Typical example: *p*-Anisyl(*p*-phenoxyphenyl)methyl chloride (**1**-OMe,OPh; 40.2 mg, 0.124 mmol) and *p*-anisyl-*p*-tolylmethyl chloride (**1**-OMe,Me; 72.4 mg, 0.293 mmol) were dissolved in 0.6 mL of CD_2Cl_2 in an NMR tube. 1,1,2,2-Tetrachloroethane (20.0 μL, 31.5 mg, 0.188 mmol) was added as standard. Partial ionization of the mixture is accomplished by addition of 2.3 mL (0.094 mmol) of BCl_3 gas at −70 °C. The signals of para methyl (δ = 2.33, **1**-OMe,Me; δ = 2.58, **1**$^+$-OMe,Me), para methoxy (δ = 3.75, **1**-OMe,Me, **1**-OMe,OPh; δ = 4.14, **1**$^+$-OMe,OPh; δ = 4.22, **1**$^+$-OMe,Me), and methine protons (δ = 6.14, **1**-OMe,OPh; δ = 6.17, **1**-OMe,Me; δ = 8.94, **1**$^+$-OMe,OPh; δ = 9.13, **1**$^+$-OMe,Me) in both carbenium ion and precursors were recorded with those of tetrachloroethane (δ = 6.01). The signal integrals gave nine equations for the determination of the concentrations of **1**-OMe,OPh, **1**$^+$-OMe,OPh, **1**-OMe,Me, and **1**$^+$-OMe,Me. Regression analysis[21] led to $K_{203} = 0.0480$ and $\Delta G_{203}^\circ = 5.13$ kJ/mol. Further determinations of ΔG_{203}° for six different samples (ΔG_{203}° = 4.84, 5.15, 5.36, 4.71, 5.02, 5.60 kJ/mol) gave an average value of $\Delta G_{203}^\circ = 5.1 \pm 0.3$ kJ/mol.

Calorimetric Studies. General Procedures. A calorimeter of the type previously described[22] was used with minor modifications. Experimental details and procedures closely followed the description given there[22] if not otherwise reported. Each measurement was repeated at least twice. A determination of the heat capacity of the calorimeter was undertaken before and after every calorimeter run. The reliability of the data was checked independently by the determination of the heat of interaction of tetrahydrofuran with $SbCl_5$ in CH_2Cl_2 at −55 °C.[23] All further determinations were run in CH_2Cl_2 at −70 °C.

Heats of Addition of Diarylmethyl Chlorides to 2-Methyl-1-pentene. A 1 M solution of BCl_3 in CH_2Cl_2 (10 mL) or of $ZnCl_2\cdot(OEt_2)_{1.5}$ in CH_2Cl_2 (5 mL) was added to a solution of the alkene (≈1 mmol) in CH_2Cl_2 (≈10^{-2} M). The heat of reaction upon introduction of 0.50–0.75 mmol of the neat diarylmethyl chloride was recorded. Heats of solution of the diarylmethyl chlorides in CH_2Cl_2 were determined separately.

Heats of Addition of Diarylcarbenium Ions to Alkenes. Ampules of less than stoichiometric amounts (0.2–2 mmol) of the alkene were introduced into a 10^{-3}–10^{-2} M solution (≈200 mL) of the carbenium tetrachloroborates. For 2-methyl-1-pentene the integral heat of solution in CH_2Cl_2 was determined subsequently. All other alkenes have been introduced as 5–20% solutions in ≈1 mL of CH_2Cl_2 and heats of dilution were neglected.

Heats of Interaction with BCl_3. Solutions of the addition products in ≈1.5 mL of CH_2Cl_2 were sealed in an ampule. The heat of reaction upon its introduction into excess BCl_3/CH_2Cl_2 was recorded.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie at Lübeck, the Duke Chemistry Department, and National Science Foundation Grant No. CHE-8641817 to E.M.A. at Durham. C.S. gratefully acknowledges help by John Harrelson and Frank Fisher and financial assistance of the Fonds der Chemischen Industrie/Stiftung Volkswagenwerk by a Kekulé grant.

Supplementary Material Available: ^{1}H NMR spectral data for diarylmethyl chlorides **1**-X,Y and diarylcarbenium tetrachloroborates in CD_2Cl_2 at −70 °C and compilations of NMR spectroscopic determinations of K and ΔG° (5 pages). Ordering information is given on any current masthead page.

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Host–Guest Complexation. 45. A Highly Preorganized Chromogenic Spherand Indicator System Specific for Sodium and Lithium Ions[1]

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Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received July 9, 1987*

Abstract: The synthesis and chromogenic properties of **1** as a sodium and lithium ion selective indicator system are described. The pK_a values of **1** in the absence and presence of various metal ions were measured in 80% dioxane–20% water (v/v). Observed values were as follows: Li$^+$, 5.9; Na$^+$, 6.9; K$^+$, 12.7; Ca^{2+}, 12.8; Mg^{2+}, 13.2; 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 13.0. The noncomplexing model system **21** gave a pK_a of 10.8 in the same medium. Spherand **1** is yellow (λ_{max} 396 nm; ϵ_{max} 17 500 L/(mol·cm)), whereas spheraplexes **1**$^-\cdot$Li$^+$ (λ_{max} 586 nm, ϵ_{max} 35 500 L/(mol·cm)), and **1**$^-\cdot$Na$^+$ (λ_{max} 596 nm, ϵ_{max} 35 500 L/(mol·cm)) as well as uncomplexed **1**$^-$ (λ_{max} 610 nm, ϵ_{max} 53 000 L/(mol·cm)) are deep blue or violet in 80% dioxane–20% water (v/v) and other solvents. Thus **1** is a chromogenic ion-selective indicating system capable of detecting Li$^+$ and Na$^+$ at concentrations as low as 10^{-8} M in the presence of other common ions. The binding free energies of spherands **4–6** binding lithium picrate and sodium picrate at 25 °C in $CDCl_3$ saturated with D_2O were measured and found to range between 8.4 and 12.5 kcal mol^{-1}, somewhat higher than those for **7**, but much lower than those for **2**.

This paper describes the synthesis and properties of **1** as an ion-selective chromogenic indicator system for Na$^+$ and Li$^+$. The binding properties and ion selectivities of analogues **2–8** are compared.

Spherand **2** binds lithium, sodium, and potassium picrates at 25 °C in $CDCl_3$ saturated with D_2O with $-\Delta G^\circ$ values of >23, 19.3, and <6 kcal mol^{-1}. The very strong binding of Li$^+$ and Na$^+$ and nondetectable binding to K$^+$ have been attributed to the high complementarity and preorganization of the cavity in **2**.[2] The crystal structure of **2** shows it contains a hole lined with 24 electrons having a diameter between that of Li$^+$ and Na$^+$. The six octahedrally arranged oxygens defining the cavity are shielded from solvation by six aryl and six methyl groups to provide a microdielectric environment for complexation between that of a vacuum and that of a hydrocarbon. The potassium ion is too large to enter this structurally defined cavity. Divalent ions of small enough diameters (e.g., Mg^{2+} or Ca^{2+}) do not enter this cavity because of their very high heats of hydration.[3,4]

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Chart I

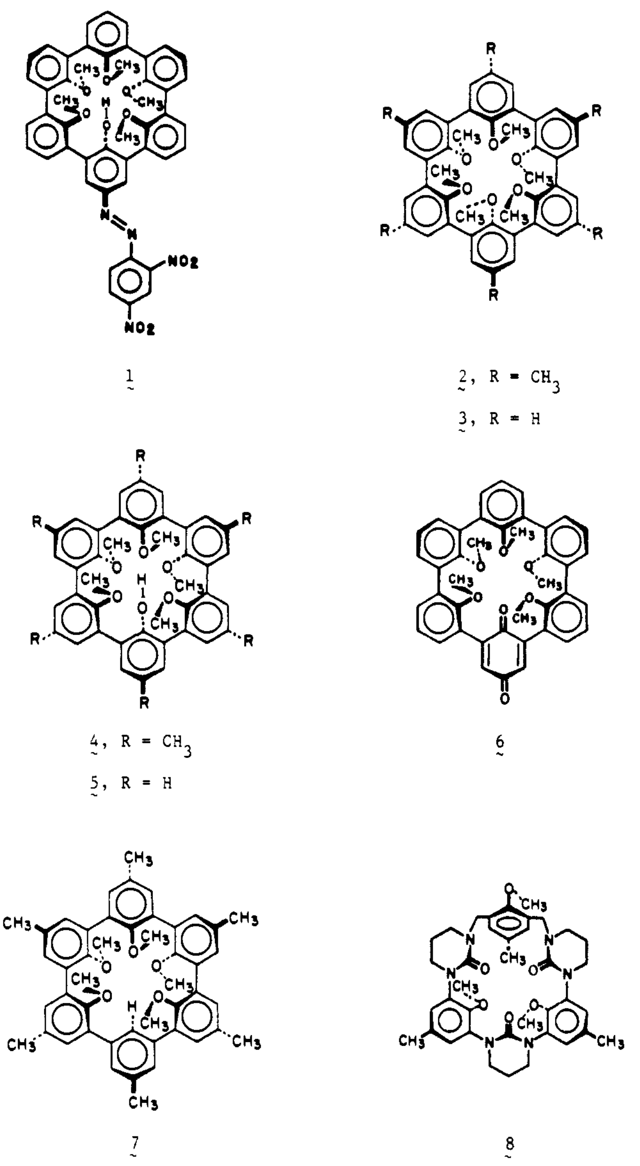
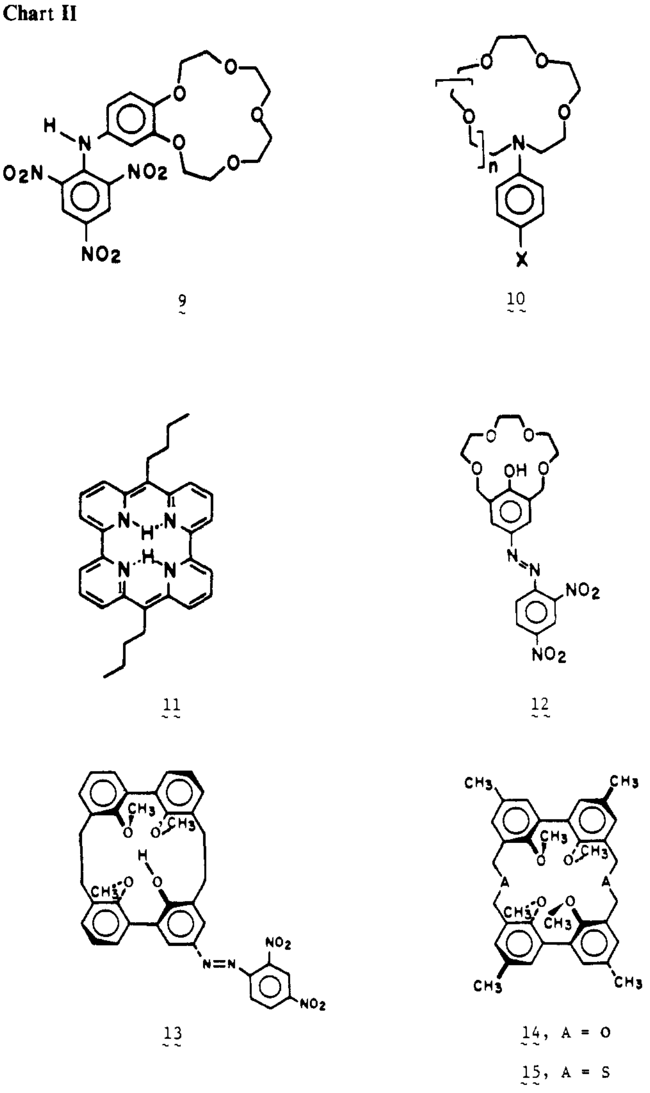


Chart II



In early work corands **9** and **10**, which complex alkali metal ion guests, have been made chromogenic by attachment of chromophores to the binding site. Takagi et al. reported that dissociation of the picramide proton of **9** and complexation of the anion with K^+ were accompanied by a 55-nm bathochromic shift, the difference between λ_{max} for Na^+ and K^+ being 4 nm.[5] Without the presence of an acidic proton, Vögtle et al. found that host **10** gave chromophoric shifts of 3–20 nm in λ_{max} upon complexation of alkali metal ion guests.[6] Vögtle concluded that hosts which rely on deprotonation for chromophoric changes had similar absorption maxima for all cations, and were not capable of differentiating between them.[6d] Ogawa et al. reported that **11** as a CH_2Cl_2 solution when contacted with *solid* LiCl turned from red to colorless.[7] In work the most similar to ours, Kaneda and Misumi et al. reported that a yellow solution of **12** in $CHCl_3$ gave a 160-nm bathochromic shift to a purple-red color upon contact with excess, *solid* LiCl or $LiClO_4$ (but not other salts) in the presence of pyridine.[8a] Later,[8b] **12** was used to analyze for Li^+ in *solid* Li_2CO_3. Uncomplexed **12**, when deprotonated in EtOH, gave hypsochromic shifts that varied from 10 nm for Cs^+ to 50 nm for Li^+. Recently, chromogenic spherand **13** acted as a lithium-specific chromogenic indicator system for *solid* lithium salts of *soft anions*.[4] Apparently **13** is a strong enough complexing agent to break up the lattice of crystalline LiBr, LiI, or $LiClO_4$ but is too weak for that of solid LiF, $LiNO_3$, or Li_2SO_4. It also appears to be too weak to take Li^+ away from $Li(H_2O)_6{}^+$. We had found earlier that **14** and **15** were too poorly preorganized to bind any of the alkali metal ions well enough to measure their $-\Delta G°$ values at 25 °C in $CDCl_3$ saturated with D_2O with any accuracy.[9a]

Results and Discussion

Synthesis. By procedures already described,[9b] **16** was converted through **17** and **18** to **19**, and finally to **20**[9b] in an overall yield of 25%. The critical macroring-closing step was accomplished by metalation of **20** in the two positions ortho to the methoxyl

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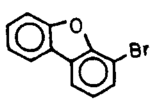
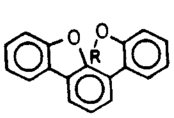
Chart III

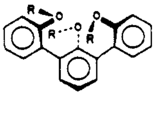


16



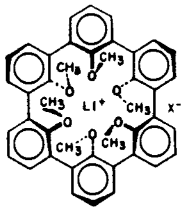
17, R = CH_3

18, R = H



19, R = H

20, R = CH_3



3·$LiFeCl_4$

3·LiCl

groups with BuLi in Et_2O and by oxidation of the diorganometallic formed with $Fe(acac)_3$ in refluxing benzene. The macrocycle **3** was isolated as **3**·$LiFeCl_4$, which when treated with EDTA produced **3**·LiCl (69%). As in the similar synthesis of **2**·$LiFeCl_4$, the yield of **3**·$LiFeCl_4$ produced in the macroring closure was enhanced by the presence of LiBr, generated in the reaction medium by treatment of BuLi with *t*-BuBr.[3] Thus **20** (15 mmol) in 1 L of benzene in the presence of 30 mmol of LiBr led to 26–28% yields of **3**·$LiFeCl_4$ to give 17–20% overall yields of **3**·LiCl. The reaction probably goes through radical-coupling stages templated by Li^+. Substitution of NaBr for LiBr resulted in a 9% yield of **3**·NaCl.

The demethylation of **2**·LiCl to give phenol **4** was reported to occur in a sealed tube in 1:6 pyridine–water at 200 °C (150 min).[3] As a suspension in 1:1 pyridine–water at reflux, **3**·LiCl gave the corresponding lithium salt of **5**, acidification of which gave phenol **5** (98% overall). The Li^+ ion probably acts as an electrophilic catalyst and the chloride ion or pyridine as the nucleophile in the demethylation. Oxidation of phenol **5** with thallium nitrate[10] gave quinone **6** (84%). Condensation of **6** with 2,4-dinitrophenylhydrazine gave indicator system **1** (54%) as an orange crystalline solid.

Binding Properties. The binding properties of **4**–**6** toward Li^+, Na^+, and K^+ picrates at 25 °C in $CDCl_3$ saturated with D_2O were determined. Solutions of the spherands in $CDCl_3$ and of the picrate salts in D_2O were stirred in sealed tubes over a period of days, aliquots being taken to determine by UV analysis when equilibrium was reached.[2] Once equilibrated, the concentrations of the picrate ion were determined in the usual way.[11] The equilibration took 2 to 5 days. Equilibrium was reached faster with Na^+Pic^- than with Li^+Pic^- as guest. No complexation of K^+Pic^- by **4** and **5** could be detected. Addition of a solution of $KClO_4$ in $(CD_3)_2SO$ to a solution of phenol **3** in $CDCl_3$ failed to produce any change in the 1H NMR spectrum of the spherand. The ^1H NMR spectra of **2**, **2**·$LiClO_4$, and **2**·$NaClO_4$ are easily differentiated from one another.[3] The K_a and $-\Delta G°$ values for complexation are recorded in Table I and represent the average of two determinations that differed from one another by less than 8% in free energy values. Table I also includes the K_a and $-\Delta G°$ values for spherand **2** and **7** and hemispherand **8**[12] binding the same ions at 25 °C in $CDCl_3$ saturated with D_2O.

Table I. Association Constants (K_a, mol^{-1}) and Free Energies of Binding ($-\Delta G°$, kcal mol^{-1}) of Alkali Metal Picrate Salts at 25 °C in $CDCl_3$ Saturated with D_2O

	guest picrate salts of					
	Li^+		Na^+		K^+	
hosts	K_a[a]	$-\Delta G°$[b]	K_a[a]	$-\Delta G°$[b]	K_a[a]	$-\Delta G°$[b]
2[c]	7.0×10^{16}	>23	1.2×10^{14}	19.2	$<2.5 \times 10^4$	<6
4	2.2×10^8	11.4	7.7×10^6	9.4	$<2.5 \times 10^4$	<6
5	1.1×10^9	12.3	1.4×10^6	8.4	$<2.5 \times 10^4$	<6
6	1.4×10^9	12.5	1.5×10^7	9.8	5.8×10^4	6.5
7[c]	4.1×10^7	10.4	4.9×10^4	6.4	$<4.6 \times 10^3$	<5
8[d]	7.3×10^8	12.1	1.9×10^{11}	15.4	2.7×10^{11}	15.6

[a] mol^{-1}. [b] kcal mol^{-1}. [c] Reference 2. [d] Reference 12.

As observed in earlier studies[9,13-15] substitution of hydroxyl for ether oxygens in hosts lowers their binding abilities toward the alkali metal ions. Comparison of the $-\Delta G°$ values for **2** vs **4** binding LiPic and NaPic shows a reduction in binding free energy of >11.6 and 9.8 kcal mol^{-1}, respectively (Table I). This dramatic decrease is attributed to the following effects: (1) the phenolic hydroxyl hydrogen in **4** is undoubtedly turned inward and hydrogen bonds the methoxyl oxygens of the adjacent anisyl units; (2) to bind Li^+ or Na^+, these hydrogen bonds must be broken and the hydroxyl group reorganized; (3) some steric inhibition of solvation is lost when the methyl of **2** is substituted by the hydrogen of **4**, and more solvent reorganization must occur when **4** becomes complexed as compared to **2**; (4) the microdielectric properties of the cavity of **2** are between those of a vacuum and a hydrocarbon, whereas that of **4** is increased by the polarizability of the hydroxyl group. Phenol host **4**, containing six methyl groups para to the six oxygens, is comparably good at binding Li^+ and Na^+ to phenol host **5** without the methyl groups. Phenolic hosts **4** and **5** retain the high ion selectivity exhibited by the parent spherand **2**. Neither **4** nor **5** complexed K^+ detectably, and Li^+ was better bound than Na^+ by 2 to 4 kcal mol^{-1}.

In spherand **6** a quinone carbonyl group is substituted for an anisyl oxygen of **2** in the six-oxygen binding site. The resulting change in binding properties is particularly interesting because of the enforced orientation of the two sp^2 orbitals containing the unshared electron pairs of this carbonyl oxygen. The axes of these orbitals presumably are coplanar with the carbons of the quinone ring. Accordingly, the orbital containing these unshared electron pairs is tangent to the cavity, and is not positioned to contribute appreciably to the cation-binding ability of the cavity without some rehybridization of these orbitals. This question of directionality of electron density on sp^2- and sp^3-hybridized oxygens has been addressed experimentally through a statistical treatment of large numbers of X-ray crystal[16] and neutron diffraction[17] structures containing A—H···O═C and A—H···OR_2 moieties. The results conformed roughly to theory.

The present results provide a dramatic confirmation of expectation. Thus **6** binds Li^+ >10 kcal mol^{-1} and Na^+ ~10 kcal mol^{-1} less strongly than does **2**. The fact that **6** binds K^+ weakly (6.5 kcal mol^{-1}) correlates with the "soft–soft" character of K^+···O═C binding, as compared to the "hard–soft" binding of Li^+···O═C or Na^+···O═C or the "hard–hard" binding of Li^+···OR_2 or Na^+···OR_2. The reduced binding and specificity in binding of **6** as compared to **2** is also attributed to the loss in **6** of the shielding effect of the sixth methyl group, which in **2** completely protects the cavity from solvation.

A comparison of the binding properties of **6** and **8** is instructive. Host **8** contains three cyclic urea units and three anisyl units, whereas **6** contains a benzoquinone and five anisyl units. The two hosts are comparably strong binders of Li^+, but **8** is a much stronger binder of Na^+ and K^+ than is **6**. Thus the carbonyl in the quinone group of **6** appears to be much "harder" than the very "soft" urea oxygen in **8**.[12]

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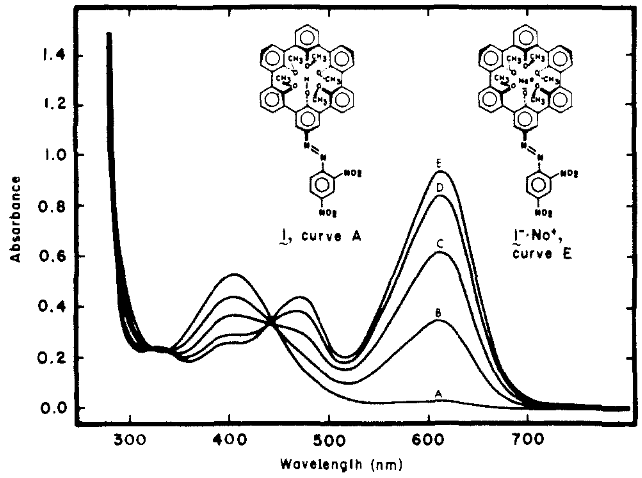


Figure 1. Change in electronic spectrum as $NaClO_4$ in $(CH_3)_2SO$ solution is added to a solution of spherand **1** in $CHCl_3$ containing an equivalent of pyridine: curve A, no salt; curve B, 0.25 equiv of salt; curve C, 0.50 equiv of salt; curve D, 0.75 equiv of salt; curve E, 1.0 (or more) equiv of salt.

In spherand **7**, the sixth methoxyl group of **2** has been replaced by a hydrogen. Interestingly, **4–7** are comparably good binders of Li^+ (10.4 to 12.5 kcal mol^{-1}), but the $-\Delta G°$ value for **7** at 6.4 kcal mol^{-1} is about 3 kcal mol^{-1} lower than those for **4–6**, which contain six oxygens. We conclude that Na^+ as a softer ion makes more use of the sixth oxygen as a binding site than does Li^+.

Host 1 as a Sodium- and Lithium-Specific Colorimetric Indicator. Dilute solutions of **1** in CH_3CN, $CHCl_3$, CH_2Cl_2, EtOH, dioxane, or dioxane–water went from faint yellow to green to deep blue when the solutions came in contact with trace amounts of Na^+. For example, a yellow 2×10^{-6} M solution of **1** in $CDCl_3$ turned blue due to the complete conversion of **1** to $\mathbf{1}^-\cdot Na^+$ by extraction of Na^+ from a Pyrex or Kymax volumetric flask upon standing for 24 h. Transfers of solutions containing **1** with Pasteur pipets made of soda lime resulted in immediate color changes. Undistilled solvents such as dioxane, ethanol, pyridine, and even some samples of CH_2Cl_2 and $CHCl_3$ contained enough Na^+ to provide instantaneous color changes when traces of **1** were dissolved in them. Accordingly, **1** was handled in quartz, Vycor, Teflon, or polypropylene containers that had been soaked in 1 N aqueous hydrochloric acid (1 h) and rinsed three times with conductivity water and dried. All solvents were freshly distilled and stored in polypropylene or Teflon containers. Yellow solutions of **1** could be stored in $CDCl_3$ in quartz NMR tubes for several days without change.

Figure 1 records changes in the UV–visible range of 0.98 mL of a 3.19×10^{-5} M solution of **1** in chloroform (3.4×10^{-5} M in pyridine) as successive portions of 1.1×10^{-5} mL of pure $(CH_3)_2SO$ containing 7.8×10^{-9} mol each of $NaClO_4$ were added. Curve A was obtained before any salt was added, and is obviously the spectrum of unionized **1**, pyridine being too weak a base to generate $\mathbf{1}^-$ (the same was true of Et_3N). Curves B, C, D, and E were obtained after additions of 0.25, 0.50, 0.75, and 1.0 equiv of $NaClO_4$. Addition of more than 1 equiv of $NaClO_4$ had no effect on spectrum E. Complexation occurred instantaneously. Similar curves were obtained in which $LiClO_4$ was substituted for $NaClO_4$, and where 75% dioxane–25% water (v/v) was substituted for $CHCl_3$–$(CH_3)_2SO$. Substitution of ultrapure (99.999%, Alfa) KCl or $KClO_4$ for the lithium or sodium resulted in no change in spectrum. *Thus reaction 1 occurs with Na^+ or Li^+, but not with K^+.*

$$\underbrace{1 + NaClO_4}_{\text{yellow}} + C_5H_5N \longrightarrow \underbrace{1^-\cdot Na^+}_{\text{blue to violet}} + C_5H_5NH^+ClO_4^- \qquad (1)$$

When a yellow solution of $\mathbf{1}\cdot NaClO_4$ in $CDCl_3$ with $\lambda_{max} = 476$ (ϵ_{max} 45 000) was treated with a trace of pyridine, it went to $\mathbf{1}^-\cdot Na^+$ with $\lambda_{max} = 606$ (ϵ_{max} 54 000). Addition of an excess of CF_3CO_2H to the resulting solution regenerated the original spectrum, as expected. Similar experiments were carried out with $\mathbf{1}\cdot LiClO_4$ in $CHCl_3$, and for both $\mathbf{1}\cdot NaClO_4$ and $\mathbf{1}\cdot LiClO_4$ in EtOH, dioxane, dioxane/water (3/1 v/v), and dioxane/water (1/1 v/v). Table II records values for λ_{max} and ϵ_{max} for the various species in these media. The differences in λ_{max} for the various sodium-containing complexes compared to the corresponding lithium-containing complexes vary from as low as 0 nm ($\mathbf{1}\cdot NaClO_4$ vs $\mathbf{1}\cdot LiClO_4$ in EtOH) to a high of 24 nm ($\mathbf{1}^-\cdot Na^+$ vs. $\mathbf{1}^-\cdot Li^+$ in dioxane/water (1/1 v/v)). These latter solutions were deep blue–violet in color.

Table II. Absorption Maxima (λ_{max}) and Molar Absorptivity Coefficients (ϵ_{max}) of Spherand **1**, Its Complexes $\mathbf{1}\cdot M^+ClO_4^-$, and Salts $\mathbf{1}^-\cdot M^+$ in Various Solvents

species	solvent	λ_{max} (nm)	ϵ_{max} (L/(mol·cm))
1	$CHCl_3$	408	26 000
$\mathbf{1}\cdot NaClO_4$	$CHCl_3$	476	45 000
$\mathbf{1}^-\cdot Na^+$	$CHCl_3$	606	54 000
$\mathbf{1}$-$LiClO_4$	$CHCl_3$	483	36 000
$\mathbf{1}^-\cdot Li^+$	$CHCl_3$	600	47 000
1	EtOH	388	17 000
$\mathbf{1}\cdot NaClO_4$	EtOH	382	13 000
		470	12 000
$\mathbf{1}^-\cdot Na^+$	EtOH	576	27 000
$\mathbf{1}\cdot LiClO_4$	EtOH	382	14 000
$\mathbf{1}^-\cdot Li^+$	EtOH	564	20 000
1	dioxane	396	19 500
$\mathbf{1}\cdot NaClO_4$	dioxane	385	15 000
		480	6 750
$\mathbf{1}^-\cdot Na^+$	dioxane	584	27 500
$\mathbf{1}\cdot LiClO_4$	dioxane	384	14 750
		480	6 500
$\mathbf{1}^-\cdot Li^+$	dioxane	576	29 000
1	dioxane/H_2O (3/1)[a]	396	17 500
$\mathbf{1}\cdot NaClO_4$	dioxane/H_2O (3/1)[a]	384	17 000
		474	15 500
$\mathbf{1}^-\cdot Na^+$	dioxane/H_2O (3/1)[a]	596	34 500
$^1\cdot LiClO_4$	dioxane/H_2O (3/1)[a]	382	16 000
		485	5 500
$\mathbf{1}\cdot LiClO_4$	dioxane/H_2O (3/1)[a]	586	35 500
1	dioxane/H_2O (1/1)[a]	400	21 000
$\mathbf{1}\cdot NaClO_4$	dioxane/H_2O (1/1)[a]	insoluble	insoluble
$\mathbf{1}^-\cdot Na^+$	dioxane/H_2O (1/1)[a]	628	25 750
$\mathbf{1}\cdot LiClO_4$	dioxane/H_2O (1/1)[a]	insoluble	insoluble
$\mathbf{1}^-\cdot Li^+$	dioxane/H_2O (1/1)[a]	604	14 500

[a] By volume.

A lithium picrate solution in water was stirred with a $CHCl_3$ solution of **1** in a quartz–Teflon chamber. Within 10 min color changes in the $CHCl_3$ layer were visible, and within 30 min, the layer was dark green. Equilibrium was reached with moderate stirring several hours later, at which point the UV–visible spectrum of the $CHCl_3$ layer showed all of the host to be in the form of $\mathbf{1}^-\cdot Li^+$ and all of the picrate acid generated to be in the water layer.

Indicator system **1** in dioxane, when treated with ultrapure (99.999%, Alfa) K_2CO_3 in a minimum amount of H_2O, did deprotonate to give the phenoxide anion, $\mathbf{1}^-$, which provided a λ_{max} of 592 nm and an ϵ_{max} of 39 250. These values compare with those in the same medium for $\mathbf{1}^-\cdot Na^+$ of 584 nm and 27 500, and for $\mathbf{1}^-\cdot Li^+$ of 576 nm and 29 000.

Changes in ^{1}H NMR when 1 and 5 Are Complexed. Changes in the ^{1}H NMR spectrum of **1** in $CDCl_3$ were observed upon addition of $NaClO_4$ or $LiClO_4$ solutions in $(CD_3)_2SO$. The methoxy peaks of uncomplexed **1** found at 2.767, 2.999, and 3.147 ppm (2:1:2 integrals, respectively) upon addition of $NaClO_4$ produced two peaks at 3.039 and 3.092 ppm (integrals 2:3, respectively, attributed to $\mathbf{1}\cdot NaClO_4$) and two additional peaks at 3.335 and 3.373 ppm (integrals 2:3, respectively, attributed to $\mathbf{1}^-\cdot Na^+$). Similarly, addition of $LiClO_4$ to **1** in $CDCl_3$ produced one set of peaks at 3.039 and 3.092 ppm (integrals 2:3, respectively, attributed to $\mathbf{1}\cdot LiClO_4$) and two additional peaks at 3.400 and 3.434 ppm (integrals 2:3, respectively, attributed to $\mathbf{1}^-\cdot Li^+$).

Similar experiments in $CDCl_3$ with the less acidic phenol **5** indicated that the ^{1}H NMR methoxy peaks at 3.072, 2.986, and 2.769 ppm (integrals 2:1:2, respectively) upon addition of 1 equiv of $NaClO_4$ moved in the complexed phenol to 3.017, 2.992, and

Table III. Values of pK_a for **1**, **1**·NaClO$_4$, **1**·LiClO$_4$, and Model Compounds **21** and **22** in 80% Dioxane–20% Water (v/v) at 30 ± 2 °C

present in solution	λ_{max} (nm)	average pK_a	range pK_a values
1, DBN	618	13.0	12.90, 13.18
1, K_2CO_3[a]	614	12.7	12.70, 12.74
1, $CaCl_2$[a]	616	12.8	13.02, 12.67
1, $MgCl_2$[a]	616	13.2	13.22, 13.20
1·LiClO$_4$	584	5.9	5.91, 5.98
1·NaClO$_4$	592	6.9	6.81, 7.04
21, DBN	624	10.8	10.80, 10.78
22, DBN	404	11.2	11.0,, 11.40

[a] 99.999%, Alfa.

2.946 (integrals 2:1:2, respectively). Addition of 1 equiv of LiClO$_4$ to **5** gave methoxy peaks at 3.113, 3.063, and 2.970 (integrals 2:1:2). When less than 1 equiv of either salt was added, all six different kinds of methoxyl peaks were present, indicating that cation–host–complex exchange was slow on the NMR time scale. Addition of a KClO$_4$ solution in $(CD_3)_2SO$ to a CDCl$_3$ solution of **1** resulted in little change in the ^{1}H NMR spectrum of **1**.

Comparisons of the spectral patterns for **1** and **5** indicate that **1** forms two different complexes with Li$^+$ or Na$^+$. Spheraplex **1**·MClO$_4$ retains its proton and counterion and is yellow. Spheraplex **1**$^-$·M$^+$ has lost a mole of HClO$_4$ to the medium and is blue. Superposition of the yellow of the former on the blue of the latter explains the green color observed when sodium or lithium salts are added to solutions of **1** in the absence of added pyridine. The ^{1}H NMR spectral results also demonstrate that **1**·MClO$_4$ and **1**$^-$·M$^+$ equilibrate rapidly on the human but slowly on the ^{1}H NMR time scales.

Differences in Acidity between Spherand 1 and Spheraplexes 1·Na$^+$ and 1·Li$^+$. The qualitative results of the previous sections indicate that **1**·Na$^+$ and **1**·Li$^+$ are much stronger acids than phenol **1**. This section reports the pK_a values of **1** in our standard medium of 80% dioxane–20% water (v/v) in the presence of Li$^+$, Na$^+$, K$^+$, Mg^{2+}, Ca^{2+}, and the bases diazabicyclo[4.3.0]non-5-ene (DBN) or K$_2$CO$_3$. Attempts to employ $(CH_3)_4NOH$ led to precipitation of Mg(OH)$_2$ and Ca(OH)$_2$ when these ions were present. An aqueous basic solution of deionized water was added to **1** in dioxane to give a solution of fully deprotonated indicator in 80% dioxane–20% water (v/v) when the base–dye combinations were **1** + DBN, **1** + NaClO$_4$ + DBN, **1** + LiClO$_4$ + DBN, **1** + K$_2$CO$_3$, model system **21**[18] + DBN, and the model system **22** + DBN. The λ_{max} and ϵ_{max} values of these solutions were measured. In the presence of MgCl$_2$ and CaCl$_2$, **1** was only 85% deprotonated by DBN. Extrapolation of ϵ_{max} values of **1**$^-$ in the presence of these salts matched the ϵ_{max} value for **1** + DBN alone. Table III records the λ_{max} values observed.

In the pK_a determinations, the concentrations of protonated and unprotonated indicator were adjusted by incremental additions of solutions of hydrochloric acid (or base where necessary) until concentrations of the protonated and unprotonated indicators equaled one another. The pHs of the resulting solutions were then measured with a pH meter calibrated against appropriate aqueous buffers. The absorbance of the phenoxide peak of **1**$^-$ and its complexes at ~600 nm provided a convenient means of measuring the concentration of the deprotonated dye. Additionally, the position of λ_{max} = 592 nm for **1**$^-$·Na$^+$ served as an indicator for partial sodium ion contamination. The observed pH readings were adjusted with ionic activity factors that correct for ionic strength changes in aqueous–dioxane mixtures at 30 °C.[19,20] The factors we used ranged from 1.5 to 3.0 pK_a units (0.4 to 0.5 mol fraction of dioxane). Model compounds **21**[18] and **22** were included in the study, and their pK_a values were similarly obtained. The same pK_a value of 10.8 was obtained for **21** when either DBN or NaOH was used as base. Table III represents duplicate determinations of the pK_a values for **1**, **1**·NaClO$_4$, **1**·LiClO$_4$, **1** in the presence of comparable molar amounts of K$^+$, Mg^{2+}, and Ca^{2+}, and **21** and **22**.

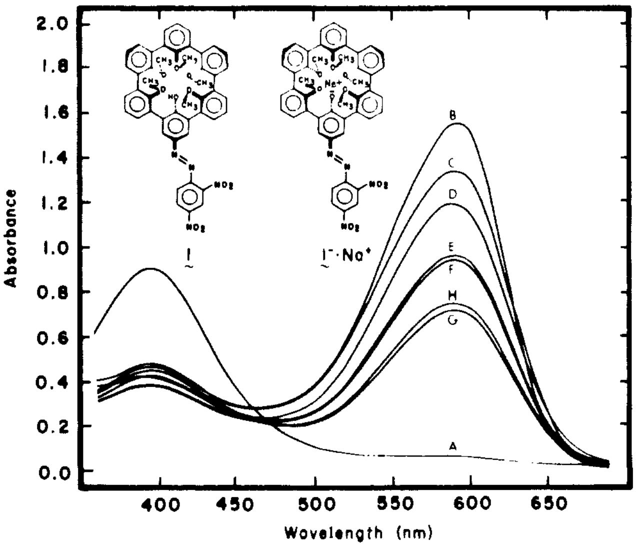
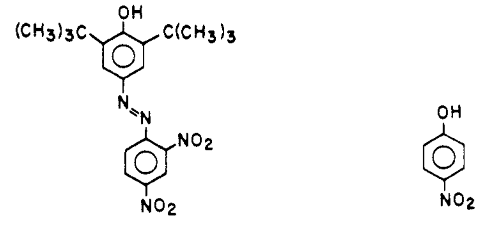


Figure 2. Changes in electronic spectrum upon additions: curve A, 0.800 mL of 4.45 × 10^{-3} M **1** in dioxane; curve B, 0.0100 mL of 0.33 M NaClO$_4$ in water; curve C, 0.1000 mL of water; curve D, 0.0200 mL of 0.0012 M HCl in water; curve E, 0.0200 mL of 0.0012 M HCl in water; curve F, 0.0300 mL of water; curve G, 0.0100 mL of 0.0012 M HCl in water; H, 0.0100 mL of water.

Chart IV



21 22

Figure 2 exemplifies the kinds of absorbance–wavelength plots obtained during the incremental approach to the equivalence point and to the 80% dioxane–20% water (v/v) solvent composition for the **1**·NaClO$_4$–**1**$^-$·Na$^+$ system. In both this and the **1**·LiClO$_4$–**1**$^-$·Li$^+$ system, no added base was needed since the anionic form of the indicator system predominated. In Figure 2, curve A is the spectrum of 0.80 mL of a 4.45 × 10^{-3} M solution of **1** in purified dioxane. Incremental additions of deionized water or of HCl in deionized water produced curves B–H, in which the solvent composition approached 80% dioxane–20% water (v/v) and [**1**·NaClO$_4$] = [**1**$^-$·Na$^+$]. The peaks at 398 nm are due to **1**·NaClO$_4$, and those at 592 nm are due to **1**$^-$·Na$^+$.

The protonated forms of **21**, **22**, and **1** predominated with spherand **1** in the absence of Na$^+$ or Li$^+$ or **1** in the presence of K$^+$, Mg^{2+}, or Ca^{2+}. In these determinations the equivalence point and standard solvent composition were reached by additions of aqueous base and deionized water. All observed pH readings represent minimum values. Although readings were taken quickly, the liquid junction in the glass microelectrode (KCl, AgCl) slowly liberated Na$^+$, electrolyte, and acid over time. Each type of contamination lowered the observed pH, manifested by downward drift of the pH with time. Corrections for solvent and electrolyte concentrations[19,20] were applied to the observed pHs to give the pK_a values of Table III.

The pK_a of **1** changes from about 13 to 5.9 when it is complexed with Li$^+$, and to 6.9 when complexed with Na$^+$. The presence of K$^+$, Mg^{2+}, or Ca^{2+} in the medium has minor, if any, effects

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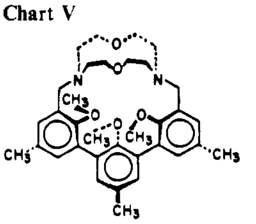
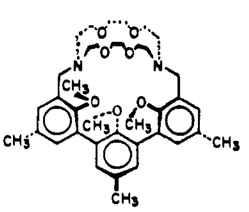
Chart V



23



24

on the pK_a of **1**. *Thus Li^+ complexed to **1** (to form **1**·Li^+) acidifies the system by a factor of about seven powers of ten, whereas Na^+ complexed to **1** acidifies the system by a factor of about six powers of ten.* This dramatic effect demonstrates the great power of preorganization in designing both high sensitivity and specificity into a chromogenic ionophore.[4] Molecular models (CPK) show **1**$^-$·Li^+ and **1**$^-$·Na^+ to be capsular complexes and indicate that **1**$^-$·K^+ as a capsular complex has little chance of forming. The 1.0 pK_a difference between **1**$^-$·Li^+ and **1**·Na^+ was spectroscopically verified. Dilute dioxane solutions of **1**·$LiClO_4$ were fully deprotonated without adding base to give **1**$^-$·Li^+ (deep violet color) whereas similar solutions of **1**·$NaClO_4$ were only partially deprotonated to provide a mixture of **1**$^-$·Na^+ and **1**·Na^+ (green color). When 89% dioxane–10% water–1% $(CH_3)_2SO$ was used as solvent, the pK_as of **1**·$LiClO_4$ and **1**·$NaClO_4$ were estimated to be 8.0 and 8.1, respectively. These results, coupled with those of Table II, suggest that **1** might be used as a chromogenic indicator system to analyze for Li^+ in the presence of Na^+ in solvents as rich in water as the solubility of the system will tolerate.

The pK_a of the noncomplexing indicator system **21** was 10.8, 2.2 pK_a units below the pK_a of **1** at 13.0. This difference is attributed to stabilization of the acid form of **1** due to the hydrogen bonding of the phenolic hydroxyl to the methoxyl of an adjacent anisyl group present in **1** but absent in **21**. The pK_a of spherand **13** in 90% dioxane–10% water (v/v) was reported to be 13.5.[8h] We determined the pK_a of **1** to be 14.0 in this same medium through the use of K_2CO_3 as base. Thus the pK_a values of spherands **1** and **13** are close to one another as expected. The pK_a of the Li^+ complex of **13** was not reported, probably because it decomplexes in the presence of water.[8h]

These results demonstrate that the high binding and selectivity associated with spherand **3** can be expressed colorimetrically through attachment of a chromogenic group. Highly preorganized cryptaspherand **23** shows both very strong and specific binding for Na^+ and **24** for K^+.[22] It is likely that by attachment of appropriate chromogenic groups to these and similar hosts, new sensitive and highly ion-specific colorimetric indicating systems can be designed and prepared that are useful for measuring alkali metal ions in body fluids.

Experimental Section

General. Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled twice from CaH_2. Benzene was distilled from $LiAlH_4$. Other solvents were dried over 3 Å molecular sieves. Ferric acetylacetonate was dried at 100 °C under vacuum prior to use. Column chromatography was performed on silica gel 60 (E. Merck, particle size 0.063–0.200 nm, 70–230 mesh ASTM). Thin-layer chromatography was performed on silica gel precoated plastic sheets (E. Merck, thickness 0.2 mm). Preparative thin-layer chromatography was conducted on 2-mm silica gel 60 plates (E. M. Merck). Melting points were measured on either a Mel-Temp or Thomas Hoover melting point apparatus and are uncorrected. Proton NMR spectra were observed on a Bruker WP-200 spectrometer in $CDCl_3$. Chemical shifts are reported in parts per million with TMS as a reference and coupling constants in hertz (Hz). Mass spectra were taken on an AE 1 Model 9 spectrometer at 70 eV. Ultraviolet spectra were recorded on a Varian Cary 219 spectrometer or a Hewlett Packard diode array spectrometer with a 7470A plotter. An Orion 901 ionanalyzer with a Sargent-Welch 30070 miniature combination electrode was used to make the pH measurements.

31,32,33,34,35,36-Hexamethoxyheptacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}]hexatriaconta-1(31),2,4,6(36),7,9,11(35),12,14,16(34),17,19,21(33),22,24,26(32),27,29-octadecaene Lithium Chloride (3·LiCl). To a 4.1-g (20 mmol) solution of dry *t*-BuBr in 120 mL of dry Et_2O was added 28 mL of 2.1 M *n*-BuLi in hexane (59 mmol). The solution was stirred at 25 °C for 30 min, and 4.8 g (15 mmol) of **20** and 28 mL of 2.1 M *n*-BuLi in hexane (59 mmol) were added. The mixture was refluxed under N_2 for 5 h. Dimetalated **20**[9b] began to precipitate within the first hour. The heterogeneous mixture was cannulated over 30 min into a flask containing a distillation apparatus, 1 L of dried benzene (at reflux temperature), and 43 g (116 mmol) of dried $Fe(acac)_3$. *CAUTION*: This cannulation must be done slowly! The ether was flash distilled. The remaining mixture was heated until gentle distillation removed 500 mL of benzene. The mixture was cooled to 25 °C, and 24.0 g of $FeCl_3$·$6H_2O$ and 900 mL of 2 N HCl were added. The solution was stirred for 24 h. The benzene and 400 mL of water were evaporated under reduced pressure, leaving a dark organic solid. The solid was filtered, dried, and triturated with Et_2O. The mixture was filtered to provide crude **3**·$LiFeCl_4$ as a light green powder (1.78 g, 28%). The solid was dissolved in 600 mL of CH_2Cl_2 and washed with two 500-mL portions of saturated aqueous solution of EDTA that was 0.24 M in LiCl and with two 500-mL portions of water. The solvent was evaporated until 200 mL of reaction mixture remained, to which 100 mL of toluene was added. The remaining liquid was evaporated under reduced pressure, leaving an organic precipitate. This solid was filtered and recrystallized from $CH_2Cl_2/C_6H_5CH_3$ at 25 °C to give **1**·LiCl as a light tan powder, 1.00 g (19.6%): mp 330 °C dec: ^{1}H NMR δ 3.112 (s, 3 H, $ArOCH_3$), 7.452–7.616 (m, 3 H, ArH); mass spectrum, 629 (30), M^+ - CH_3 628 (69), 622 (10), 597 (42), 551 (16). Anal. Calcd for $C_{42}H_{36}O_6ClLi$: C, 74.28; H, 5.34. Found: C, 73.97; H, 5.38.

31-Hydroxy-32,33,34,35,36-pentamethoxyheptacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}]hexatriaconta-1(31),2,4,6(36),7,9,11(35),12,14,16(34),17,19,21(33),22,24,26(32),27,29-octadecaene (5). Freshly distilled pure pyridine through which dry pure N_2 had just been bubbled was used in the following experiments. A solution of 89.2 mg (0.131 mmol) of **3**·LiCl in 8 mL of pyridine was bubbled with pure nitrogen for 15 min. Eight milliliters of oxygen-free conductivity water was added to produce a fluffy white precipitate. The suspension was heated at reflux under pure N_2 for 2 h and cooled to 25 °C, and the solid product was collected. This material was dissolved in 18 mL of pyridine, and the solution was added dropwise to 400 mL of refluxing 6 N hydrochloric acid. The resulting mixture was cooled to 25 °C and extracted with two 200-mL portions of $CHCl_3$. The organic layers were combined, and the solvent was removed under reduced pressure. The resulting solid was triturated with methanol and filtered to give 79.6 mg (98%) of phenol **5** as a white solid: mp 342–360 °C dec; ^{1}H NMR δ 2.769 (s, $ArOCH_3$, 6 H), 2.986 (s, $ArOCH_3$, 3 H), 3.072 (s, $ArOCH_3$, 6 H), 6.748 (s, ArOH, 1 H), 7.144–7.538 (m, ArH, 18 H); mass spectrum, 644 (11), 628 (14), 623 (46), M^+ 622 (100), 608 (18), 589 (12), 573 (18), 559 (17), 527 (11). Anal. Calcd for $C_{41}H_{34}O_6$: C, 79.08; H, 5.50. Found: C, 78.93; H, 5.52.

31,32,33,34,35-Pentamethoxyheptacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}]hexatriaconta-1(31),2,5,7,9,11(35),12,14,16(34),17,19,21(33),22,24,26(32),27,29-heptadecaene-4,26-dione (6). A 4.0-g (9.0 mmol) portion of thallium nitrate trihydrate was dissolved in 120 mL of methanol, and 360 mL of absolute ethanol was added.[10] A solution of 189 mg (0.304 mmol) of phenol **5** in 100 mL of $CHCl_3$ was added, and the resulting orange suspension was stirred for 10 min. Addition of 150 mL of water and 150 mL of $CHCl_3$ gave a brown mixture that was stirred for 15 min. The orange organic layer was separated and washed twice with water. The solvent was removed under reduced pressure, and the crude product was recrystallized from CH_2Cl_2 and EtOH to give 162 mg (84%) of quinone **6** as an orange solid: mp 285–294 °C dec; ^{1}H NMR, δ 2.868 (s, $ArOCH_3$, 6 H), 2.949 (s, $ArOCH_3$, 3 H), 3.255 (s, $ArOCH_3$, 6 H), 6.823 (s, vinyl H, 2 H), 7.10–7.55 (m, ArH, 15 H); mass spectrum, 652 (20), 645 (10), 644 (29), 640 (11), 639 (37), 638 (88), 630 (11), 625 (24), 624 (57), 613 (15), 575 (10), 78 (100). Anal. Calcd for $C_{41}H_{32}O_7$: C, 77.34; H, 5.07. Found: C, 76.94; H, 5.19.

29-[(2,4-Dinitrophenyl)azo]-32,33,34,35,36-pentamethoxyheptacyclo[25.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{22,26}]hexatriaconta-1(31),2,4,6(36),7,9,11(35),12,14,16(34),17,19,21(33),22,24,26(32),27,29-octadecaen-31-ol (1). This procedure is a modification of one applied to simpler compounds.[23] To an orange solution of 161.7 mg (0.254 mmol) of quinone **6** in 40 mL of $CHCl_3$ was added 50 mL of absolute EtOH. A solution of 5.0 g (25.2 mmol) of 2,4-dinitrophenylhydrazine and 10 mL of concentrated sulfuric acid in 75 mL of EtOH was prepared. A 4-mL (1.3 mmol) portion of this solution was added to the solution of 6 to give a red mixture, which

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was gently heated and stirred to produce an orange suspension and a yellow-orange precipitate. After 25 min the mixture was cooled to 25 °C and filtered to give 147 mg of nearly pure **1** (^{1}H NMR spectrum). This material was recrystallized from a mixture of 5 mL of $CHCl_3$ and 15 mL of EtOH to give 113 mg (54%) of pure **1** as an orange solid: mp 320–322 °C dec; ^{1}H NMR, δ 2.768 (s, $ArOCH_3$, 6 H), 3.000 (s, $ArOCH_3$, 3 H), 3.148 (2, $ArOCH_3$, 6 H), 7.167–7.563 (m, ArH, 15 H), 7.931 (d, ArH, 1 H, $J = 8.8$ Hz), 8.208 (s, ArH, 2 H), 8.538 (d of d, ArH, 1 H, $J_o = 8.8$ Hz, $J_m = 2.3$ Hz), 8.806 (d, ArH, 1 H, $J = 2.3$ Hz); mass spectrum, 818 (9), 817 (50), M^+ 816 (92), 802 (20), 785 (14), 784 (41), 755 (22), 754 (45), 741 (11), 740 (18), 643 (11) 639 (14), 638 (58), 637 (100). Anal. Calcd for $C_{47}H_{36}N_4O_{10}\cdot H_2O$: C, 67.62; H, 4.59. Found: C, 67.52; H, 4.48.

Determination of Binding Free Energies for Slowly Equilibrating Hosts. This procedure is illustrated as applied to phenol **5** and lithium picrate. A 0.00112 M solution of 3.48 mg (0.0056 mmol) of **5** in $CDCl_3$ was prepared in a 5.00-mL volumetric flask. A 1.00-mL aliquot was placed in a quartz tube fitted with a Teflon stopper and sleeve. A 1.00-mL aliquot of 0.000962 M lithium picrate in D_2O was added. The tube was stoppered, sealed with parafilm, and stirred at 25 °C with magnetic stirring. After 2 days, stirring was discontinued, the layers were allowed to separate, and 0.100-mL samples of each layer were diluted to 5.00 mL with acetonitrile with use of volumetric glassware. Absorbance readings were taken at 380 nm. Aliquots were taken at intervals until the absorbance readings remained constant. From the equilibrium–UV–absorbance values, the K_a and binding free energies were determined.[11] Table I reports the results.

Determinations of $\mathbf{p}K_a$ Values of Host 1 in the Presence of Potential Complexing Agents. The following procedures were representative. A yellow 4.45×10^{-5} M solution of **1** was prepared in a polypropylene volumetric flask with freshly distilled dioxane. An 0.800-mL portion of this solution gave an absorbance of 0.89 at 400 nm in a quartz UV cell. All additions were made directly into the UV cell with SMI micro/pettors. Solutions of more than 0.200 mL were added with disposable polypropylene cartridges. Solutions of less than 0.200 mL were added with disposable glass pipets which had been rinsed ten times with deionized water just prior to use to remove residual surface sodium. Solutions were added as quickly as possible with the glass pipets to minimize leaching of sodium ion from the glass. A 0.0100-mL portion of a 0.33 M aqueous solution of $NaClO_4$ was added to give a mixture of $\mathbf{1}\cdot NaClO_4$ and $\mathbf{1}^-\cdot Na^+$ with absorbances of 0.48 and 1.51 at 394 and 590 nm, respectively. Addition of 0.1800 mL of deionized water gave absorbances of 0.40 and 1.27 at 393 and 592 nm, respectively. Addition of 0.0100 mL of purified pyridine gave a blue solution of $\mathbf{1}^-\cdot Na^+$ with an absorbance of 1.51 at 592 nm.

A solution of 0.800 mL of **1** in dioxane, 0.0100 mL of an 0.33 M aqueous $NaClO_4$, and 0.1000 mL of deionized water was prepared to provide absorbances of 1.29 at 592 nm and 0.38 at 396 nm. Addition of two 0.0200-mL portions of a 1.2×10^{-3} M hydrochloric acid solution gave final absorbances of 0.95 at 590 nm and of 0.45 at 394 nm. The addition of 0.0300 mL of water gave absorbances of 0.93 at 592 nm and 0.43 at 395 nm. A 0.0100-mL portion of 1.2×10^{-3} M hydrochloric acid was added and gave absorbances of 0.71 at 590 nm and 0.49 at 396 nm. The microelectrode was inserted into the UV cell to give a reading of 4.59. Addition of 0.0100 mL of deionized water gave absorbances of 0.74 at 592 nm and 0.47 at 395 nm. An observed pH of 4.81 was recorded for this 80% dioxane–20% water (v/v) solution. A correction factor of 2.0 pK_a units for a solution with 3×10^{-3} M electrolyte in a 0.45 mol fraction of dioxane[20] was added to our pK_a observed value to give a corrected pK_a value of 6.81. The experiments involving **21**, **22**, DBN, K_2CO_3, $LiClO_4$, $CaCl_2$, and $MgCl_2$ were conducted with use of similar procedures and molar concentrations of salts and acids or bases. Each time the microelectrode was used it was calibrated with 4.05 and 7.00 aqueous buffers, or with 7.00 and 10.00 aqueous buffers, whichever was appropriate.

The pK_a values determined for $\mathbf{1}\cdot NaClO_4$ and $\mathbf{1}\cdot LiCl_4$ were shown to be rather insensitive to the exact amount of acid added as the equivalence point for $[\mathbf{1}\cdot MClO_4] = [\mathbf{1}^-\cdot M^+]$ was approached. For example, when 75% of the acid had been added to reach the equivalence point for **1** complexing lithium, the corrected[20] pH of the medium was 6.0. When 112% of the acid needed had been added, the corrected[20] pH of the medium was 5.8. At the equivalence point, the pH was 5.9.

The pK_a values of the nonhost model compound **21** were determined with both NaOH and DBN as base by the above method in 80% dioxane–20% water (v/v). The pK_a value was 10.8 in each case. The pK_a values of $\mathbf{1}\cdot LiClO_4$ and $\mathbf{1}\cdot NaClO_4$ were estimated to be 8.0 and 8.1, respectively, in 89% dioxane–10% water–1% $(CH_3)_2SO$. That of **1** titrated with K_2CO_3 in 90% dioxane–10% water was estimated to be 14.0. The correction factors used with solvent systems of greater than 86% dioxane–water required extrapolation of reported values.[20]

Registry No. **1**, 111615-33-9; $\mathbf{1}^-$, 111583-16-5; $\mathbf{1}^-\cdot Li^+$, 111583-20-1; $\mathbf{1}^-\cdot Na^+$, 111583-21-2; $\mathbf{1}\cdot NqClO_4$, 111583-28-9; $\mathbf{1}\cdot LiClO_4$, 111583-30-3; **2**, 72526-85-3; $\mathbf{3}\cdot LiFeCl_4$, 111583-23-4; $\mathbf{3}\cdot LiCl$, 111583-24-5; $\mathbf{3}\cdot NaCl$, 111583-25-6; **4**, 72526-87-5; **5**, 111583-17-6; $\mathbf{5}^-\cdot Li^+$, 111583-26-7; **6**, 111583-18-7; **7**, 111583-19-8; **16**, 89827-45-2; **20**, 83604-34-6; **21**, 33349-21-2; **22**, 100-02-7; Na^+, 17341-25-2; Li^+, 17341-24-1; K^+, 24203-36-9; Ca^{2+}, 14127-61-8; Mg^{2+}, 22537-22-0; lithium picrate, 18390-55-1; sodium picrate, 3324-58-1; dioxane, 123-91-1; DBN, 3001-72-7; 2,4-dinitrophenylhydrazine, 119-26-6.

Enzymes in Organic Synthesis. 38.[1] Preparations of Enantiomerically Pure Chiral Hydroxydecalones via Stereospecific Horse Liver Alcohol Dehydrogenase Catalyzed Reductions of Decalindiones[2,3]

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Abstract: Preparative-scale horse liver alcohol dehydrogenase catalyzed reductions of symmetrical and racemic *cis*- and *trans*-decalindiones occur with concurrent regio- and stereospecificity to give good yields of enantiomerically pure keto alcohol products. In each case, the reduction occurs to give the (*S*)-chirality alcohol in a manner that is completely predicted by the cubic section active-site model. The chiral synthon utility of such keto alcohols is illustrated by a direct and efficient synthesis of (+)-(4*R*)-twistanone from *cis*-decalin-2,7-dione in 51% overall yield.

The broad spectrum of asymmetric synthetic opportunities provided by the use of enzymes as chiral catalysts is now well documented.[4] Horse liver alcohol dehydrogenase (HLADH[5]), a commercially available nicotinamide coenzyme dependent en-