ratio of free to complexed spherand with the integral of the ^1H NMR resonances indicated in Table VII not dependent on the deuterium label. This ratio was determined at each kinetic point, and the average was used in the calculations. The value of [H] was determined from the ratios of integrals of the methoxy peaks as the reaction progressed and $[HG]_i$. Table III lists the values for the complexation rate constants obtained.

Table VII. Chemical Shifts of Spherands and Their Complexes in $CDCl_3$ (Saturated with D_2O at 25 °C) Used in Decomplexation Kinetics

	δ used in calculation of			
complex	$[H^*]_i$	$[HG]_i$	[H]	[HG]
1·NaPic	7.167	7.316	2.848	2.944
1·LiPic	7.167	7.349	2.848	3.035
2·NaPic	7.600	7.826	2.800	2.870
2·LiPic	7.600	7.826	2.800	2.884
3·NaPic[a]	6.959	6.819	2.130	1.996
3·NaPic[a]	6.940	6.785	2.127	1.910

[a] Chemical shifts in the presence of $Pr(fod)_3$ shift reagent.

General Methods for Detecting Homogeneous Complexation. (1) Exploratory Experiments. The method is illustrated with $[B(A)(M_3)B]_2$ (**2**) complexing $NaClO_4$. A 500-μL aliquot of a 0.0015 M solution of **2** in $CDCl_3$ was added to an NMR tube, followed by a 10-μL aliquot of a 0.05 M solution of $NaClO_4$ in $(CD_3)_2SO$. The tube was shaken well, and the ^1H NMR spectrum of its contents was taken immediately. In runs where heat was applied, tubes were cooled to −78 °C and sealed at atmospheric pressure. Tubes that were not heated but were allowed to stand were well wrapped with parafilm at the cap. No changes were observed in ^1H NMR spectra at times longer than 5 min. The salts examined included Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, and La^{3+} perchlorates, Li^+, Na^+, Ca^{2+}, Mg^{2+}, and Sr^{2+} bromides, Li^+ and Na^+ chlorides, and Li^+ and Na^+ picrates. Also examines were $HClO_4$ and HPic in CD_3CN and CF_3CO_2H in $CDCl_3$. *Attempts to add $HClO_4$ to $(CD_3)_2SO$ led to violent explosions!*

(2) Cation Exchange Experiments. An example involves exchange of **2**·$NaClO_4$ with $LiClO_4$ as follows. A 500-μL aliquot of a 0.0016 M solution of **2** in $CDCl_3$ was added to an NMR tube, and a 13.8-μL aliquot of a 0.070 M solution of $NaClO_4$ in $(CD_3)_2SO$ was added. The tube was shaken well, and an ^1H NMR spectrum was run to ensure that no free **2** remained (δ = 2.800 for OCH_3). A 13-μL aliquot of a 0.070 M solution of $LiClO_4$ in $(CD_3)_2SO$ was added. The tube was shaken again, and the ^1H NMR spectrum was taken at intervals. When periods in excess of a few hours were involved or when the tube was to be heated, it was sealed.

(3) Rate Ratios for a Spherand Complexing NaPic and LiPic. Similar methods were applied to determining the rate constant ratios for complexation. Due to the hygroscopicity or the solubility properties of some of the lithium and sodium salts, the concentrations of their solutions could not be determined by weighing. In these cases, the relative concentrations of two spherands–one salt or one spherand–two salt combinations were determined by the following ^1H NMR method (this was applied to part 2 above based on the spherand solution concentration of 0.015 M). Each time a new spherand or salt solution was prepared, the concentrations were checked. The method is illustrated. To 500 μL of **2** in $CDCl_3$ (0.0015 M) was added an aliquot of 6 μL (<1 equiv) of NaPic solution in $(CD_3)_2SO$. After 5 min the ^1H NMR spectrum was recorded and the relative concentration of salt and spherand were calculated by using the mean of two determinations. The chemical shifts (δ) used for determining the rate constant ratios for **1** or **2** complexing NaPic and LiPic in $CDCl_3$–2% $(CD_3)_2SO$ were the following: **1**, 2.848; **1**·NaPic, 2.955; **1**·LiPic, 3.023; **2**, 7.597; **2**·NaPic, 7.826; **2**·LiPic, 7.787. Peak heights were employed. The method is illustrated. Aliquots of NaPic (120 μL) and LiPic (130 μL) solutions in $(CD_3)_2SO$ were well mixed to produced equal concentrations of each salt. A 25-μL aliquot of this solution was transferred to an NMR tube containing 500 μL of a $CDCl_3$ solution of **2** (0.0015 M) to give [NaPic]/[**2**] = 1.1. The tube was shaken well, and the ^1H NMR spectrum was run immediately. For **2**, a slow exchange of Na^+ for Li^+ occurs, but it is negligible if the spectrum is taken in 2–5 min. No such exchange occurs with **1** and **3**.

(4) Rate Ratios for Two Spherands Complexing NaPic or LiPic. Relative concentrations of the salt and spherand solutions were determined as in section 3 above. Rate ratio determinations are illustrated. Aliquots (500 μL each) of stock solutions of **1** and **2** in $CDCl_3$ (0.0015 M) were well mixed in an NMR tube. A 5-μL aliquot of a 0.070 M LiPic stock solution in $(CD_3)_2SO$ was added, the tube was shaken, and the ^1H NMR spectra were recorded immediately. The chemical shifts (δ) used to calculate the rate constant ratios were as follows: **1**, 2.848; **1**·LiPic, 3.041; **1**·NaPic, 2.969; **2**, 2.800; **2**·LiPic, 2.907 and 7.817; **2**·NaPic, 2.844 and 7.848.

(5) Transfer of NaPic from 2·NaPic to 1. A 9-μL liquot (1 equiv) of stock solution of 0.088 M NaPic in $(CD_3)_2SO$ was added to a 500-μL aliquot of **2** in $CDCl_3$ (0.0016 M), and the ^1H NMR spectrum was taken

to ensure the absence of uncomplexed **2** (δ 2.800, OCH_3). To this solution was added 450 μL of a 0.0015 M solution of **1** in $CDCl_3$, and the ^1H NMR spectra were run at intervals up to 1 week. Tubes that stood for more than several hours were sealed with parafilm. The exchange was followed from the peak height ratio of complexes **2** (δ 7.803, Ar–H) to free **2** (δ 7.601, Ar–H). The transfer of Na^+ or Li^+ from **3** to **1** was too slow to observe.

Complexation Rate Constants for Spherands with NaPic. Stock solutions (0.002 M) in $CDCl_3$ (saturated with D_2O at 25 °C) of spherands **1**–**3** and B[Aa][EOE][$(MOE)_2O$]B (**7**) and a mixture of B[A][EOE]-[$(MOE)_2O$]B (**6**) (0.003 M) and NaPic (0.0027 M) in the same solvent were prepared. Solubilization was aided by placing the volumetric flasks in an ultrasonic cleaner for several minutes. The ^1H NMR spectra were run on three separate aliquots of the **6**·NaPic–free **6** (integrals at δ 5.196 and 4.723, respectively) to determine their relative concentrations. Equations 9–13 involve measurements of $[C]_i$, $[S]_i$, $[CG]_i$, and [S] where C is **6**, CG is **6**·NaPic, S is spherand, the subscript i applies to initial concentrations, and its absence applies to concentrations at time t. In all cases $[CG]_i$ was calculated from the picrate ion absorbance of 380 nm (ϵ 16 900) of a 5-mL CH_3CN solution containing 50 μL of the reaction mixture and $[C]_i$ from the value of $[CG]_i$ and the $([\mathbf{6}\cdot\text{NaPic}]/[\mathbf{6}])_i$ ratio mentioned above. For spherands **1** and **2**, $[S]_i$ was determined from the ratio $[S]_i/([C]_i + [CG]_i)$ from integrals of ^1H NMR O–CH_3 peaks at δ: for **1**, 2.848 (**1**·NaPic absorbs at 3.035); for **2**, 2.800 (**2**·NaPic absorbs at 2.944). This ratio was calculated for each point, and the mean value for all points was used to calculate $[S]_i$. Values of [S] were calculated for each point from the integrals of the above CH_3–O peaks at time t.

A typical kinetic run involved a 200-μL aliquot of a 0.202 M solution of **2** in $CDCl_3$ (D_2O saturated at 25 °C) and a 200-μL aliquot of a solution of **6** (0.003 M) and NaPic (0.0027 M) in the same solvent mixed well and placed in the Bruker WP-200 probe equilibrated at 25 °C. After the tube had temperature equilibrated, the ^1H NMR spectra were taken (20 points, 3.5 half-lives). Twenty scans were needed for good resolution, and the time for each point was taken at one-half the total accumulation time of 82 s. All pairs of resonances used were expanded to full scale before integration. An infinity point was taken after 5–10 half-lives, after which a 50-μL aliquot of the solution was diluted with spectral grade CH_3CN and the absorbance was determined. For runs with **1**, no inifinity point was taken.

Modifications of the procedure were as follows. For runs with **3**, only 1 half-life was followed and then the tube was wrapped well with parafilm and allowed to stand in the dark for 14 days before an infinity point was taken. The methoxyl resonances of **3** could not be used to follow the reaction. Therefore $[S]_i$ and [S] were calculated from the infinity point and the integrals of the resonances of **6** and **6**·NaPic as the reaction proceeded. The 50-μL aliquot was removed after 1 half-life in the runs involving **3** and after the last kinetic point for **1**. A ratio of only [NaPic]/[**3**] = 1.1 was used in kinetic runs involving **3**. A control run was made in which a 0.003 M solution of hemispherand **7** was substituted for those of the spherands, and the temperature equilibration time was omitted. The equilibrium, **6**·NaPic + **7** $\rightleftarrows$ **6** + **7**·NaPic, was reached in <2 min.

Relative Rates of Complexation of Spherands by Exchange with LiPic or NaPic Complexes of Cy(OEOEO)$_2$Cy (8). (1) Two Spherands Competing for a Single Salt. The method is illustrated with the competition of **1** and **2** complexing NaPic in $CDCl_3$ saturated with D_2O at 25 °C. Aliquots (250 μL) of each of two solutions, 0.0018 M in **2** and 0.0017 M in **1**, were mixed in an NMR tube, and the spectrum was run to determine the relative amounts of each (see General Methods of Detecting Homogeneous Complexation, section 3). The solution was transferred to a quartz tube to which was added with ultrasonic mixing a 50-μL solution of $CDCl_3$–D_2O, 0.010 M in Cy(OEOEO)$_2$Cy (**8**) and 0.0085 M in NaPic (prepared with ultraonic mixing). The content of the quartz tube was immediately transferred back to the ^1H NMR tube, and the spectrum was taken as quickly as possible. The resonance integrals used to determine the concentrations of the species present were (δ) as follows: **1**, 2.848 (used to calculate only $([\mathbf{1}]_i/[\mathbf{2}]_i)$ before salt addition—after salt addition, overlap occurs and then 7.167 was used); **1**·NaPic, 2.944; **1**·LiPic, 3.035; **2**, 7.600, 7.029; **2**·NaPic, 7.826, 7.368; **2**·LiPic, 7.785, 7.563. For calculating $[\mathbf{2}]_i$, the total integrals were used of the peak for **2** at 7.029 and that for **2**·NaPic at 7.046 which overlap, or for the peak for **2** at 7.029 and that for **2**·LiPic at 7.061 which overlap. Only in runs involving **2**·NaPic forming or decomplexing required short mixing and transfer times.

Table VIII. Chemical Shifts of Spherands and Their Complexes and of Cryptand Complexes Used in Equilibria at 25 °C in $CDCl_3$ Saturated with D_2O

		δ used in the calculation of		
S	CG	$[CG]_i$	[S]	[SG]
1	**10**·NaPic	8.786	7.167	7.316
1	**9**·LiPic	8.802	7.167	7.349
2	**10**·NaPic	8.819	7.600	7.826
2	**9**·LiPic	8.781	7.600	7.785
3	**10**·NaPic	8.811	7.335	7.648
3	**9**·LiPic	8.810	7.330	7.513

(2) Sodium and Lithium Picrates Competing for a Single Spherand. The method is illustrated as follows. A 300-μL aliquot of a 0.0017 M solution of **1** in $CDCl_3$–D_2O (saturated) was added to a clean quartz tube. With ultrasonic mixing was added a 250-μL solution in $CDCl_3$ (D_2O saturated at 25 °C) which was 0.03 M in Cy(OEOEO)$_2$Cy (**8**), 0.0188 M in NaPic, and 0.00602 M in LiPic. The resonance integrals used to determine the concentrations of the species present were (δ) as follows: **1**·LiPic, 3.035, 8.84; **1**·NaPic, 2.944, 8.84; **2**·LiPic, 7.785, 2.884, 8.84; **2**·NaPic, 7.826, 2.870, 8.84; **3**·LiPic, 7.563, 8.84; **3**·NaPic, 7.638, 8.84. Since integrations of picrate Ar–H proton peaks were used, a 5-s relaxation delay was used. When **2** was involved, the ^1H NMR spectrum was run as soon as possible.

Equilibration of Salts between Cryptand and Spherand Complexes. Equilibrations of salt between cryptand and spherand complexes involve a method illustrated by equilibration of N(EOE)(EOEOE)$_2$N·NaPic (**10**·NaPic) with $[B(A)(M_3)B]_2$ (**2**). Aliquots (200 μL) of a 0.0017 M solution of **2** and of a 0.0016 M solution of **10**·NaPic in $CDCl_3$ (D_2O saturated at 25 °C) were transferred via a long syringe needle to an NMR tube without solution touching the tube near where it was to be sealed. A 50-μL aliquot of a 0.044 M $(Et)_3N$ solution in $CDCl_3$ (D_2O saturated at 25 °C) was similarly transferred. The tube was cooled to −78 °C and sealed at atmospheric pressure. The tube was allowed to warm to 25 °C and was stored in the dark at this temperature. The ^1H NMR spectrum of the solution was taken after 2, 4, and 8 weeks. Since the integral of the picrate Ar–H signals was used in the analyses, the ^1H NMR spectra (60 scans) were run with a 5-s delay to allow full relaxation of the protons. The chemical shifts used in the calculations of the equilibrium constants are recorded in Table VIII. The values for the ratios of concentration terms of eq 18 were calculated as follows. The ratios $([CG]_i/[S]_i)$ and $[SG]_e/[S]_i$ were obtained from the integrals of the peaks listed in Table VIII. These values and eq 19–21 provided the ratios $[SG]_e/[CG]_e$ and $[C]_e/[S]_e$ needed in eq 18.

$$[CG]_e/[S]_i = [CG]_i/[S]_i - [SG]_e/[S]_i \quad (19)$$

$$[C]_e/[S]_i = [SG]_e/[S]_i \quad (20)$$

$$[S]_e/[S]_i = 1 - [SG]_e/[S]_i \quad (21)$$

Registry No. 1, 72526-85-3; **1**·LiPic, 82484-54-6; **1**·NaPic, 82475-14-7; **2**, 95782-47-1; **2**·LiPic, 82484-56-8; **2**·NaPic, 82484-55-7; **3**, 95782-50-6; **3**·LiPic, 82489-41-6; **3**·NaPic, 82489-39-2; **6**, 82475-15-8; **8**, 16069-36-6; **9**, 31250-06-3; **9**·LiPic, 80103-61-3; **9**·LiBr, 57064-18-3; **10**, 31364-42-8; **10**·NaPic, 80103-60-2; **10**·NaBr, 74008-66-5; **11**, 57064-18-3; N-(EOEOE)$_3$N·KPic, 95784-26-2; Li, 7439-93-2; Na, 7440-23-5.