Host–Guest Complexation. 3. Organization of Pyridyl Binding Sites[1a,2]

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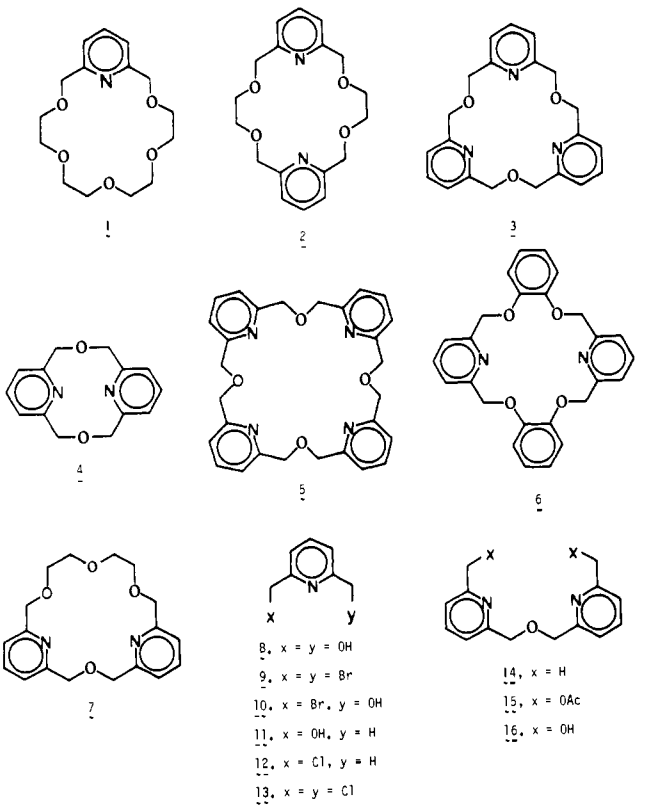
Abstract: Six new multiheteromacrocycles have been prepared containing as part of the major ring system from one to four 2,6-pyridinedimethylyl units. The pK_as of these compounds were comparable to those of open-chain models except for that of *sym*-dipyridyl-12-crown-4, whose conjugate acid was 4 kcal/mol more stable than the others. The 18-membered cycles gave free energies of association for complexation with *t*-$BuNH_3SCN$ in $CDCl_3$ about 5 kcal/mol more negative (complexes more stable) than either the 12- or the 24-membered ring systems. In $CDCl_3$ for five 18-membered host compounds containing widely different binding units, *t*-$BuNH_3SCN$ was better complexed than *t*-$BuNH_3Cl$ by 2.9 ± 0.1 kcal/mol at 0 °C. Of the 13 possible 18-membered ring pyridocycles containing six binding sites that are either O or N, three were synthesized. The free energies of complexation of these cycles and 18-crown-6 with *t*-$BuNH_3Cl$ in $CDCl_3$ were determined at 0 °C and estimated at 24 °C. The values for three of these cycles were dissected into six host–guest contact site parameters (four different kinds) whose addition equaled the free energies of association of host and guest. The parameters taken in appropriate combinations dictated by host structure were then used to calculate the free energies of association of the fourth cycle. The measured and calculated values were in reasonable agreement. The four different kinds of free-energy contact site parameters were then used to predict the free energies of association of the remaining unsynthesized ten cycles.

The preceding paper of this series[3] reported the synthesis and binding properties of a series of macrocyclic polyethers containing pentamethylene, *m*-xylyl, *p*-phenylene, furan-2,5-dimethylyl, and tetrahydrofuran-2,5-dimethylyl combined with dimethylene and oxygen units. The association constants of these, of 18-crown-6,[4] of benzo- and of dibenzo-18-crown-6[4] with *tert*-butylammonium thiocyanate in $CDCl_3$ were estimated at 24 and 0 °C. The free energies of association were calculated and dissected into free-energy contact site parameters which for similarly shaped complexes were roughly additive. The enthalpies of complexation rather than the entropies provided the main driving force for forming the complexes in $CDCl_3$. Convergence of binding sites in a preorganized array in the host and a stereoelectronic matching of binding sites in hosts and guests provided the highest binding free energies.

This paper reports the study of cycles **1–7** that incorporate from one to four pyridine-2,6-dimethylyl units into macrocyclic polyethers. The Results section presents the syntheses of compounds **1–7**, the pK_a values of monoprotonated cycles **1–5**, and the association constants of **1–7** and model ethers with *tert*-butylammonium thiocyanate and chloride in $CDCl_3$. The Discussion section includes the following topics: the relationship between structure and pK_a values; complementary vs. noncomplementary relationships between hosts and guests; the effect of counterion on the free energies of binding of *tert*-butylammonium ion; free-energy contact site parameters; and entropy and enthalpy contributions to binding.



Results

Syntheses and pK_a Determinations. Macrocycles that contain 2,6-disubstituted pyridine units as part of the major ring have been reported combined with CH_2CH_2 units,[5a,b] with CH_2SCH_2 units,[5c] with CH_2SCH_2 coupled to CH_2OCH_2 units,[5d] and with CH_2OCH_2 coupled to *o*-$C_6H_4O_2$ units.[5e] We report here the synthesis of cycles **1–6**, and of **7** in an impure state. All of the cycles possess the common feature of heteroatoms separated by two carbons as the framework of the macroring.

Treatment of diol **8**[6] with hydrobromic acid at 120 °C gave recovered **8** (39%), **9** (16%), and **10** (41%). In tetrahydrofuran (THF) at 25 °C, **11**[5a] was metalated with NaH, and the product was coupled with **12**[5a] to give **14** (74%). This dipyridine ether was oxidized (AcOOH) to its corresponding *N,N'*-dioxide, which when heated in acetic anhydride[6] at 100 °C gave **15** (17% overall). Hydrolysis of **15** gave diol **16** (90%).

Monopyrido compounds **8–10** and **13**[5a] and dipyrido compound **16** were the starting materials for the critical ring closing reactions. Treatment of diol **8** with tetraethylene glycol ditosylate in THF–*t*-BuOK gave monopyridocycle **1** (29%). To a mixture of ethylene glycol and NaH in THF was added dibromide **9** to give dipyridocycle **2** (18%). Diol **16** and dibromide **9** in THF–NaH gave tripyridocycle **3** (32%). Tripyridocycle **3** was also produced (1%) along with dipyridocycle **4** (6%) and tetrapyridocycle **5** (6%) when bromo alcohol **10** was treated with NaH in THF. These oligomeric compounds were separated by gel permeation chromatography. Dipyridocycle **4**

Table I. Conjugate Acid pK_as of Pyridocycles and Open-Chain Models in Water at 20 °C

Compound		Values of pK_a	
Name	No.	Monoprotonated	Diprotonated
Pyridine[a]		5.1	
2,4,6-Trimethylpyridine[a]		7.4	
2,6-Bis(methoxymethyl)pyridine		4.9	
Monopyrido-18-crown-6	**1**	4.8	
sym-Dipyrido-18-crown-6	**2**	5.3	3.6
Tripyrido-18-crown-6	**3**	5.3	3.7[b]
sym-Dipyrido-12-crown-4	**4**	7.9	<3
Tetrapyrido-24-crown-8	**5**	4.8[b]	>3

[a] An equimolar mixture of pyridine and 2,4,6-trimethylpyridine gave pK_as of 5.1 and 7.4. [b] Calculated as the pH at half titration.

Table II. Molar Ratios of *t*-BuNH$_3^+$ X$^-$ to Hosts (R).[a] Association Constants (K_a), and Free Energies ($\Delta G°$) for Association in $CDCl_3$

Host no.	X$^-$	Temp 24 °C			Temp 0 °C		
		R	K_a, M^{-1}	ΔG, kcal/mol	R	K_a, M^{-1}	ΔG, kcal/mol
1	SCN	0.61	5 800 000	−9.20	0.92	186 000 000	−10.34
2	SCN	0.40	1 830 000	−8.52	0.79	46 300 000	−9.59
4	SCN	0.08	780[b]	−3.93	0.09	2 260[b]	−4.20
5	SCN	0.07	690[b]	−3.86	0.12	3 110[b]	−4.37
17	SCN	0.51	3 000 000[c]	−8.81	0.76	32 800 000[d]	−9.40
18	SCN	0.22	615 000	−7.88	0.55	10 600 000	−8.79
19	SCN	0.10	209 000	−7.24	0.19	1 240 000	−7.62
1	Cl	0.52	123 000[e]	−6.93	0.90	888 000[f]	−7.44
2	Cl	0.30	47 300	−6.36	0.64	157 000	−6.50
3	Cl	0.45	94 600	−6.77	0.84	508 000	−7.14
17	Cl	0.50	113 500[g]	−6.88	0.73	244 000[h]	−6.74
18	Cl	0.17	18 900	−5.82	0.37	48 200	−5.86
19	Cl	0.08	9 460	−5.41	0.09	7 610	−4.86

[a] ^{1}H NMR measured. [b] Values twice these numbers were obtained on scale C and were divided by 2 to normalize them to scale A (ref 3) on which the other SCN salts were obtained. The normalized values are recorded here. [c] Corrected for 15% of total host dissolved at equilibrium in D_2O phase, which changed K_a by 6%. [d] Corrected for 12% of total host dissolved at equilibrium in D_2O phase, which changed K_a by 11% (see ref 3). [e] Corrected for 6% of total host dissolved at equilibrium in D_2O phase, which changed K_a by 1% (see ref 3). [f] Corrected for 2% of total host dissolved at equilibrium in D_2O phase, which changed K_a by 1% (ref 3). [g] Corrected for 11% of total host dissolved at equilibrium in D_2O phase, which changed K_a by 1% (ref 3). [h] Corrected for 5% of host dissolved at equilibrium in D_2O phase, which changed K_a by 1% (ref 3).

(1%) and tetrapyridocycle **5** (20%) were also obtained by treating diol **8** in THF–NaH with dibromide **9**. From catechol and dichloride **13**[5a] in THF–*t*-BuOK was produced dibenzodipyridocycle **6** (9%).[7] Unsymmetrical dipyridocycle **7** was produced in about 90% purity (^{1}H NMR) when diol **16** in THF–NaH was treated with diethylene glycol ditosylate. From **9** and sodium methoxide was produced 2,6-bis(methoxymethyl)pyridine.

A crystalline 1:1 complex of *t*-BuNH$_3^+$SCN$^-$ and tripyridocycle **3** was isolated when tetramethylsilane was added to a solution of the two components in chloroform. The complex gave a good analysis, and the major peak in its mass spectrum corresponded to the mass of the free cycle. Although the complex could be recrystallized from CH_2Cl_2–pentane to give clear crystals, they become cloudy and shattered within 1 day at either 25 °C or 70 K. Therefore an x-ray crystal structure determination was not made.

The pK_as of the conjugate acids of pyridocycles **1**–**5** were determined (±0.2) in water with a glass electrode and pH meter at 20 °C by titrations with aqueous lithium hydroxide and hydrochloric acid solutions. Table I reports the values obtained as well as those of pyridine itself, 2,4,6-trimethylpyridine,[8] and 2,6-bis(methoxymethyl)pyridine.

Determination of Association Constants. Association constants in $CDCl_3$ at 24 and 0 °C were determined for cycles **1**, **2**, **4**, and **5** as hosts (H) and *t*-BuNH$_3$SCN as guest. The extraction ^{1}H NMR method described earlier was employed, which involved extraction of D_2O solutions of guest salt with $CDCl_3$ solutions of host. Table II records the R values (ratio of guest to host in $CDCl_3$ layer) and the values for the association constants defined by eq 1. The values for a few cyclic polyethers determined previously are also listed for reference purposes.[3] A new scale was developed based on *t*-BuNH$_3$Cl for application to hosts that complex alkylammonium salts very strongly. Because of the very low solubility of *t*-BuNH$_3$Cl in $CDCl_3$, the distribution constant (K_d) at 24 °C was only very grossly estimated.[3] Since $K_a = K_dK_e$ (K_e is the extraction constant in the presence of host),[3] K_a values at 24 °C cannot be used in comparisons affected by the uncertainty of K_d. The value of K_d at 0 °C for *t*-BuNH$_3$Cl was obtained (see Experimental Section). For comparison, the R and K_a values at 24 and 0 °C on the chloride salt scale were estimated for the macrocyclic polyethers 18-crown-6 (**17**),[4] benzo-18-crown-6 (**18**),[4] and furanyl-18-crown-6 (**19**).[3,9] Table II reports the results as well as the derived free energies of complexation. The Experimental Section provides the details of the methods and equations used.[3]

$$H + t\text{-BuNH}_3^+X^- \underset{CDCl_3}{\overset{K_a}{\rightleftharpoons}} t\text{-BuNH}_3^+ \cdot H \cdot X^- \qquad (1)$$

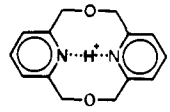
The assumptions involved in the treatment were as follows: that the salt in D_2O was dissociated; that the uncomplexed salt in the $CDCl_3$ was ion paired, but monomeric; that the complex in the $CDCl_3$ layer was 1:1 and ion paired. Experimentally (^{1}H NMR), it was observed that trivial amounts of host were in the D_2O layer at equilibrium except when **1** and **17** were used, in which cases corrections of K_a for the small amounts involved ranged from 1 to 11%.

The low solubility of dibenzodipyridocycle **6** inhibited study of its complexing properties.

Discussion

Complementary vs. Noncomplementary Relationships between Hosts and Guests. The pK_a values in water at 20 °C (Table I) of the monoprotonated pyridocycles **1**, **2**, **3**, and **5** range from 4.8 to 5.3, which places them much closer to that of 2,6-bis(methoxymethyl)pyridine (4.9) than to 2,4,6-trimethylpyridine (7.4). The methyleneoxy groups substituted in the 2,6 positions on the pyridine ring of the pyridocycles and 2,6-bis(methoxymethyl)pyridine should provide about the same steric inhibition of solvation of both the base and conjugate acid as that provided by the 2,6-methyl groups of 2,6-dimethylpyridine. Thus the ~2.4 pK_a units increased acidity of these protonated cycles and their open-chain model must be associated with the effect of the oxygens of the 2,6-CH_2O groups on the relative stabilities of base and conjugate acid. Corey-Pauling-Koltun (CPK) molecular models of the monoconjugate acids of **1**, **2**, **3**, and **5** indicate that any direct intramolecular hydrogen bonding of the NH^+ with either the ring oxygens or the nitrogens involves poor bond angles and conformations. The pK_a values for the diprotonated cycles, as expected, are depressed even more by <3-3.7 pK_a units owing to the accumulation of two positive charges in the same microenvironment.

Unlike the protonated form of the other pyridocycles, that of dipyridocycle **4** places the second pyridine ring in an ideal position to hydrogen bond the acidic proton and stabilize it (CPK molecular models). In the molecular model, which resembles **20**, the two oxygens are held very close to the sides of



20

the N-H^+···N bond, but the electron pairs are poorly positioned to stabilize the H^+. In **20**, the pyrido rings are close to being coplanar, but the oxygens lie slightly out of the plane with either both above, or one above and one below, that plane. An x-ray structure of a salt of **20** should prove interesting. Structure **20** suggests why the conjugate acid of this cycle has a pK_a of 7.9, about 4 kcal/mol more stable relative to its free base than the conjugate acids of either **1** or **5** are relative to their free bases. Thus host **4** possesses binding sites more complementary to a proton as guest than do any of the other hosts studied.

For *t*-$BuNH_3^+$ as guest, CPK models suggest that 18-membered ring cycles **1**, **2**, **3** should provide six binding sites ideally located for O···HN^+, O···N^+, and N···N^+ interactions. In contrast, the smaller cycle **4** possesses only four binding sites and these are poorly arranged to accommodate *t*-$BuNH_3^+$. Larger cycle **5** possesses eight possible binding sites, but their organization is not complementary to the tripod arrangement of the quest. The K_a values (Table II) for **1** and **2** complexing *t*-$BuNH_3SCN$ are about 5×10^4 higher than those for **4** and **5**. Thus the free energy of binding is about 4.6 kcal/mol more favorable when the numbers and locations of sites in host and guest are complementary than when they are noncomplementary.

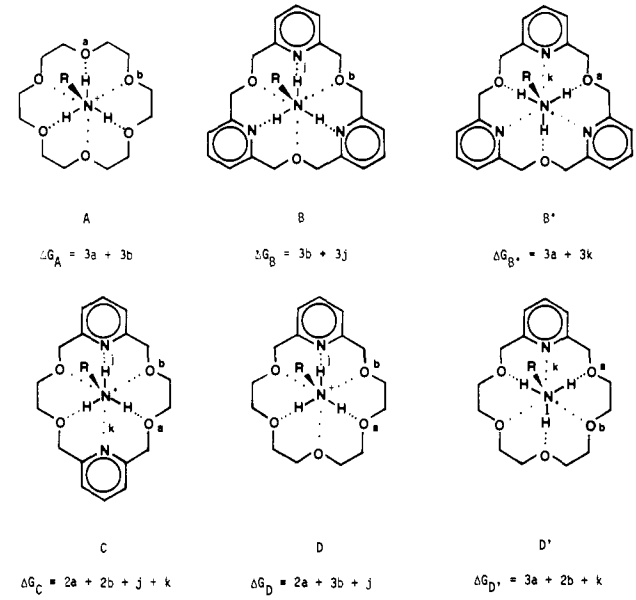
Effect of Counterion on the Free Energies of Binding. The data in Table II provide a measure of the effect of anion character on the free energies of complexation of *t*-$BuNH_3^+X^-$ with five cycles. The five hosts, **1**, **2**, **17**, **18**, and **19**, all have in common an array of six binding sites well located in the 18-membered ring for binding to *t*-$BuNH_3^+$. However, the binding electron pairs are on heteroatoms that are very different from one another. These include $(CH_2)_2O$, $(CH{=}C)_2O$, ArO, and ≥N units. The ΔG values on the SCN^- scale vary by as much as 2.7 kcal/mol, and on the Cl^- scale by as much as 2.6 kcal/mol. The interesting question arises as to whether the two scales are linearly related to one another. For the five compounds, $\Delta G^{SCN^-} - \Delta G^{Cl^-} = -2.08 \pm 0.15$ kcal/mol (standard deviation) at 24 °C and 2.87 ± 0.33 kcal/mol (standard deviation) at 0 °C. Thus the substitution of Cl^- for SCN^- in the salt costs roughly 2.9 kcal/mol at 0 °C binding energy with these highly organized hosts. Because the charge is more localized on Cl^- than on SCN^-, more charge separation is involved when host complexes *t*-$BuNH_3^+Cl^-$ than when it complexes *t*-$BuNH_3^+SCN^-$.

The existence of this roughly linear relationship allows merging of scales to generate a much broader range of comparisons of structure and binding ability than would be available should this relationship not exist. It also allows ΔG and K_a values on one scale to be estimated from their values on the other. For example, ΔG and K_a values were determined for the tripyridocycle **3** on the Cl^- but not on the SCN^- scale. The relationship predicts that on the SCN^- scale, **3** should have $\Delta G = -10$ kcal/mol and $K_a \sim 100\,000\,000\,M^{-1}$ at 0 °C. This roughly linear relationship also implies that the structures of the complexes based on the SCN^- and Cl^- salts are similarly structured.

Free Energy Contact Site Parameters. In the prior paper of this series,[3] the free energies of binding of four 18-membered macrocyclic ethers with *t*-$BuNH_3^+SCN^-$ in $CDCl_3$ were dissected into six contact site parameters. The macrocyclic ethers contained ethyleneoxy, furan-2,5-dimethyloxy, and *o*-phenyleneoxy units strung together to form similarly shaped macrocycles. It was found that the six sites contributed roughly additively (independently of their relative numbers and locations) to the total ΔG of binding in these and other similar cycles. Comparisons between calculated and determined ΔGs of association in $CDCl_3$ at 24 and 0 °C were in reasonable agreement for complexes of three additional cycles.

Similar hypotheses are applied to the *t*-$BuNH_3^+Cl^-$ complexes A, B, C, and D of Chart I. The letters *a*, *b*, *j*, and *k* de-

Chart I



fine the contributions to the total free energies of association for each complex (ΔG_A, ΔG_B, etc.). Listed below the formulas are equations that relate ΔG_A, ΔG_B, etc. to *a*, *b*, etc. Combinations of the equations for A, B, and C provide eq 2, 3, and 4 in which $(a + b)$, $(b + j)$, and $(j + k)$ are expressed in terms of ΔG_A, ΔG_B, and ΔG_C. The equation for D of Chart I is solved for ΔG_D in terms of ΔG_A and ΔG_B to give eq 5.

$$a + b = (1/3)\Delta G_A \quad (2)$$

$$b + j = (1/3)\Delta G_A \quad (3)$$

$$j + k = \Delta G_C - (2/3)\Delta G_A \quad (4)$$

$$\Delta G_D = (2/3)\Delta G_A + (1/3)\Delta G_B \quad (5)$$

If we assume that the values of ΔG reported in Table II at 24 and 0 °C for cycles **17**, **3**, **2**, and **1** and *t*-$BuNH_3^+Cl^-$ actually involved structures A, B, C, and D, respectively, then eq 5 allows ΔG_D values at the two temperatures to be calculated from ΔG_A and ΔG_B values at the two temperatures. A comparison between the calculated and observed values of ΔG_D indicates that they are in reasonable agreement with one another. Although the probable gross error in measuring the K_d value for *t*-$BuNH_3^+Cl^-$ at 24 °C is carried through into the K_a values, the error cancels when K_a values for different compounds are submitted to this analysis.

	24 °C	0 °C
Calculated ΔG_D, kcal/mol	−6.8	−6.9
Observed ΔG_D, kcal/mol	−6.9	−7.4

Rotation of the *t*-$BuNH_3^+$ ion in complexes A and C of Chart I produces the same equations as those written below the formulas. However, a similar operation applied to complex B gives B′, and to complex D gives D′. The equations for B′ and D′ are different than those for B and D, respectively. Combinations of the equations for A, B′, and C gives the additional equations 6 and 7 in which $(a + k)$ and $(b + j)$ are expressed in terms of ΔG_A, $\Delta G_{B'}$, and ΔG_C. The equation for D′ of Chart I is solved for $\Delta G_{D'}$ in terms of ΔG_A and $\Delta G_{B'}$ to give eq 8.

$$a + k = (1/3)\Delta G_{B'} \quad (6)$$

$$b + j = -(1/3)\Delta G_A - (1/3)\Delta G_{B'} + \Delta G_C \quad (7)$$

$$\Delta G_{D'} = (2/3)\Delta G_A + (1/3)\Delta G_{B'} \quad (8)$$

If we assume that the value of ΔG reported for cycle **3** and *t*-$BuNH_3^+Cl^-$ in Table I at 24 and 0 °C actually involved structure B′, and that cycle **1** and the salt gave D′, then eq 8 allows $\Delta G_{D'}$ to be calculated from ΔG_A and $\Delta G_{B'}$ values at the two temperatures. Comparison of eq 5 and 8 indicates that they have the same form, and $\Delta G_{D'}$ based on one set of structures gives values equal to ΔG_D based on the other set. Thus the values calculated for formation of complexes are independent of whether structures B and D or B′ and D′ are chosen.

The hypothesis that *a*, *b*, *j*, and *k* values are structure independent requires that if B is more stable than B′, then D must be more stable than D′, or vice versa. Equations 9 and 10 derived from the equations of Chart I for B, B′, D, and D′ indicate the basis for this assertion. If $\Delta G_B - \Delta G_{B'}$ is negative, then $\Delta G_D - \Delta G_{D'}$ must be negative. If $\Delta G_B - \Delta G_{B'}$ is positive, then $\Delta G_D - \Delta G_{D'}$ must be positive.

$$\Delta G_B - \Delta G_{B'} = 3[(j - k) - (a - b)] \quad (9)$$

$$\Delta G_D - \Delta G_{D'} = (j - k) - (a - b) \quad (10)$$

Complexes A and C of Chart I are free of the structural ambiguities encountered with B vs. B′ or D vs. D′. Combination of the equations for A and C gives eq 11. Solution of eq 11 in terms of the ΔG_A values measured for complexation of *t*-$BuNH_3^+Cl^-$ with 18-crown-6 (**17**) and ΔG_C values for complexation with *sym*-dipyridocycle **2** (Table II) provides the values listed.

$$\Delta G_A - \Delta G_C = (a + b) - (j + k) \quad (11)$$

$$\text{at 24 °C } (a + b) - (j + k) = -0.51 \text{ kcal/mol}$$

$$\text{at 0 °C } (a + b) - (j + k) = -0.24 \text{ kcal/mol}$$

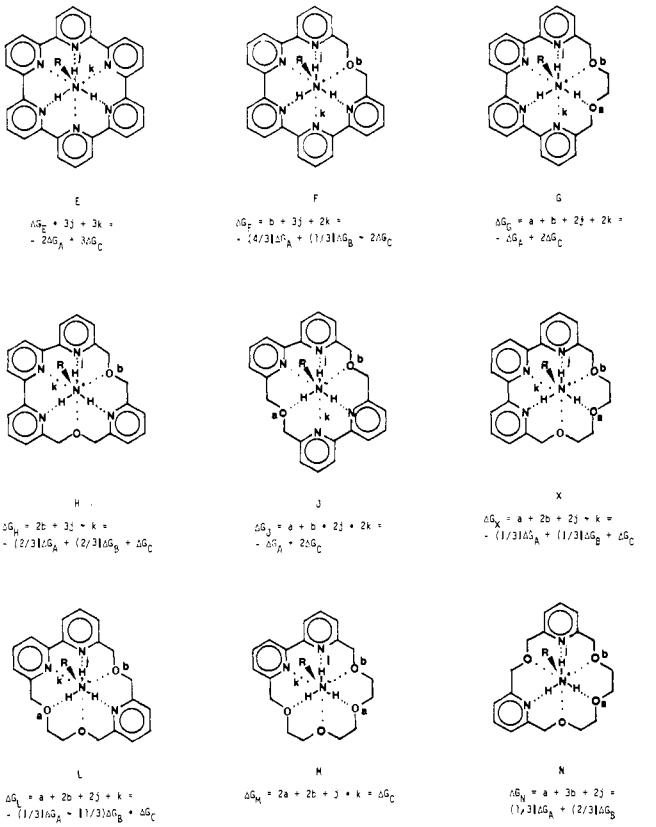
These relationships indicate that at both temperatures, $a + b$ provides more binding than $j + k$. Unfortunately, the data provide no clues as to the relative values of *a* and *b*, or of *j* and *k*, or of *a* and *j* or of *b* and *k*. Any conclusions about these relationships depend on the relative stabilities of B vs. B′, or of D vs. D′.

Table III. Predicted Free Energies of Association of *t*-$BuNH_3^+Cl^-$ with Hosts of Complexes E–N of Chart II at 0 °C

Complex	ΔG of assoc, kcal/mol	Complex	ΔG of assoc, kcal/mol
E	−6.0	K	−6.6
F	−6.4	L	−6.6
G	−6.3	M	−6.5
H	−6.8	N	−6.9
J	−6.3		

Chart II lists the structures of the nine possible additional complexes of *t*-$BuNH_3^+Cl^-$ with compounds as yet uncharacterized in which $(CH_2)_2O$ and (or) 2,6-pyrido units are combined to form 18-membered rings. Rotation of the *t*-$BuNH_3^+$ group 60° in structures E, G, J, and M reproduces the structures written, whereas different structures are obtained for F(F′), H(H′), K(K′), L(L′), and N(N′). These isomeric (primed) structures are not listed. Below each complex is placed the equation which relates its free energy of formation in $CDCl_3$ to the contact site parameters and to ΔG_A, ΔG_b, and ΔG_C. With the use of the ΔG values from Table I for formation of complexes at 0 °C between *t*-$BuNH_3^+Cl^-$ and 18-crown-6 (ΔG_A), trispyridocycle **3** (ΔG_B), and *sym*-dipyridocycle **2** (ΔG_C), estimated values for the free energies of formation of these unknown complexes are predicted. Table III lists the ΔG values calculated at 0 °C, and they range from −6.0 to −6.9. Use of alternate structures F′, H′, K′, L′, and N′ in combination with structures A, B′, and C gives the same values as those listed in Table III. If this treatment is valid, the best hosts for complexation of the *t*-$BuNH_3^+$ ion have now been synthesized except for N, which we obtained only in an impure state. However, the pyrido and ether oxygens show a different balance of complexing abilities toward different *metal* cations, and compounds E–N should be interesting hosts to

Chart II



synthesize both to test the predictions of this paper and to examine their binding properties toward metal ions.

A number of interesting relationships are visible in the complexes of Charts I and II. Thus $\Delta G_C = \Delta G_M$, $\Delta G_G = \Delta G_J$, and $\Delta G_K = \Delta G_M$. The predicted values of ΔG_E, ΔG_G, ΔG_J, and ΔG_M depend only on the values of ΔG_A and ΔG_C. Structures A and C do not have isomers. A knowledge of measured association constants for the hosts of Chart II still would not provide any information with respect to the relative values of *a* and *b*, or *j* and *k*, of *a* and *j*, or of *b* and *k*, unless B and B′, G and G′, F and F′, H and H′, etc., could be distinguished by some experimental measurement.

Experimental Section

General. Temperatures are uncorrected. Characterizing ^{1}H NMR spectra were run on a Varian T-60 spectrometer and analytical spectra on an HA-100 Varian spectrometer. All chemical shifts reported are relative to tetramethylsilane. All ether-forming reactions were run under nitrogen. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen just prior to use. Gel permeation chromatographs were run on a $^3/_8$ in. by 18 ft column of 200/400 Bio Beads SX-8 with THF as the elution solvent. Osmometric molecular weight determinations were made on a Mechrolab Model 301 A osmometer. Chloroform solutions between 0.02 and 0.10 M in solute were measured. A standard curve for eight solutions of benzil (0.004–0.09 M) was prepared for calibration. The molecular weight of triphenylmethane, determined as a test of sensitivity, was found to be 250 mass units, calculated 244. *Caution:* We urge that tests for peroxides be made on products of reactions employing peroxyacetic acid during isolation operations.

2,6-Bis(hydroxymethyl)pyridine (8). A solution of 31 g (0.186 mol) of 2,6-pyridinedicarboxylic acid in 200 mL of thionyl chloride was heated at reflux for 10 h. Thionyl chloride was distilled, and the residue was cooled in an ice bath as 250 mL of absolute methanol was added dropwise. The resulting solution was heated at reflux for 30 min, and 150 mL of methanol was distilled. The solution was cooled in an ice bath, and the dimethyl 2,6-pyridinedicarboxylate which formed was filtered and washed with cold (0 °C) methanol to yield 34.6 g (95%) of the diester, mp 115–120 °C (lit. mp 121 °C).[10a] A suspension of 29 g (0.15 mol) of the above diester in 400 mL of absolute ethanol was stirred and cooled in an ice bath as 26 g (0.7 mol) of sodium borohydride was added in portions over 15 min. A drying tube was placed on the apparatus, and the mixture was stirred at 0 °C for 1 h. The ice bath was removed, and an exothermic reaction warmed the mixture to reflux. The mixture was stirred at 25 °C for 3 h, after which it was heated at reflux on a steam bath for 10 h. The solvent was distilled in vacuo, the residue was mixed with 100 mL of acetone, and heated on a steam bath for 1 h, and the solvent was distilled in vacuo. The residue was mixed with 100 mL of aqueous potassium carbonate and heated on a steam bath for 1 h, the solvent was distilled in vacuo, and the residue was dissolved in 400 mL of water. The aqueous solution was extracted continuously with $CHCl_3$ for 10 h to give 19.3 g (93%) of diol **8**, mp 112–114 °C (lit. mp 114–115 °C).[10b]

2-Hydroxymethyl-6-methylpyridine (11). 2-Acetoxymethyl-6-methylpyridine was prepared from 2,6-lutidine via its *N*-oxide by the method of Boekelheide and Linn[6] with the following modifications. Crude 2,6-lutidine *N*-oxide (0.5 mol) was added dropwise to acetic anhydride (70 mL) at 110 °C over 2 h, and the resulting mixture was stirred at 110 °C for 4 h. The method of addition prevented accumulation of lutidine *N*-oxide during an induction period and avoided the potentially violent initial exothermic reaction. The product 2-acetoxymethyl-6-methylpyridine (102 g, 0.62 mol) was added slowly to 500 mL of concentrated hydrochloric acid. The resulting solution was heated at reflux for 3 h. The solvent was distilled in vacuo, and the resulting residue was dissolved in 200 mL of water and 200 mL of $CHCl_3$. The aqueous phase was washed with 500 mL of $CHCl_3$ in four portions, and the combined $CHCl_3$ phases were distilled in vacuo. The resulting residue was purified by filtration chromatography through 30 g of silica gel with CH_2Cl_2 as eluting agent. Fraction 1 (2 L of CH_2Cl_2) contained 25.9 g of **11** which showed no impurity by ^{1}H NMR, but was yellow. Fraction 2 (4 L of CH_2Cl_2) contained 14.1 g of colorless **11** which was pure by ^{1}H NMR. Fraction 3 (2 L of ethyl ether) contained 15.2 g of a mixture of **11** and an unknown impurity in a 2:1 ratio. Compound **11** has been made by lithium aluminum hydride reduction of methyl 6-methylpyridine-2-carboxylate and has been reported to solidify on standing, but no melting point was reported.[5a]

2-Chloromethyl-6-methylpyridine (12). This compound was made by treatment of **11** with thionyl chloride.[5a]

Bis(6-methyl-2-pyridylmethyl) Ether (14). To a solution of 10.0 g (81 mmol) of **11** in 200 mL of dry THF at 25 °C was added 4.3 g (90 mmol) of 50% NaH in oil. The mixture was stirred for 15 min, and a solution of 11.3 g (80 mmol) of **12** in 50 mL of dry THF was added. The resulting mixture was stirred for 13 h. After addition of water, the mixture was distilled in vacuo to give a residue which was dissolved in 100 mL of CH_2Cl_2 and 50 mL of water. The aqueous phase was separated and washed with 200 mL of CH_2Cl_2 in two portions. The combined CH_2Cl_2 phases were distilled in vacuo to give a crystalline residue which was purified by chromatography on 200 g of silica gel with CH_2Cl_2 elution (0.5-L fractions). Fractions 5–22 contained 13.4 g (74%) of **14**, mp 75–78 °C. Recrystallization from cyclohexane–pentane gave **4**, mp 77–78 °C, with the following spectral properties: ^{1}H NMR ($CDCl_3$) δ 6.9–7.7 (m, 6, ArH), 4.7 (s, 4, CH_2), 3.5 (s, 6, CH_3); mass spectrum (70 eV) molecular ion at *m/e* 228, $(M + 1)^+ > M^+$, base at *m/e* 107. The osmometric molecular weight of **14** was 228, calcd 228. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06. Found: C, 73.83; H, 6.90.

Bis(6-(acetoxymethyl)-2-pyridylmethyl) Ether (15). A solution of 9.0 g (40 mmol) of **14**, 100 mL of glacial acetic acid, and 10 mL of 30% aqueous hydrogen peroxide was heated at 70–80 °C and stirred for 2 h. An additional 10 mL of 30% aqueous hydrogen peroxide was added, and the resulting mixture was heated at 70–80 °C for 12 h. The mixture was cooled and distilled in vacuo. Water (50 mL) was added to the residue, and the solvent was distilled in vacuo to give a solid residue which was dissolved in chloroform. The solution was washed with 10% aqueous potassium carbonate solution, dried, filtered, and distilled in vacuo to give a residue of 8.80 g (85%) of crude di-*N*-oxide of **14**: mp 161–173 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.6 (m, 6, ArH), 5.0 (s, 4, CH_2), 2.5 (s, 6, CH_3). A solution of 2.7 g (10.4 mmol) of this material in 50 mL of acetic anhydride was heated on a steam bath for 9 h. Solvent was distilled in vacuo, and the residue was chromatographed on 200 g of silica gel with ethyl acetate elution. Early cuts were rechromatographed on 200 g of silica gel with CH_2Cl_2–acetone (9:1 v/v). No fractions contained pure **15**, but the center cut contained 0.63 g (1.8 mmol) of **15**, mp 85–95 °C, which was 95% pure by ^{1}H NMR. Recrystallization of this material from ethanol gave **15** as white plates: mp 97–98.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.8 (m, 6, ArH), 5.1 (s, 4, CH_2), 4.7 (s, 4, CH_2), 2.1 (s, 6, CH_3); osmometric molecular weight 352 (calcd, 344). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85. Found: C, 62.97; H, 5.97.

Bis(6-(hydroxymethyl)-2-pyridylmethyl) Ether (16). This substance was made by treating **15** with excess sodium hydroxide in refluxing 95% ethanol for 8 h. Solvent was distilled in vacuo, and the residue was dissolved in water. The solution was acidified (HCl), washed with $CHCl_3$, basified ($NaHCO_3$), and extracted with $CHCl_3$ (continuous extraction). Distillation in vacuo of the latter $CHCl_3$ solution gave 80–93% yield of crude **16** which was used without further purification.

2-Bromomethyl-6-hydroxymethylpyridine (10) and 2,6-Bis(bromomethyl)pyridine (9). The compounds were produced from **8** by reactions similar to those reported by Baker et al.[5a] for the synthesis of **9**. In a typical preparation, 10.0 g (72 mmol) of **8** in 100 mL of 48% aqueous hydrobromic acid was heated at reflux for 1.0 h. The resulting solution was cooled to 0 °C, neutralized by slow addition of 40% aqueous sodium hydroxide, diluted to 300 mL, and extracted with 500 mL of CH_2Cl_2 in five portions. Continuous extraction of the aqueous phase with $CHCl_3$ gave 3.9 g (28 mmol, 39%) of recovered **8**. The combined CH_2Cl_2 washings were distilled in vacuo to give a residual oil which was purified by chromatography on 200 g of silica gel. Elution of the column with 2 L of CH_2Cl_2 gave 3.0 g (16%) of **9**, mp 85–89 °C dec (lit. mp 84–89 °C dec).[5a] Elution with 2 L of wet ether gave 6.0 g (41%) of **10**: mp 74–78 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.1–7.8 (m, 3, ArH), 4.7 (broad s, 2, CH_2), 4.5 (s, 2, CH_2), 4.3 (broad m, 1, OH); mass spectrum (70 eV) molecular ion at *m/e* 201 (^{79}Br), *m/e* 202 > *m/e* 201, base at *m/e* 122. Samples of **10** and **9** stored at 0 °C for up to 2 months showed no apparent decomposition. Compound **10** is new. Anal. Calcd for C_7H_8BrNO: C, 41.61; H, 3.99. Found: C, 41.78; H, 4.04.

Caution! Dibromide **9** and monobromide **10** are strong lachrymators and trace amounts of each may be dermatitic.

***sym*-Dipyridyl-18-crown-6 (2).** To a solution of 0.45 g (7.2 mmol) of ethylene glycol in 100 mL of dry THF was added 0.80 g (17 mmol) of 50% NaH in oil. The mixture was stirred for 30 min at 25 °C, and then a solution of 1.9 g (7.2 mmol) dibromide **9** in 100 mL of dry THF was added dropwise. The resulting mixture was stirred at 25 °C for 70 h. Water (30 mL) was added, and the solvent was distilled in vacuo. The residue was partitioned between water and CH_2Cl_2. The CH_2Cl_2 phase was distilled in vacuo, and the residue was sublimed at 0.1 Torr, 130–140 °C. The sublimate was recrystallized from CH_2Cl_2–pentane to give 81 mg (7%) of **2**: mp 146.5–148 °C; ^1H NMR ($CDCl_3$), δ 7.1–7.7 (m, 6, ArH), 4.5 (s, 8, $ArCH_2$), 3.7 (s, 8, OCH_2CH_2O); mass spectrum (70 eV) molecular ion at *m/e* 330, base peak at *m/e* 287. In a similar preparation, 2.6 g (10 mmol) of **9** gave 0.29 g (18%) of cycle **2**. Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71. Found: C, 65.58; H, 6.83.

***unsym*-Dipyridyl-18-crown-6 (7).** To a solution of 0.90 g (3.5 mmol) of diol **16** in 100 mL of dry THF was added 0.40 g (8.3 mmol) of 50% NaH in oil. The mixture was stirred at 25 °C for 45 min, and a solution of 1.8 g (4.0 mmol) of diethylene glycol ditosylate in 100 mL of dry THF was added dropwise over 2 h. The resulting mixture was stirred at 25 °C for 60 h before excess water was added. The crude product was isolated in a manner similar to that described for cycle **2**. Chromatography of this material on 200 g of alumina with 1% ethanol in CH_2Cl_2 as eluent gave impure **7**. Gel permeation chromatography of this material gave 170 mg of **7** (149 mL retention volume) as an oil which was ca. 90% pure by ^1H NMR. No further purification was attempted.

Tripyridyl-18-crown-6 (3). To a solution of 1.07 g (4.1 mmol) of diol **16** in 200 mL of dry THF was added 0.50 g (10 mmol) of 50% NaH in oil, and the mixture was stirred at 25 °C for 30 min. A solution of 1.2 g (4.5 mmol) of dibromide **9** in 100 mL of dry THF was added over 1 h, and the mixture was stirred for an additional 13 h at 25 °C before addition of excess water. Crude product was isolated as in the preparation of **2**, and was chromatographed on 250 g of alumina. Products were eluted with 5 L of CH_2Cl_2 and 2 L of 1% ethanol in CH_2Cl_2. The latter fractions contained **3** and an impurity from the alumina column. Gel permeation chromatography gave 480 mg (32%) of **3** (149 mL retention volume) which crystallized on standing. Recrystallization from CH_2Cl_2–pentane give **3**: mp 125–128 °C dec; ^1H NMR ($CDCl_3$) δ 7.1–7.7 (m, 9, ArH), 4.6 (s, 12, $ArCH_2$); osmometric molecular weight 359 (calcd, 363). Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82. Found: C, 69.18; H, 6.03.

***sym*-Dipyridyl-12-crown-4 (4) and Tetrapyridyl-24-crown-8 (5).** To a solution of 1.4 g (10 mmol) of diol **8** in 100 mL of dry THF was added 1.10 g (23 mmol) of 50% NaH in oil. After 45 min at 25 °C, a solution of 2.6 g (10 mmol) of dibromide **9** in 100 mL of dry THF was added, and the mixture was stirred for 100 h at 25 °C. Excess water was added, and the mixture was filtered. Distillation of the solvent in vacuo left a residue which was purified by chromatography on 100 g of alumina with 1% ethanol in CH_2Cl_2 as eluting solvent. Cycles **4** and **5** eluted in the early fractions. Combined residues from the early fractions were chromatographed on 500 g of silica gel with CH_2Cl_2–ethanol as eluting solvent. Products were obtained in two major fractions. The first column fraction contained 320 mg of tetrapyridyl-24-crown-8 (**5**), mp 170–173 °C. The second column fraction contained a mixture of **5** and *sym*-dipyridyl-12-crown-4 (**4**), which were separated by gel permeation chromatography to give 160 mg of **5** (mp 173–176 °C) and 20 mg of **4**. Cycle **4** (1%) was identified by ^1H NMR and by gel permeation chromatography retention time comparisons with authentic **4** obtained below. Cycle **5** (20%) gave mp 173–176 °C; ^1H NMR ($CDCl_3$) δ 7.1–7.7 (m, 12, ArH), 4.6 (s, 16, $ArCH_2$); osmometric molecular weight 466 (calcd, 484). Cycle **5** was analyzed. Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.40; H, 5.82. Found: C, 69.34; H, 6.00.

Tripyridyl-18-crown-6 (3). *sym*-Dipyridyl-12-crown-4 (4), and Tetrapyridyl-24-crown-8 (5). A mixture of 5.3 g (26 mmol) of **10**, 1.5 g (31 mmol) of 50% NaH in oil, and 500 mL of dry THF was stirred at 25 °C for 100 h. Excess water was added, and the mixture was filtered. The filtrate was distilled in vacuo to give a residue which was passed through a column containing 60 g of alumina in CH_2Cl_2. Early eluting material was rechromatographed on 200 g of silica gel in CH_2Cl_2–ethanol. The cycles eluted in the order tetramer **5**, higher oligomer, trimer **3**, and dimer **4**. Early fractions contained 172 mg (5.5%) of **5**, mp 155–160 °C dec. Later fractions were further purified by fractional sublimation to give 30 mg (1.0%) of **3**, mp 120–122 °C dec, and 202 mg (6.4%) of **4**, mp 170–175 °C dec. Recrystallization of **4** from CH_2Cl_2–pentane gave material: mp 172–175 °C dec; ^1H NMR ($CDCl_3$) δ 6.7–7.4 (m, 6, ArH), 4.6 (s, 8, $ArCH_2$); osmometric molecular weight, found 239 (calcd, 242). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.45; H, 5.83.

***sym*-Dibenzodipyridyl-18-crown-6 (6).** To a solution of catechol (2.75 g, 0.025 mol) and *t*-BuOK (6.16 g, 0.055 mol) in 450 mL of THF was added 4.40 g (0.025 mol) of 2,6-bis(chloromethyl)pyridine[5a] (**13**) in 50 mL of THF. The resulting solution was stirred and heated at reflux for 24 h, the solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 phase was washed with water and the solvent evaporated on a steam bath. The residue was purified by chromatography on 250 g of alumina with CH_2Cl_2 elution; 500-mL fractions were collected. Fractions 8–20 contained 0.94 g (9%) of 6: mp 183–185.5 °C; ^1H NMR ($(CD_3)_2SO$) δ 6.6–7.2 (m, 14, ArH), 5.1 (s, 8, CH_2); mass spectrum (70 eV) molecular ion at *m/e* 426, base peak at *m/e* 209. Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20. Found: C, 73.13; H, 5.32.

Complex of Tripyridyl-18-crown-6 (3) and *tert*-Butylammonium Thiocyanate. A solution of 44.7 mg (0.123 mmol) of tripyridyl-18-crown-6 (**3**) in 1 mL of $CHCl_3$ was added to 15.4 mg (0.117 mmol) of *tert*-butylammonium thiocyanate to give a solution. A few drops of tetramethylsilane were added, and the mixture was stored at 0 °C for 1 h. Crystals which formed were filtered to give 48.3 mg (83%) of a 1:1 complex, mp 198–201 °C dec. A sample was recrystallized from CH_2Cl_2–pentane to give the complex, mp 198–201 °C dec. Clear crystals became cloudy in 1 day. The major peak in the mass spectrum (70 eV) was at *m/e* 363, the molecular weight of the cycle. Crystals stored at room temperature or 70 K shattered within 1 day, and an x-ray crystal structure determination could not be made. Anal. Calcd for $C_{26}H_{33}N_5O_3S$: C, 63.01; H, 6.71. Found: C, 62.90; H, 6.88.

2,6-Bis(methoxymethyl)pyridine. To a solution of 0.75 g (4.3 mmol) of 2,6-bis(chloromethyl)pyridine in 100 mL of dry THF was added 1.08 g (20 mmol) of sodium methoxide. The reaction mixture was then heated to reflux for 72 h. Water was added (2 mL) and the solvent was removed in vacuo. The residue was distributed between NaCl-saturated water and ether. The aqueous layer was extracted with two additional portions of ether. The organic extracts were combined and dried, and the solvent was evaporated in vacuo. The residue was then chromatographed on 50 g of silica gel with 50% ether–CH_2Cl_2 elution to give 0.62 g (86%) of product as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.3–7.9 (m, 3, ArH), 4.6 (s, 4, CH_2), 3.5 (s, 6, CH_3); mass spectrum (70 eV) shows no M^+ (167), however, a very strong $M - 30^+$ (137). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.53; H, 7.61; N, 8.43.

Determination of pK_as of Conjugate Acids of Pyridocycles. Solutions of ca. 0.1 mequiv of cycle in 40 mL of water at 20 °C were titrated with 0.10 ± 0.01 N LiOH and 0.10 ± 0.01 N HCl solutions. The pH of the solutions was monitored with a glass electrode and a pH meter. The pK_as of the acids were determined by graphical analysis of a plot of pH vs. milliliters of added titrant and are given in Table I. For the concentrations of species used here, pK_as below 3 or above 10 could not be determined. For calibration, pyridine, 2,4,6-trimethylpyridine, and a mixture of the two were titrated with the following results: compound (pK_a), pyridine (5.1, 5.0), 2,4,6-trimethylpyridine (7.4, 7.4), pyridine and 2,4,6-trimethylpyridine (5.1 and 7.3). The values for the pK_as of the conjugate acids of pyridine and 2,4,6-trimethylpyridine are 5.2 and 7.4, respectively.[8] The pK_a of open-chain model compound 2,6-bis(methoxymethyl)pyridine was also measured and found to be 4.9, close to that of pyridine.

Distribution of *tert*-Butylammonium Thiocyanate and Chloride between Deuterium Oxide and Deuteriochloroform in the Presence of Hosts. The procedure has been described.[3] The distribution constant (K_d) for *t*-$BuNH_3SCN$ between D_2O and $CDCl_3$ was 5.2×10^{-5} M^{-1} at 24 °C and 2.3×10^{-5} M^{-1} at 0 °C.[3] It was assumed that in D_2O the salt was dissociated and in $CDCl_3$ it was associated and monomeric (see eq 12). The extraction constant, K_e, is defined by eq 13. The salts were distributed between $CDCl_3$ and D_2O in the presence of host, and ^1H NMR techniques were used to measure the mole ratios of guest to host in the $CDCl_3$ layer and to set lower limits on the amounts of host (usually absent) in the D_2O layer. Equation 14 relates K_e to measurable quantities, where R is the molar ratio of guest to host in the $CDCl_3$ phase, $[t\text{-}BuNH_3^+{}_i]_{D_2O}$ is the initial concentration of this cation in the D_2O phase, $[H_i]_{CDCl_3}$ is the initial concentration of the host in the $CDCl_3$ phase, and V_{CDCl_3} and V_{D_2O} are the volumes of the two phases used. In the derivation it was assumed that the host–guest complex formed was 1:1. Equation 15 relates the association constant

of host and guest in $CDCl_3$ (K_a, see eq 1), K_d, and K_e.

$$[t\text{-BuNH}_3^+]_{D_2O} + [X^-]_{D_2O} \overset{K_d}{\rightleftharpoons} [t\text{-BuNH}_3^+ \cdot X^-]_{CDCl_3} \quad (12)$$

$$[H]_{CDCl_3} + [t\text{-BuNH}_3^+]_{D_2O} + [X^-]_{D_2O} \overset{K_e}{\rightleftharpoons} [t\text{-BuNH}_3^+ \cdot H \cdot X^-]_{CDCl_3} \quad (13)$$

$$K_e = \frac{R}{(1-R)\{[t\text{-BuNH}_3^+{}_i]_{D_2O} - R[H_i]_{CDCl_3}(V_{CDCl_3}/V_{D_2O})\}^2} \quad (14)$$

$$K_e = K_a K_d \quad (15)$$

The values of R and of K_a (normalized when scale C involving t-$BuNH_3SCN$ was employed[3]) are recorded in Table II. When 18-crown-6 (**17**) and pyridyl-18-crown-6 (**1**) were employed, the small amount of host that dissolved in the D_2O layer at equilibrium was corrected for by using the concentration of host in $CDCl_3$ at equilibrium in place of $[H_i]_{CDCl_3}$ in eq 17 (see footnotes *c*, *d*, *e*, and *f*, Table II).

Distribution of *tert*-Butylammonium Chloride between Deuterium Oxide and Deuteriochloroform in the Absence of Hosts. The K_d values for t-$BuNH_3^+Cl^-$ were determined by the fluorometric technique applied previously to t-$BuNH_3^+SCN^-$. The technique with respect to concentrations, volumes, and temperatures was identical except that the chloride was substituted for the thiocyanate salt.[3] The original D_2O solutions of t-$BuNH_3^+Cl^-$ were adjusted to pH 1 with HCl before being extracted with $CDCl_3$. Because the amounts of salt extracted at 24 °C were only slightly in excess of the blanks at 24 °C, the K_d value could only be grossly estimated to be $\approx 0.93 \times 10^{-6}$. At 0 °C, the aqueous layer was extracted successively with three $CDCl_3$ portions, which after subtraction of the blank (0.713×10^{-6}) gave K_d values of 1.07×10^{-6}, 1.75×10^{-6}, and 1.07×10^{-6} M^{-1}, respectively. The average value of $1.3 \pm 0.3 \times 10^{-6}$ M^{-1} was used in the calculation of K_a values of Table II.

References and Notes

(1) (a) This work was supported by a grant from the National Science Foundation, GP-33533X, and by the U.S. Public Health Service, Research Grant GM12640-10 from the Department of Health, Education and Welfare. (b) Upjohn Graduate Research Fellow, 1973–1975.
(2) Preliminary accounts of some of this work have been published: (a) M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 6810 (1974); (c) J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *ibid.*, **96**, 7097 (1974).
(3) J. M. Timko, S. S. Moore, D. M. Walba, P. Hiberty, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 4207 (1977).
(4) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 2495, 7017 (1967).
(5) (a) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958); (b) W. Jenny and H. Holzrichter, *Chimia*, **22**, 306 (1968); (c) F. Vögtle and L. Shunder, *Chem. Ber.*, **102**, 2677 (1969); (d) F. Vögtle and E. Weber, *Angew. Chem.*, **86**, 126 (1974); (e) G. R. Newkome and J. M. Robinson, *J. Chem. Soc., Chem. Commun.*, 831 (1973).
(6) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).
(7) The authors warmly thank Dr. G. W. Gokel for this preparation.
(8) D. D. Perrin, *Pure Appl. Chem., Suppl. 1* (1965), reports pK_a values of 5.2 for pyridine and 7.4 for 2,4,6-trimethylpyridine.
(9) J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 7159 (1974).
(10) (a) H. Meyer, *Monatsh. Chem.*, **24**, 206 (1903); (b) Japanese Patent 8620 (1967); *Chem. Abstr.*, **68**, 2815 (1968).
(11) J. V. Karabinos and K. T. Serijan, *J. Am. Chem. Soc.*, **67**, 1856 (1945).

Host–Guest Complexation. 4. Remote Substituent Effects on Macrocyclic Polyether Binding to Metal and Ammonium Ions[1]

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Abstract: Seven 5′-substituted 1′,3′-xylyl-18-crown-5 macrocyclic polyethers (hosts) are reported with substituents H (**1**), Br (**2**), $C(CH_3)_3$ (**3**), $CO_2C_2H_5$ (**4**), OCH_3 (**5**), SCH_3 (**6**), and CN (**7**). The association constants (K_a) of these hosts at 24 °C with *tert*-butylammonium thiocyanate, perchlorate, and picrate and the picrate salts of lithium, sodium, ammonium, potassium, rubidium, and cesium in $CDCl_3$ were measured by D_2O extraction–spectroscopic techniques. The K_a values obtained were submitted to Hammett linear free energy treatments. For *tert*-butylammonium, ammonium, potassium, rubidium, and cesium, the K_a values were only poorly correlated by existing σ constants. For lithium and sodium, no trends were visible in the data. For *tert*-butylammonium perchlorate as guest, the complex with **7** as host was about 2.4 kcal/mol less stable than with **3** as host. For ammonium, potassium, rubidium, and cesium ions, the differences between the complexes with **7** vs. **5** as host ranged from ~1.4 to ~1.7 kcal/mol. The OCH_3 substituent stabilized and the CN destabilized the complexes relative to H. Good linear free energy correlations were observed when ammonium picrate as a standard guest was compared with *tert*-butylammonium perchlorate and thiocyanate, potassium picrate, rubidium picrate, and cesium picrate as alternative guests. The effects of the substituents on the π basicity of the benzene ring appear to control the patterns of changes in K_a values with changes in substituent. The ^1H NMR spectra of the complexes of *tert*-butylammonium salts with **1–3** and **5** gave signals for the *tert*-butyl protons that were about 0.4 ppm upfield of the complex with 18-crown-6 and varied little with changes in substituent and counterion. This fact indicates that the complexes possess a conformation that places the *tert*-butyl group in the shielding cone of the aryl group.

The synthesis and properties of macrocyclic polyethers[2,3] and polythioethers[4] whose structures incorporate 1,3-xylyl units have been investigated recently. The complexing properties have been reported of host compounds containing 1,3-xylyl units substituted in the 2 position with functional groups whose *convergence* on bound guest ions is enforced by the rigidity of the aryl group.[5] We report here a study of the binding properties of cycles **1–7** in which substituents in the 5′ position of the 1′,3′-xylyl group are both remote and *divergent* from the site of complexation.[6] The association constants (K_a) defined by eq 1 have been determined at 24 °C in $CDCl_3$ in which H is the host, G^+X^- is the guest salt, and $G^+ \cdot H \cdot X^-$ is the com-