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Host–Guest Complexation. 2. Structural Units That Control Association Constants Between Polyethers and *tert*-Butylammonium Salts[1a,2]

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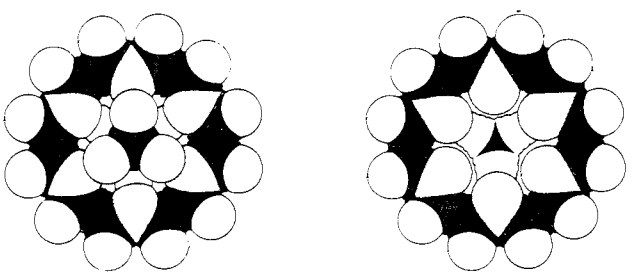
Abstract: The synthesis and characterization of 12 new macrocyclic polyethers are reported which contain pentamethylene, *m*-xylyl, *p*-phenylene, furan-2,5-dimethylyl and tetrahydrofuran-2,5-dimethylyl units combined with oxygen and ethylene units. A technique is reported for determining the association constants of these polyether hosts with *tert*-butylammonium thiocyanate in chloroform at 24 and 0 °C. For 13 18-membered ring systems, the free energies of association with the salt were calculated at 24 and 0 °C, and found to range from −9.0 to <−2.9 kcal/mol at 24 °C, depending on the units incorporated in the cycle. The values for four cycles were dissected into six host–guest contact site parameters whose addition equaled their free energies of association. The parameters taken in appropriate combinations were then used to calculate the free energies of association for three other cycles that combined the same units in other ways. The calculated and measured values agreed within experimental error. Ab initio molecular orbital calculations of relative values of binding energies of the contact site parameters were in qualitative agreement with those observed. The dimethyl ether of hexaethylene glycol at 24 °C was found to bind the salt ~5.9 kcal/mol less well than did 18-crown-6. Benzo-18-crown-6 bound the salt >5.0 kcal/mol better than its isomer, *p*-phenylene-18-crown-6, whose binding sites are mislocated. Tetrahydrofuranyl-18-crown-6 bound the salt ~4.2 kcal/mol better than tetrahydrofuranyl-15-crown-5 and ~3.0 kcal/mol better than *sym*-bis(tetrahydrofuranyl)-30-crown-10. A fully complementary location of binding sites is present in the first, but not in latter cycles.

The systematic study of the structural features of organic molecular complexes in solution not involving proteins largely has been limited to the cyclodextrins as hosts dissolved in aqueous media. A variety of guest compounds has been studied.[3] The main driving force for inclusion of an organic guest in the interior of a cyclodextrin appears to be the tendency of water to bind to itself better than to either the interior of a cyclodextrin or the exterior of the guest compounds. The molecular organization of the host–guest complex is dictated largely by the rigid torus shape of the host and the relative molecular dimensions of the guest. The hydroxyl and other attached groups on the rims of the cyclodextrins have been used as binding sites for transition states in transacylation reactions of ester hosts.[3]

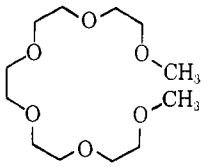
The first paper of this series[4] indicated how cyclic polyether hosts could be used to complex in chloroform, *tert*-butylammonium, guanidinium, and arenediazonium salts as guests. Three important qualitative conclusions emerged. (1) Space-filling scale molecular models of potential complexes can be used roughly to evaluate potentially complementary organic host–guest relationships. (2) Convergence in host compounds that organizes binding sites prior to complexation provides better binding than when guests must impose convergence during complexation. (3) Matching of sizes, shapes, and electronic properties of binding portions of hosts and guests is necessary for strong binding.

This paper reports the beginning of a systematic study of the effects of structural relationships on the binding properties of organic hosts and guests. The highly structured relationship suggested by the Corey–Pauling–Koltun (CPK) molecular models of hydrogen-bonded complexes of alkylammonium ions and cyclic polyethers provides a starting point that has the following advantages. The cyclic polyethers of the "crown" type[5] are relatively easily made hosts that are subject to wide structural modification. A variety of alkyl and substituted alkyl groups can be attached to the ammonium ion, and the counterion is subject to manipulation. Drawings I and II are made



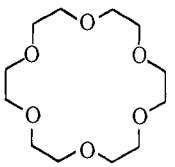
I II

from photographs (taken from front and back) of CPK models of the complex between methylammonium ion and 18-crown-6.



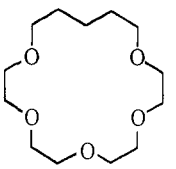
1

(130)*
(850)*



2

(3 000 000)
(32 800 000)



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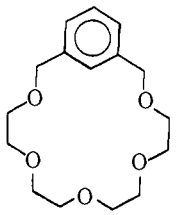
(18400)*



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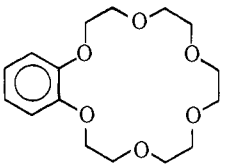
(51000)*



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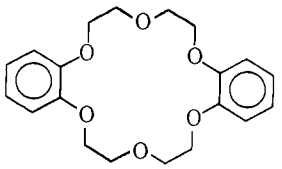
(10 500 000)



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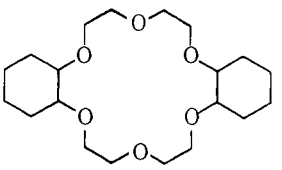
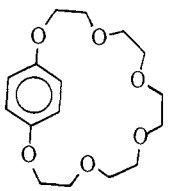
(850 000)



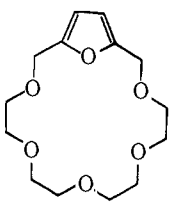
7 (isomer mixture)

(360 000)
(9 600 000)



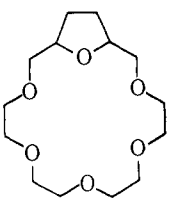
8

(<130)*
(<1400)*



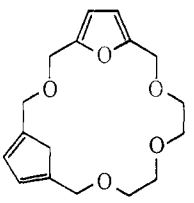
9

(209 000)
(1 240 000)



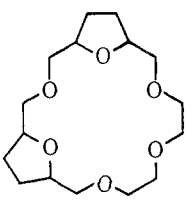
10 (cis) (cis + trans)

(4 180 000) (4 840 000)
(18 800 000) (24 900 000)



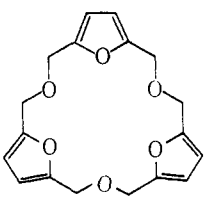
11

(13 800)*
(144 000)*



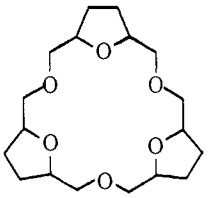
12 (syn-cis-cis + anti-cis-cis)

(1 370 000)
(4 630 000)



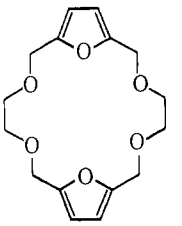
13

(1020)*
(11000)*



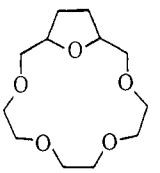
14 (syn-cis-cis-cis + syn-cis-cis-anti-cis)

(4 180 000)
(32 800 000)



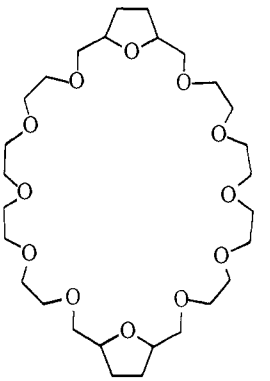
15

(260)*
(2000)*



16

(3250)*
(18400)*



17 (syn-cis-cis + anti-cis-cis)

(25 800)*
(144 000)*

The *tert*-butylammonium thiocyanate salt was selected as a standard guest for several reasons. The compound possesses an appropriate hydrophilicity–lipophilicity balance that strongly favors water over nonpolar solvents, but still is extractable into chloroform in the presence of hosts. The three methyl groups provide an intense singlet in ^{1}H NMR spectra that allows determination of the salt's concentration in distribution experiments between phases.

The steric requirements of the *tert*-butyl group are great enough to make steric inhibition of complexation detectable when steric barriers are present in the host compound. Here estimates are reported for the values of association constants (K_a) in chloroform for complex formation between *tert*-butylammonium thiocyanate and the 17 host compounds formulated. Beneath each formula are listed the estimated K_a values. The upper values were determined at 24 °C and the lower values at 0 °C.

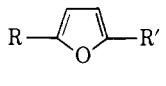
$$H + G \underset{CDCl_3}{\overset{K_a}{\rightleftharpoons}} H \cdot G$$

The first section of the discussion describes the synthesis of the 12 new cyclic ethers (**2, 5, 6,** and **7** have been reported previously).[5] The second indicates how the K_a values were obtained. The third analyzes the relationships between structure and the free energies of association derived from the K_a values.

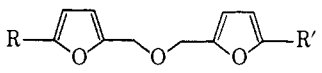
Results and Discussion

Synthesis of Host Compounds. Treatment of tetraethylene glycol ditosylate with 1,4-pentanediol and NaH in dimethylformamide (DMF) produced **3** (26%).[6a] Condensation of 1,3-bis(hydroxymethyl)benzene with tetraethylene glycol ditosylate in DMF and base gave **4** (30%).[6b] Hexaoxacyclophane **8** was produced (2%) along with its cyclic dimer (7%) when pentaethylene glycol ditosylate was mixed with hydroquinone and base under nitrogen.

The key starting material for the preparation of the furan-containing cycles and their derivatives was hydroxyaldehyde



18, R = CHO; R' = CH_2OH
19, R = R' = CH_2OH
20, R = R' = CH_2Cl
21, R = CHO; R' = CH_2Cl
22, R = CHO; R' = $CH_2OCH_2CH_2Cl$
23, R = CH_2OH; R' = $CH_2OCH_2CH_2Cl$
24, R = R' = $CH_2OCH_2CH_2OTHP$
25, R = R' = $CH_2OCH_2CH_2OH$

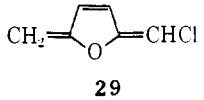


26, R = CHO
27, R = CH_2OH
28, R = CH_2Cl

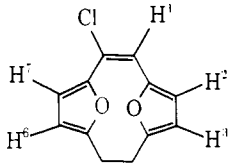
18. The substance was prepared from sucrose (41%),[7] which by conventional methods was converted to diol **19**,[8] dichloride **20**,[9] and chloroaldehyde **21**,[10] which was also prepared directly from sucrose (50%).[7] Treatment of **21** with chloroethanol and base produced **22**, reduction of which ($NaBH_4$) gave **23**. Condensation of diol **19** with the tetrahydropyranyl ether derivative (THP) of chloroethanol (DMF-NaH) gave **24** (57%) which was cleaved to diol **25**. The bisfuran dialdehyde **26** was prepared (44%)[11] by acid treatment of aldehyde alcohol **18**, and the dialdehyde **26** was reduced ($NaBH_4$) to diol **27**, which was chlorinated to give **28**.

Compounds **19**, **20**, **23**, **25**, **27**, and **28** were used in the critical ring-closing reactions, whose yields were not maximized. The monofuranocycle (**9**)[12] was prepared (36%) from diol **19** and tetraethylene glycol ditosylate (THF-*t*-BuOK). The unsymmetrical difuranocycle **11** (35%) came from diol **27** and diethylene glycol ditosylate (THF-*t*-BuOK), whereas the symmetrical difuranocycle **15** (11%) involved condensation of 2 mol of chloro alcohol **23** (DMF, NaH). When dichloride **20** was treated with ethylene glycol (DMF-NaH), <1% of **15** was produced, and furanophane **30** was the main product (30%). This cycle probably arose by dimerization of 2 mol of triene **29**, a reaction for which there is good analogy.[13] Formation of **29** from **20** involves a base-catalyzed 1,6-elimination reaction.

Dimerization of **29** probably occurred by head-to-head coupling of two molecules of **29** followed by ring closure of a diradical and a base-catalyzed elimination reaction to give **30**.



29



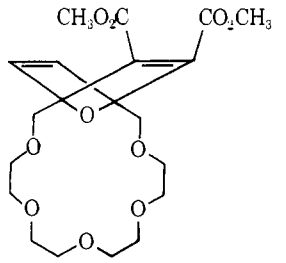
30

The structural assignment of **30** is based on its mass and ^1H NMR spectra. As with furanophane itself and similar cyclophanes, **30** exhibited temperature-dependent ^1H NMR spectra characteristic of the two furan planes slipping past one another at rates detectable on the ^1H NMR time scale.[14] The symmetrical difuranocycle **15** also was prepared (2%) from dichloride **20** and diol **25** (DMF-NaH), but again **30** was the dominant product (22%).

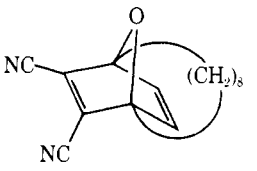
The trisfuranocycle **13** was prepared by two routes. The first (10%) involved condensation of diol **27** with dichloride **20** (THF-*t*-BuOK), but 70% of **27** was recovered and 29% of **30** was produced. A better synthesis (40%) that avoided this troublesome side reaction involved diol **19** and dichloride **28** (DMF-NaH).

Interestingly, the monofuranocycle formed a 1:1 crystalline complex with dimethyl acetylenedicarboxylate, which crystallized readily from benzene (74%), mp 72–73 °C. The ^1H NMR spectrum of the complex in $CDCl_3$ exhibited signals identical with those of the two components taken separately. Upon gel permeation, the two components partially separated, indicating that lattice forces are needed to hold the parts together. Formation of this complex led to treatment of 18-crown-6 with the same acetylenic ester. Again a crystalline 1:1 complex (^1H NMR evidence) formed (mp 100–101 °C), whose osmometric molecular weight in $CHCl_3$ was 201, not far from half the molecular weight of the complex (406).[6c] Its x-ray crystal structure[15] demonstrated that the diester stretches between two crowns that roughly occupy two parallel planes. Two of the hydrogens of each methyl group somewhat penetrate the partial holes of the two cycles.[15] Similarly, 18-crown-5 (**3**) formed a crystalline 1:1 complex with the same acetylenic ester.[6a] Other complexes of 18-crown-6 with neutral molecules have also been reported.[16]

When heated in toluene, the two components of the furanocycle complex underwent cycloaddition to give adduct **31**.



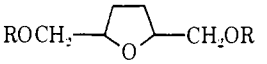
31



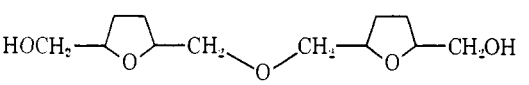
32

The ^1H NMR spectra of **31** in *o*-dichlorobenzene taken at 25–163 °C indicated an activation energy of >21 kcal/mol[17a] for the carbon bridges of the bicyclic system passing through the center of the macroring. A temperature-dependent spectrum has been observed for the related compound, **32**, which provided a coalescence temperature between −80 and −100 °C.[17b] In both **31** and **32**, the oxygen, but not the vinyl, bridges appear able to pass through the center of the macroring at high rates at 25 °C. Upon attempted GLC purification of adduct **31** at 255 °C, the compound reverted to the two starting materials.

The tetrahydrofuranocycles were prepared either by direct catalytic reduction of the furanocycles, or by ring closures of their reduced precursors. Both approaches involved configurational complications. Catalytic reduction of furan diol **19** with hydrogen and 10% Pd-C in absolute ethanol gave about 40% of *trans*- and 60% of *cis*-**33**.[18a] With Raney nickel as catalyst in absolute ethanol only *cis*-**33** (98%) was produced. It has been reported previously[18b] that 2,5-dimethylfuran gives only the cis isomer, a fact confirmed here (GLC and ^1H NMR criteria). Diol *cis*-**33** was converted to ditosylate **34** by the



33, R = H (cis or cis + trans)
34, R = Ts (cis)



35 (syn-cis-cis and anti-cis-cis)

usual method. Diol **27** was also reduced with a Raney nickel catalyst to give the reduced diol **35**, which was probably a mixture of the syn-cis-cis and anti-cis-cis isomers.

Catalytic reduction of monofuranocycle **9** with 10% Pd-C gave approximately a 1:1 mixture of *cis*- and *trans*-**10** (97%), whereas with Raney nickel **9** gave (97%) only *cis*-**10** (lan-

Table I. Molar Ratios of *tert*-Butylammonium Thiocyanate to Hosts (R), Association Constants (K_a), and Free Energies (ΔG) for Association in $CDCl_3$

Host no.	Scale	Temp 24 °C			Temp 0 °C		
		R	K_a, M^{-1}	ΔG, kcal/mol	R	K_a, M^{-1}	ΔG, kcal/mol
1	C	0.01	~260	~−2.88[a]	0.04	1 700	~−3.66
2	A	0.51	3 000 000	−8.81	0.76	32 800 000	−9.40
3	C	0.15	3 300	−4.38[a]	0.40	36 700	−5.33
4[b]	C	0.25	6 540	−4.78[a]	0.63	102 000	−5.89
5	A	0.22	615 000	−7.88	0.55	10 500 000	−8.78
6	A				0.12	680 000	−7.29
6	B	0.37	85 000	−6.71	0.65	850 000	−7.41
6	C	0.88	220 000				
7	A	0.15	360 000	−7.56	0.45	9 600 000	−8.73
8	C	<0.01	<260	<−2.88[a]	<0.04	<2 800	<−3.94
9	A	0.10	209 000	−7.24	0.19	1 240 000	−7.62
9	B	0.55	203 000	−7.22			
10 (cis)	A	0.55	4 180 000	−9.01	0.65	18 800 000	−9.10
10 (cis + trans)	A	0.58	4 840 000	−9.10	0.70	24 900 000	−9.25
11	B				0.36	198 000	−6.63
11	C	0.53	26 800	−5.62[a]	0.80	288 000	−6.45[a]
12	A	0.35	1 370 000	−8.35	0.40	4 630 000	−8.34
13	C	0.10	2 030	−4.09[a]	0.30	22 000	−5.06[a]
14	A	0.55	4 180 000	−9.01	0.74	32 800 000	−9.40
15	C	0.03	520	−3.29[a]	0.08	4 000	−4.12[a]
16	C	0.25	6 500	−4.78[a]	0.40	36 700	−5.33[a]
17	C	0.60	51 600	−6.00[a]	0.80	288 000	−6.45[a]

[a] The K_a values of scale C recorded here are those measured. They are divided by two for the calculation of ΔG values. Thus the ΔG values of scale C are normalized to those of scales A and B. [b] The authors warmly thank Dr. M. Newcomb for these determinations.

thanide shift reagent criterion).[19] Condensation of cis-diol **33** and tetraethylene glycol ditosylate (THF-*t*-BuOK) also gave (34%) *cis*-**10.** Catalytic reduction of unsymmetrical difuranocycle **11** with the Raney nickel catalyst gave 95% of what is probably a mixture of the syn-cis-cis and anti-cis-cis isomers of **12,** the latter of which is a racemate. Catalytic reduction of trisfuranocycle **13** with the Raney nickel catalyst gave (97%) what is probably a mixture of syn-cis-cis-cis and syn-cis-cis-anti-cis isomers of **14.** Only two all cis isomers are possible, and neither of them is chiral. Reaction of diol **35** with cis-ditosylate **34** (DMF-NaH) also gave (44%) what is probably a mixture of the same two isomers of **14.** Treatment of triethylene glycol ditosylate with cis-diol **33** (THF-*t*-BuOK) gave 23% of the five-oxygen cycle *cis*-**16** and 8% of the ten-oxygen cycle **17,** which is probably a mixture of syn-cis-cis and anti-cis-cis isomers, neither of which is chiral.

An interesting feature of the synthesis of the trisfuranocycle **13** and its reduction product **14** is the fact that sucrose was the only *organic starting material* employed. The wealth of reactions of the furan system coupled with the ease of preparation of the furanocycles suggests these cycles and others like them might serve as the starting points for a variety of highly shaped host compounds. The tetrahydrofuranyl unit is commonly encountered in antibiotics which complex cations and affect their permeability to natural and synthetic membranes.

Association Constants. In the previous paper,[4] a means was developed for estimating the values of K_e defined by eq 1,[4] in which H is the host. The salts, *t*-$BuNH_3ClO_4$ and *t*-$BuNH_3PF_6$, were distributed between chloroform and water in the absence of host, and no ^1H NMR detectable amounts of *t*-$BuNH_3^+$ salts were found in the $CDCl_3$ layer. It was assumed that in water the salt was dissociated, and in chloroform it was present as tight ion pairs. It was also assumed that only 1:1 complexes between host and guest are important, and that these are monomeric. The salts were then 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 (virtually absent) in the D_2O layer.[20] The extraction constant, K_e, is defined by the equation

$$[H]_{CDCl_3} + [t\text{-}BuNH_3^+]_{D_2O} + [X^-]_{D_2O} \overset{K_e}{\rightleftharpoons} [t\text{-}BuNH_3^+ \cdot H \cdot X^-]_{CDCl_3} \quad (1)$$

In the absence of an inert common ion salt in the aqueous phase, K_e was related to measurable values by

$$K_c = \frac{R}{(1-R)\{[t\text{-}BuNH_3^+{}_i]_{D_2O} - R[H_i]_{CDCl_3}(V_{CDCl_3}/V_{D_2O})\}^2} \quad (2)$$

In eq 2, 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 chloroform phase, and V_{CDCl_3} and V_{D_2O} are the volumes of the two phases.

In this investigation, association constants (K_a) have been determined for hosts **1–17** with *t*-$BuNH_3SCN$ as guest at 24 and 0 °C and are reported in Table I. The association constant (K_a) in $CDCl_3$ is defined in eq 3 and is derived from K_e of eq 1 and 2 and the distribution constant (K_d) defined by eq 4. Equation 5 relates K_a to K_e and K_d, and to measurable quantities, provided K_d is determined.

$$H + t\text{-}BuNH_3^+ \cdot X^- \underset{CDCl_3}{\overset{K_a}{\rightleftharpoons}} t\text{-}BuNH_3^+ \cdot H \cdot X^- \quad (3)$$

$$[t\text{-}BuNH_3^+]_{H_2O} + [X^-]_{H_2O} \overset{K_d}{\rightleftharpoons} [t\text{-}BuNH_3 \cdot X^-]_{CHCl_3} \quad (4)$$

$$K_a = K_a/K_d = \frac{R}{K_d(1-R)\{[t\text{-}BuNH_3^+{}_i]_{D_2O} - R[H_i]_{CDCl_3}(V_{CDCl_3}/V_{D_2O})\}^2} \quad (5)$$

Values of K_d were estimated for *t*-$BuNH_3SCN$ by both con-

ductometric and fluorescent spectroscopic methods (see Experimental Section) in multiple determinations. At 24 °C, K_d = (4.0 ± 2.0) × 10^{-5} M^{-1} by conductivity, and (6.7 ± 1.0) × 10^{-5} M^{-1} by spectroscopy, so the average of 5.2 × 10^{-5} M^{-1} was used. At 0 °C, K_d = (2.7 ± 0.7) × 10^{-5} M^{-1} by conductivity, and (1.9 ± 0.7) × 10^{-5} M^{-1} by spectroscopy, so the average of 2.3 × 10^{-5} was used. The gravimetric method used initially for determining K_d values turned out to be spurious. Therefore, the absolute (not relative) K_a values reported in a preliminary form[2b] are corrected here.

The differences in binding abilities of the host were too great for determination of their K_a values at one set of concentrations and volumes for the two phases. Accordingly, the initial concentration of host for all determinations was 0.140 M in $CDCl_3$, and the volume was 0.60 mL. Three different scales of K_a were developed by varying the volumes and concentrations of the D_2O phases. Scale A involved 1.60 mL of 0.10 M salt, scale B, 0.60 mL of 0.40 M salt, and scale C, 0.30 mL of 1.0 M salt. From the integrated 100-MHz ^1H NMR spectra of the equilibrated $CDCl_3$ solutions, the relative concentrations of guest (*t*-Bu protons) to host (all protons) were measured (±2%). The host distributed in the D_2O layer was ≲0.5% of the total used except for 18-crown-6 (**2**), in which up to 15% of the total used was found in the D_2O layer at equilibrium. In calculating K_a values for **2**, the concentration of host in the $CDCl_3$ layer at equilibrium was used in place of $[H_i]_{CDCl_3}$. This correction changed K_a for **2** by 6% at 24 °C and by 11% at 0 °C. Values of R on the three scales ranged from a high of 0.88 to a low of 0.01, but only a few were out of the most accurate 0.1–0.7 range (see Table I).

The K_a values of hosts **6**, **9**, and **11** were determined with reasonable accuracy (R values, 0.1–0.88) on more than one scale. Host **6** at 0 °C gave a K_a value of 680 000 on scale A and 850 000 on B, and at 24 °C gave 85 000 on B and 220 000 M^{-1} on C (Table I). Similarly, **9** at 24 °C gave 209 000 on A and 203 000 M^{-1} on B. Host **11** at 0 °C gave 198 000 on B and 288 000 M^{-1} on C. Thus the K_a values are in reasonable agreement with one another when obtained on the more dilute solutions of aqueous salt of scales A and B. However, the K_a values of scale C are an average of a factor of about 2 higher than those of B, probably because at 1 M concentration the ions in water were somewhat associated. Thus the K_a values of scale C were corrected to those of A and B by dividing them by a factor of 2 to give the association constant values placed below the formulas of those compounds determined on scale C. These corrected values are marked with an asterisk.

This merging of scales allows rough comparisons to be made of the binding power of a wide variety of hosts. Table I lists the estimated ΔG values of the complexes vs. their uncomplexed components in $CDCl_3$ at 24 and at 0 °C. The values of K_a from scale C normalized to scales A and B were used in calculation of ΔG values. The large number of individual experimental observations, coupled with the assumptions made in the derivations and merging of scales, means that the association constants and ΔG values are estimates only. The most refined comparisons are possible when the values are determined on one scale with R values in the middle range. Equation 5 indicates that $K_a \propto K_e$ with K_d as the proportionality constant. Thus ratios of K_a values for different hosts on the same scale are independent of K_d (as are their $\Delta\Delta G$ values), and provide the most refined comparisons.

Relationships Between Structure and Complexing Abilities. The host structures with the normalized association constants listed below them provide conclusions about how various structural features affect their binding power. Cycle 18-crown-6 (**2**) and its open-chain model **1** differ in their molecular formulas by only two hydrogens, and yet the cycle binds by a factor of $>10^4$ better than the open-chain compound. Thus the enforced convergence of binding sites provided by the cycle increases the stabilities of the complexes over the separated states of host and guest by ~5.9 kcal/mol at 24 °C. Molecular models (CPK) of the complexes of **1** and **2** show that no steric inhibition of complexation need exist in ideal structures.

Hosts **2–7** and **9–15** contain 18-membered macrorings whose five to six oxygens in CPK models of their complexes linearly hydrogen bond the three acidic hydrogens of the NH_3^+ group to provide three O···HN^+ interactions. The remaining three oxygens of cycles **2**, **5–7**, and **9–15** are located in the model complexes at van der Waals contact distances of the N^+ in between the hydrogen bonds, and provide three O···N^+ interactions (see drawings I and II). In the complex of **3**, a CH_2···N^+ interaction replaces one O···N^+ interaction of the complex of **2**. In that of **4**, a π-aryl···N^+ interaction replaces one O···N^+ interaction of that of **2**. Introduction of furan or tetrahydrofuran ring structures as in **9–15** of benzo groups as in **5** or **6** or of hexahydrobenzo groups as in **7** induce little geometric change in models of either the cycles or their complex. Thus the *location* of attracting and repelling sites in the hosts and their complexes are very similar. Furthermore, *no steric interactions* between the *t*-Bu group and any of the parts of the hosts are visible in models of the complexes except in those of some of the stereoisomers of **7**.

These facts suggest that the six units of hosts **2–6** and **9–15** in contact with the NH_3^+ group in the complexes might contribute cumulatively to the ΔG values of complexation listed in Table I. This additivity assumption is made in the following empirical analysis, in which rough estimates are made of the free energy contributions of sums of the different kinds of contacts found in complexes A through J (Chart I). The different kinds of contacts in each structure are labeled with letters *a*, *b*, etc. Their individual contributions to the ΔG values are assumed to be the same in each complex. The further assumption is made that the structures formulated represent the major component in an equilibrium between these and complexes of other structures. Rotation of the NH_3^+ group 60° within the host gives alternate structures for some of the complexes of Chart I. The effects of these alternate structures on the results of this treatment will be discussed later.

Combinations of the equations for A, B, and C (Chart I) give eq 6–8, in which $(a + b)$, $(a + d)$, and $(c + d)$ are expressed in terms of ΔG_A, ΔG_B, and ΔG_C. The equations for D and E (Chart I) are then solved for ΔG_D and ΔG_E in terms of ΔG_A, ΔG_B, and ΔG_C in eq 9 and 10.

$$a + b = \tfrac{1}{3}\Delta G_A \quad (6)$$

$$a + d = \tfrac{1}{3}\Delta G_B \quad (7)$$

$$c + d = \Delta G_C - \tfrac{2}{3}\Delta G_A \quad (8)$$

$$\Delta G_D = \tfrac{2}{3}\Delta G_A + \tfrac{1}{3}\Delta G_B \quad (9)$$

$$\Delta G_E = \tfrac{1}{3}\Delta G_A + \tfrac{2}{3}\Delta G_B \quad (10)$$

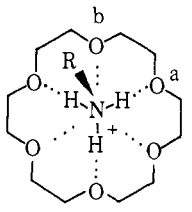
Combination of eq 6 and that for ΔG_G of Chart I gives eq 11, in which $(e + f)$ is expressed in terms of ΔG_A and ΔG_G. The equation for ΔG_F is then solved in terms of ΔG_A and ΔG_G in eq 12.

$$e + f = \tfrac{1}{2}\Delta G_G - \tfrac{1}{6}\Delta G_A \quad (11)$$

$$\Delta G_F = \tfrac{1}{2}\Delta G_A + \tfrac{1}{2}\Delta G_G \quad (12)$$

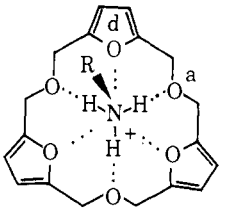
From the values of ΔG_A, ΔG_B, and ΔG_C reported in Table I and eq 9, 10, and 12, values for ΔG_D, ΔG_E, and ΔG_F are calculable. A comparison of calculated and found values provides a measure of the predictive and correlative power of this analysis. The listed calculated and found values are in reasonable agreement with one another. Although to some extent the agreement probably reflects cancellation of errors in the measurements and the assumptions, the integrated picture that emerges is reasonably consistent.

Chart I



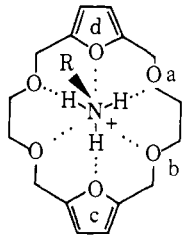
A

$\Delta G_A = 3a + 3b$



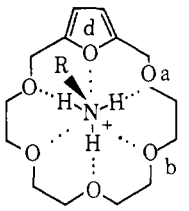
B

$\Delta G_B = 3a + 3d$



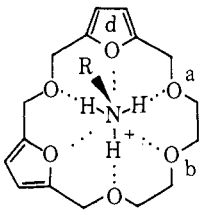
C

$\Delta G_C = 2a + 2b + c + d$



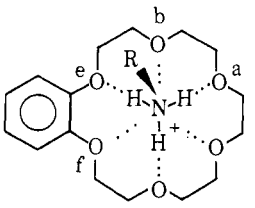
D

$\Delta G_D = 3a + 2b + d$



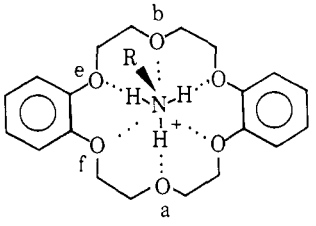
E

$\Delta G_E = 3a + b + 2d$



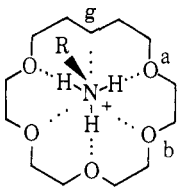
F

$\Delta G_F = 2a + 2b + e + f$



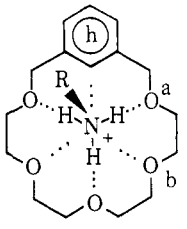
G

$\Delta G_G = a + b + 2e + 2f$



H

$\Delta G_H = 3a + 2b + g$

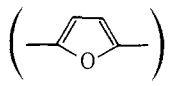


J

$\Delta G_J = 3a + 2b + h$

Host no.	Complex structure	Values of ΔG, kcal/mol T = 24 °C Calcd	Found	T = 0 °C Calcd	Found
9	**D**	−7.2	−7.2	−7.9	−7.6
11	E	−5.7	−5.6	−6.5	−6.5
5	F	−7.8	−7.9	−8.4	−8.8

This hypothesis of additivity of the free energy of contact sites can be used to predict the association energies for *t*-$BuNH_3SCN$ and many 18-crown-6 compounds containing furano and benzo units that have not as yet been made. For example, at 24 °C the cycle $(o\text{-}CH_2OC_6H_4OCH_2)_3$ should have $\Delta G = 3e + 3f = {}^3/_2\Delta G_G - {}^1/_2\Delta G_A = -5.7$ kcal/mol. Similarly, compound III below should have $\Delta G = 3c + 3d =$



III

$3\Delta G_C - 2\Delta G_A = 7.8$ kcal/mol. Thus we conclude that the former compound should act as a moderately good host, provided steric interactions do not interfere. However, the latter should not bind.

The free energies of binding of *t*-$BuNH_3^+SCN^-$ by the parent 18-crown-6 compound (**2**) and the various tetrahydrofurano-18-crown-6 compounds (**10, 12,** and **14**) are −8.81, −9.01, −8.35, and −9.01 kcal/mol at 24 °C and −9.40, −9.10, −8.34, and −9.40 kcal/mol at 0 °C, respectively. The fact that these sets of values differ by a maximum of about 9–11% indicates that the enforced inward orientations of the oxygens (particularly in **14**) do not greatly change the binding abilities of the oxygens toward RNH_3^+ in $CDCl_3$. This fact correlates well with the observation that 18-crown-6 possesses an all-gauche arrangement even in solution.[21] A maximum difference in binding abilities of **14** and **2** toward cations is expected in water. In aqueous media, hydrogen bonding of **2** to water is probably greater than that of **14** due to the greater flexibility of **2**. In other words, **2** probably fits into the liquid water structure better than **14.** The binding abilities of the various stereoisomers of the perhydrofuranocycles are also expected to vary somewhat.

Equations 6-8, 9, and 11 provide binding energies for $a + b$, $a + d$, $c + d$, and $e + f$. If energy values could be assigned to each individual parameter, the analysis would be more useful. In the absence of any measurements that bear on the relative values of a vs. b, c vs. d, or e vs. f, the proportionality assumption of eq 13 is made. Since the $O\cdots HN^+$ and $O\cdots N^+$ interactions are both electrostatic in character, the intuitive assumption that their relative values are constant, even though the substitutents on oxygens change, is appealing. Merging of eq 6-8, 9, and 11 with 13 provides eq 14-19, which express contact site parameters a through f in terms of calculable quantities. Values of g and h were then calculated from the values of a and b and eq 20 and 21. The values of a through h are listed in Table II.

$$a/b = c/d = e/f \tag{13}$$

$$a = \frac{{}^1/_3\Delta G_A\Delta G_C - {}^1/_9\Delta G_A\Delta G_B - {}^2/_9\Delta G_A{}^2}{\Delta G_C - \Delta G_A} \tag{14}$$

$$b = {}^1/_3\Delta G_A - a \tag{15}$$

$$c = a + \Delta G_C - {}^1/_3\Delta G_B - {}^2/_3\Delta G_A \tag{16}$$

$$d = {}^1/_3\Delta G_B - a \tag{17}$$

$$e = \frac{{}^1/_2\Delta G_G - {}^1/_6\Delta G_A}{1 + (b/a)} \tag{18}$$

$$f = \frac{{}^1/_2\Delta G_G - {}^1/_6\Delta G_A}{1 + (a/b)} \tag{19}$$

$$g = \Delta G_H - 3a - 2b \tag{20}$$

$$h = \Delta G_J - 3a - 2b \tag{21}$$

In this treatment, the structures for the complexes listed in Chart I were assumed. In complexes A, C, F, and G, rotation of the NH_3^+ group 60° within the host gives the original structures. However, a similar rotation in complexes B, D, H, and J results in *alternative* structures B′, D′, H′, and J′ (not formulated). If the above treatment is applied consistently to

Table II. Host-Guest Energy Contact Site Parameters[a]

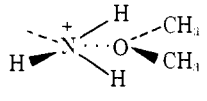
Parameter	Interaction	Structures used in calculations[b]	Contributions to $\Delta G^{a,c}$ 24 °C	0 °C
a	$(CH_2)_2O\cdots HN^+$	A, B, and C	−2.10	−2.27
b	$(CH_2)_2O\cdots N^+$	A, B, and C	−0.84	−0.86
c	$(CH{=}C)_2O\cdots HN^+$	A, B, and C	1.85	1.56
d	$(CH{=}C)_2O\cdots N^+$	A, B, and C	0.74	0.59
e	$ArO\cdots HN^+$	A, B, C, and G	−1.35	−1.55
f	$ArO\cdots N^+$	A, B, C, and G	−0.54	−0.59
g	$(CH_2)_2CH_2\cdots N^+$	A, B, C, and H	3.59	3.21
h	π-$Ar\cdots N^+$	A, B, C, and J	3.19	2.65

[a] In kilocalories per mole. [b] See Chart I. [c] Values not rounded off because they may be used to calculate other value which are rounded off.

these *alternative* structures, the calculated values of $\Delta G_{D'}$, $\Delta G_{E'}$, and $\Delta G_{F'}$ are identical with those of ΔG_D, ΔG_E, and ΔG_F, respectively. If the *alternative* structures are assumed, the contact site parameter values of Table II change in the following way: *a* and *b* interchange; *c* and *d* interchange; and *e* and *f* interchange.

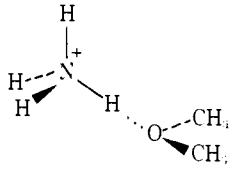
The assignments of values to the free energy contact site parameters of Table II depend on structures A–J of Chart I and the assumption that $a/b = c/d = e/f$. The data of Table II indicate that $a/b \sim 2.6$. Had structures alternative to those of Chart I been assumed, a/b would have been ~0.4. The near correspondence between the ab initio calculated value of a/b (~3) and that based on the parameters of Table II (~2.6) supports the structures of Chart I over their alternatives (see below). This near correspondence also supports the assumption that $a/b = c/d$, and by implication, $a/b = e/f$. Thus the hydrogen bonding contributions to the stabilization of the complexes appears to be substantially greater than the direct O···N^+ contributions.

Ab initio molecular orbital calculations of the energies of binding in the gas phase have been performed for NH_4^+ and $O(CH_3)_2$ and for NH_4^+ and $HOCH_2CH_2OH$.[22] The stabilization energies of structures **36–40** are listed. Comparisons of



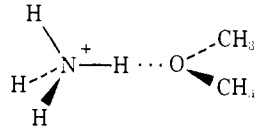
36

(Enthalpy = −14.4 kcal/mol)



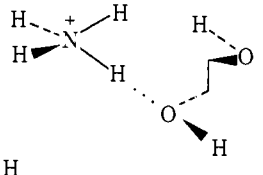
37

(−36.2 kcal/mol)



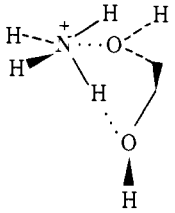
38

(−38.5 kcal/mol)



39 (anti)

(−36.1 kcal/mol)



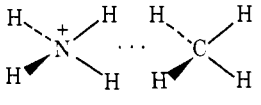
40 (gauche)

(−47.3 kcal/mol)

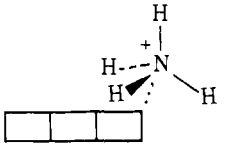
the energies for **36** and **37** or **38** indicate that the O···HN^+ binding energy is about 2.6 times that of the O···N^+ interaction. Comparison of the energies for **39** and **40** indicates the O···HN^+ interaction is about 3.2 times that of the O···N^+ interaction. Since the energy difference between **39** and **40** (present as *anti*- and *gauche*-ethylene glycol, respectively) is only ~1 kcal/mol, it is disregarded. Thus in **40**, ~75% of the binding is derived from the hydrogen bonding and ~25% from the direct electrostatic interaction.

Values of *c* and *d* in Table II which involve furan oxygens are positive, and the $(CH{=}C)_2O$ oxygens are not as repelling to HN^+ and N^+ as the $(CH_2)_2O$ oxygens are attracting. Although the furan oxygens formally possess nonbonded electron pairs, they are delocalized, and the oxygen carries a partial positive charge. Apparently the $O^{\delta+}\cdots HN^+$ and $O^{\delta+}\cdots N^+$ repulsions outweigh the O:···HN^+ or O:···N^+ attractions. Of course, the terms repulsion or attraction are relative to the competing solvent interactions with uncomplexed host and guest. Values of *e* and *f* which involve aryl oxygens are negative and therefore binding. However, the values of *e* and *f* are only about 60–70% as large as *a* and *b* values. This reduction in binding capacity associated with $ArOCH_2$ oxygens as compared to $(CH_2)_2O$ oxygens is probably due to slight delocalization of the aryl oxygen electron pairs into the aryl π system. This effect is small compared to the delocalization involving the furan system. The value of $g = 3.6$ kcal/mol at 24 °C indicates that a CH_2 group (in place of one oxygen of 18-crown-6) destabilizes the complex by about 0.7 kcal/mol less than the two flanking $(CH_2)_2O\cdots HN^+$ contacts that stabilize the complex. The value of $h = 3.19$ kcal/mol at 24 °C indicates that a 1,3-disubstituted aryl group in place of a CH_2OCH_2 unit of 18-crown-6 destabilizes the complex. This value is less than the 3.6 kcal/mol of stabilization available from the two flanking *a* type interactions visualized in structure J of Chart I. Structure J as written does not distinguish between the three conformations that can be made with CPK models. In one conformation, the hydrogen substituted in the 2-position contacts the N^+ of the guest and places the CH_3 groups in the deshielding cone of the C_6H_4 group. The second conformation places the aryl anti to the *t*-Bu group, and the N^+ contacts the π system at the 2-position of the aryl. The third conformation places that aryl hydrogen in contact with N^+ on the side remote from the CH_3 groups, two hydrogens of which are almost in contact with the π system of the aryl and lie in its shielding cone. The proton singlet of the $(CH_3)_3C$ group of the complex of **4** occurs at 0.46 ppm higher field in the ^1H NMR spectrum than the complex of **2**. Thus structure J (Chart I) of the third type of conformation is compatible with the ^1H NMR spectrum of the complex as well as with the −4.78 kcal/mol of binding free energy at 24 °C. This conformation places N^+ in contact with the π system of carbon 2 of the 1,3-disubstituted aryl group of the complex, so apparently *h* is a π-Ar···N^+ interaction. This contact is less destabilizing by about 0.5 kcal/mol than the $CH_2\cdots N^+$ contact. This decreased effect is attributable to the greater polarizability of a π as compared to a σ electron system.

Ab initio molecular orbital calculations of the interactions between N^+ and CH_2 pictured in **41** indicated them to be repulsive as observed in contact *g* of complex H of Chart I.[22] The interaction pictured in **42** between C_6H_6 and an NH_4^+ (at a



41
(destabilizing)



42
(−3.0 kcal/mol)

3.27-Å distance and a 120° bond angle between C···N and the plane of the benzene ring) is stabilizing. This interaction corresponds to that of *h* of complex J of Chart I, which was found to be stabilizing relative to contact *g*, but destabilizing relative to the competing contacts between host and solvent and guest and solvent. Paper 4 of this series reports large effects on K_a values of substituents in the remote 5′-position of 1′,3′-xylyl-18-crown-5 compounds.[4b]

A molecular model (CPK) of the complex between the tetrahydrofurano-15-crown-5 host (**16**) and the *t*-$BuNH_3^+$ ion suggests the complex might contain two *a* contacts and one *b* contact. These add to give a calculated ΔG of binding at 24 °C of −5.0 kcal/mol. The observed value (Table I) is −4.8 kcal/mol at 24 °C. A molecular model (CPK) of a complex between bistetrahydrofurano-30-crown-10 (**17**) and *t*-$BuNH_3^+$ suggests the guest might organize the host to develop three *a* and two *b* contacts to give a maximum binding energy of −8.0 kcal/mol at 24 °C. The observed ΔG value is −6.0 kcal/mol at 24 °C. The lack of correspondence between these calculated and observed binding energies indicates that the contact parameter values apply only to the 18-membered cycles with appropriately fixed contact sites.

A striking illustration of the importance of complementary placement of sites to good binding is found in the comparison of the ΔG values for the complexes between *t*-$BuNH_3^+$ and isomeric hosts **5** and **8.** In benzo-18-crown-6 (**5**), the six oxygens are fully complementary in their locations to the tripod arrangement of the *t*-$BuNH_3^+$ ion. In the 1,4-disubstituted host **8,** a maximum of four oxygens (if four are used, one must be an aryloxy) can be involved in binding the guest. As a consequence, the mislocation of binding sites in **8** as compared to the ideal location in **5** decreases the free energy of binding by >5.0 kcal/mol at 24 °C. These comparisons emphasize how important to good binding is the enforced ideal geometry of the host, in which all binding sites can act cooperatively. They also indicate that the additivity of the contact site free energy parameters are useful only when applied to systems of proper geometry.

Experimental Section

General. All chemicals were reagent grade unless otherwise specified. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from calcium hydride prior to use. All reactions utilizing *t*-BuOK or NaH were conducted in a nitrogen atmosphere. Most of the furan intermediates are sensitive to acid, heat, and/or light, and were therefore stored in the cold (dark) and utilized as soon as possible. Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given in δ ppm from internal tetramethylsilane. Spectra (^1H NMR) were recorded on a Varian HA-100 spectrometer. All IR bands are given in centimeters^{-1}; spectra were recorded on a Beckman IR-5. Gel permeation chromatography was done on a ⅜ in. × 18 ft column of Bio-Rad SX-8 beads (1000 molecular weight exclusion limit) at a flow rate of 3 mL min^{-1}, with THF as solvent. Gas-liquid chromatography (GLC) was done on a Varian Aerograph Autoprep A-700 GLC, with a ¼ in. × 6 ft column of 5% SE-30 on fluoropack at a flow rate of approximately 60 ml min^{-1}. Mass spectra were taken on an AEI model MS-9 double focusing mass spectrometer. The polyethylene glycols[23] and their ditosylates[4,23] were purified or prepared as described elsewhere.

5-Hydroxymethyl-2-furaldehyde (18). Method A. In a modification of the procedure of Haworth et al.,[7] 266 g of sucrose (0.78 mol) was dissolved in 800 mL of water at 90 °C, 1.8 g of oxalic acid was added (0.014 mol), the solution was added to an autoclave (Parr 2-L capacity, preheated to 90 °C), which was sealed and pressurized to 50 psi with nitrogen (only small amounts of **18** were obtained when the vessel was not pressurized) and placed in the heater (preheated to 145 °C). After 1 h, the internal temperature reached 145 °C, where it was maintained for 15 min. The autoclave was then cooled to 125 °C (which takes ca. 20 min), and held there for 2.5 h. Higher yields were obtained when the contents of the autocalve were mixed during the heating process. The autoclave was cooled, the solution was filtered, neutralized with 10% sodium hydroxide, and saturated with carbon dioxide (dry ice) and sodium chloride. The solution was then "extracted" six times with 1000-mL portions of ethyl acetate. In order to avoid disasterous emulsion formation, this was done by gently stirring the two-phase system for about 3 h, decanting the ethyl acetate solution, and repeating the process. It is especially important that the first "extraction" be done as gently as possible, or stable emulsions form. The extracts were dried (magnesium sulfate), solvent was distilled, and the residues were combined to give ca. 40 g of crude **18** as a brown oil (ca. 40% yield), solidifying at 0 °C. Although **18** of this purity is suitable for subsequent reactions, the oil can be distilled in small batches [bp 120–125 °C (0.3 mm) (lit. bp 110 °C (0.02 mm)][7] to give a colorless oil (25% overall). This material solidified at 0 °C: mp 28–31 °C (lit. 31.5–32 °C);[24] ^1H NMR ($CDCl_3$) 3.0 (s, 1, OH), 4.63 (s, 2, CH_2), 6.48 (d, 1, J = 3.6 Hz, H-4), 7.18 (d, 1, J = 3.6 Hz, H-3), 9.54 (s, 1, CHO); IR (neat oil) 3333 (alcohol), 2825 (aldehyde CH), 1667 (CO), 1024 (vinyl ether); mass spectrum, molecular ion at *m/e* 126.

Method B.[25] A pressure bottle equipped with a magnetic stirrer was charged with 39 mL of dioxane, 7 mL of water, 20 g of sucrose, 48 mg of chromium(III) chloride hexahydrate, and 30 mg of concentrated hydrochloric acid. The bottle was immersed in a 210 °C bath, with stirring, for 4 min, then removed and allowed to cool to 25 °C. The mixture was made basic with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic extract was dried and the solvent was evaporated to give 3.7 g of **18** (50%). When the reaction was repeated, after removing the pressure bottle from the 210 °C bath, the bottle *exploded with tremendous force, and this method is not recommended.*

2,5-Bishydroxymethylfuran (19). Crude reaction product **18** (12.6 g, 0.1 mol) was dissolved in 600 mL of absolute ethanol, 4 g of sodium borohydride (excess) was added, and the solution was stirred for 16 h at 25 °C. Concentrated hydrochloric acid was added to make the mixture acidic. The mixture was *immediately* neutralized with solid sodium bicarbonate, dried, filtered, and the solvent was evaporated (0.1 mm) to give 12.5 g of **19** (98%), which was crystallized from hot chloroform (rapidly, to avoid decomposition) to give a white solid: mp 75–76 °C (lit. mp 76 °C);[8] ^1H NMR (acetone-d_6) 3.0 (s, 2, OH), 4.47 (s, 4, CH_2), 6.17 (s, 2, CH); mass spectrum, molecular ion at *m/e* 128.

Monofuranyl-18-crown-6 (9). Tetraethylene glycol ditosylate (54 g, 0.108 mol) in THF (200 mL) was added to 1000 mL of THF containing 12.5 g of diol **19** (0.098 mol) and 24 g of *t*-BuOK (0.215 mol). The solution was stirred at 25 °C for 12 h, refluxed for 12 h, cooled, filtered, and the solvent was distilled. The crude residue (34.7 g) was chromatographed on alumina (1 kg) with ether–dichloromethane (1:1) as eluent to give 10 g of **9** (36%) as a colorless liquid; mp ca. 0 °C; ^1H NMR ($CDCl_3$) 3.60 (br s, 16, OCH_2CH_2O), 4.46 (s, 4, CCH_2O), 6.11 (s, 2, CH); mass spectrum, molecular ion at *m/e* 286. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73 H, 7.74. Found: C, 58.43; H, 7.88.

Complex between Monofuranyl-18-crown-6 (9) and Dimethyl Acetylenedicarboxylate. Cycle **9** (1.0 g, 0.0035 mol) and dimethyl acetylenedicarboxylate (0.95 mL, 0.0105 mol) were added to 5 mL of benzene. A precipitate appeared immediately. The solid was filtered and dried to give 1.1 g (74%) of complex: mp 72–73 °C (from benzene); ^1H NMR ($CDCl_3$) 3.60, 3.88, 4.46, and 6.11 (all singlets that are superimposable on the spectra of the individual components); peak of highest mass in mass spectrum occurs at *m/e* 286, the same as the molecular ion for **9.** Anal. Calcd for $C_{20}H_{28}O_{10}$: C, 56.07; H, 6.59. Found: C, 56.02; H, 6.67. When the complex was subjected to gel

permeation chromatography a very broad band resulted, the leading edge of which was mainly cycle **9**, and whose trailing edge was mainly dimethyl acetylenedicarboxylate. Attempts to sublime the complex were unsuccessful. Low-temperature ^{1}H NMR studies (CH_2Cl_2 solvent) revealed no line broadening of the methyl peak down to −100 °C.

Diels–Alder Adduct (31) between Monofuranyl-18-crown-6 (9) and Dimethyl Acetylenedicarboxylate. Cycle **9** (1.0 g, 0.0035 mol) and excess dimethyl acetylenedicarboxylate (5 mL) were added to 20 mL of toluene and heated to reflux for 15 h. Distillation of the solvent and purification of the product by gel permeation chromatography gave 1.5 g of crude adduct **31** (quantitative yield), which solidified upon standing: mp 55–60 °C; ^{1}H NMR ($CDCl_3$) 3.6 (br s, 16, OCH_2CH_2O), 3.72 (s, 6, CH_3), 4.18 (AB quartet, V_A = 3.94, V_B = 4.19, J_{AB} = 11 Hz, 4, CCH_2O), 6.94 (s, 2, CH); mass spectrum, molecular ion at *m/e* 428. Upon heating a solution of **31** in an NMR tube, the AB quartet started coalescing toward a singlet. The separation between the inner two lines of the AB quartet was recorded as a function of temperature in *o*-dichlorobenzene solvent: 13 Hz (25 °C), 7 Hz (95 °C), 5 Hz (116 °C) 4 Hz (136 °C), 3 Hz (163 °C). From these data, a minimum free energy of activation of 21 kcal/mol was calculated for the interconversion of conformers.[17a]

Upon attempted GLC purification of adduct **31** at 255 °C, it underwent retro-Diels–Alder addition to give peaks corresponding to the two starting materials. It was not possible to prepare an analytically pure sample of **31**. Spectra (^{1}H NMR) and microanalytical combustion data implicated a small amount of starting diester as the contaminant (~5%). This small amount of diester eluted on gel permeation and alumina adsorption columns with the main fraction of **31**. Attempts to distill out the diester (100 °C (0.1 mm)) resulted in partial decomposition of the adduct (retro-Diels–Alder reaction). When the complex of the two components (0.2 g) was dissolved in 10 mL of toluene and the solution refluxed for 10 h, adduct **31** was obtained (0.2 g).

Reduction of 2,5-Bishydroxymethylfuran (19) to 2,5-Bishydroxymethyltetrahydrofuran (33). Method A. Diol **19** (0.9 g, 0.007 mol) was dissolved in 50 mL of absolute ethanol containing 0.15 g of 10% palladium on carbon and stirred at 25 °C under 1 atm of hydrogen for 16 h. Isolation and distillation of the product gave 0.4 g of *trans*-**33** (bp 70–75 °C (0.1 mm)) followed by 0.6 g of *cis*-**33** (bp 80–90 °C (0.1 mm)). Boiling points and NMR spectra corresponded to those previously reported.[18]

Method B. Treatment of diol **19** as in method A, but with freshly prepared W-2 Raney nickel as catalyst, led to the isolation of a single diol, identical in physical properties with *cis*-**33**[18] prepared by method A.

Method C. Diol **19** (8.8 g, 0.0687 mol) was dissolved in a minimum amount of absolute ethanol (ca. 5 mL; the Raney nickel reduction of alcohols was found to proceed very slowly in ethanol when done on a large scale) and the solution was added to 250 mL of ethyl acetate containing 1.0 g Raney nickel. The mixture was stirred at 25 °C under 1 atm of hydrogen for 72 h. The product was distilled to give 8.8 g (98%) of *cis*-**33**, whose properties were identical with those reported above.

Reduction of Monofuranyl-18-crown-6 (9) to Monotetrahydrofuranyl-18-crown-6 (10). Method A. Cycle **9** (0.2 g) was added to 10 mL of absolute ethanol containing 30 mg of 10% palladium on carbon. The mixture was stirred at 25 °C under 1 atm of hydrogen for 1 h to give 0.2 g of **10**. That this material was a cis/trans mixture was indicated by the following ^{1}H NMR experiment with the lanthanide shift reagent europium(III) trisdipivalomethide (Eu(dpm)$_3$, LSR).[21] Incremental addition of the LSR to a solution of **10** in CCl_4 led to methine signals that were shifted downfield and broadened, with the subsequent appearance of two signals (approximately 1:1) as more LSR was added. Comparison of this with the behavior shown by that of *cis*-**10** (vide infra) suggests the differential shift is due to the presence of both the cis and trans isomers.

Method B. Treatment of cycle **9** (0.2 g) as described in method A, but with the Raney nickel catalyst, led to the isolation of 0.2 g (98%) of *cis*-**10** as an oil: ^{1}H NMR ($CDCl_3$) 1.85 (m, 4, tetrahydrofuryl CH_2), 3.5–3.7 (m, 20, all other CH_2), 4.1 (m, 2, tetrahydrofuryl CH); mass spectrum, molecular ion at *m/e* 290; GLC retention time 8.6 min at 260 °C. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.99; H, 9.08. Treatment of *cis*-**10** with the LSR as described in method A led to a downfield shift of the methine peak (stays a broadened singlet) corresponding to the lower field peak seen in the experiment above.

Thus palladium on carbon as a reduction catalyst led to a mixture of *cis*- and *trans*-**10**, whereas Raney nickel selectively produced only the cis isomer.

***cis*-Monotetrahydrofuranyl-18-crown-6)10) from *cis*-2,5-Bis(hydroxymethyl)tetrahydrofuran (33).** Tetraethylene glycol ditosylate (8 g, 0.016 mol) in 100 mL of THF was added to 400 mL of THF containing 2 g of cis-diol **33** (0.0151 mol) and 3.6 g of *t*-BuOK (0.032 mol). The solution was refluxed for 24 h, cooled, filtered, the solvent was evaporated, and the crude material (6 g) was purified by adsorption chromatography on alumina (180 g) with dichloromethane as eluent to give 1.5 g of *cis*-**10** (34%), identical with that isolated from the hydrogenation of cycle **9** (vide supra). A large amount of diethylene glycol divinyl ether (elimination of TsOH from starting ditosylate) was also isolated. Possibly if the reaction were stirred at 25 °C for 12 h before commencing refluxing (as done in other reactions) this elimination would not occur to such a large extent, and a higher yield of cycle would have been obtained.

5-Chloromethyl-2-furaldehyde (21). Sucrose (72 g, 0.21 mol) was treated with hydrogen chloride gas according to the method of Haworth et al.[7] to give 16.5 g (0.114 mol) of chloro aldehyde **21** (54%), ^{1}H NMR spectrum identical with that reported.[10]

5-Formylfurfuryl 2′-Chloroethyl Ether (22). Chloro aldehyde **21** (13.9 g, 0.096 mol) was added to 210 mL of 2-chloroethanol containing 28 g of barium carbonate and the mixture was stirred at 70 °C for 16 h. The solution was cooled, filtered, 200 mL of dichloromethane was added, and the mixture was extracted three times with water. From the organic layer, after drying, was distilled dichloromethane, residual chloroethanol, and then chloro aldehyde **22** (15.1 g, 87% yield) as a colorless liquid: bp 117 °C (0.4 mm); ^{1}H NMR ($CDCl_3$), 3.72 (m, 4, OCH_2CH_2Cl), 4.62 (s, 2, CCH_2O), 6.57 (d, 1, J = 3.5 Hz, H-3), 7.22 (d, 1, J = 3.5 Hz, H-4), 9.62 (s, 1, CHO); IR (neat) 2850 (aldehyde CH), 1680 (aldehyde CO), 1025 (vinyl ether); mass spectrum, molecular ion at *m/e* 188. Anal. Calcd for $C_8H_9ClO_3$: C, 50.95; H, 4.81. Found: C, 50.90; H, 4.81.

5-Hydroxymethylfurfuryl 2′-Chloroethyl Ether (23). Chloro aldehyde **22** (8.7 g, 0.046 mol) was dissolved in 300 mL of absolute ethanol, 1.75 g of sodium borohydride (excess) was added, and the solution was stirred at 25 °C for 16 h. The solution was acidified with concentrated hydrochloric acid, solid sodium bicarbonate was *immediately* added, the solution was filtered, the solvent distilled, and the residue was distilled to give 8.5 g of chloro alcohol **23** (97%) as a colorless liquid: bp 104–105 °C (0.2 mm); ^{1}H NMR ($CDCl_3$), 3.0 (s, 1, OH), 3.65 (m, 4, OCH_2CH_2Cl), 4.48 (s, 2, C-5-CH_2O), 4.52 (s, 2, C-2-CH_2O), 6.24 (AB quartet, V_A = 6.21, V_B = 6.28, J_{AB} = 3.3 Hz, CH); IR (neat) no carbonyl bands, 1020 (vinyl ether); mass spectrum, molecular ion at *m/e* 190. Anal. Calcd for $C_8H_{11}ClO_3$: C, 50.40; H, 5.82; Cl, 18.59. Found: C, 50.32; H, 5.86; Cl, 18.32.

2,5-Bischloromethylfuran (20). Treatment of diol **19** with either thionyl chloride and lutidine[9a] or *N*-chlorosuccinimide and triphenylphosphine[9b] led to crude dichloride **20** (78% and 70%, respectively) as an unstable yellow oil: ^{1}H NMR ($CDCl_3$) 4.53 (s, 4, CH_2), 6.30 (s, 2, CH); mass spectrum, molecular ion at *m/e* 164. Crude **20** was used immediately without further purification.

***sym*-Bisfuranyl-18-crown-6 (15). Method A.** Chloro alcohol **23** (5 g, 0.026 mol) in 250 mL of THF was added to 350 mL of THF containing 3.33 g of *t*-BuOK (0.030 mol). After stirring at 25 °C for 12 h, the solution was filtered, the solvent was evaporated, and the residue (6 g) was purified by chromatography on alumina (300 g) with CH_2Cl_2 as eluent. Approximately 10 mg of cycle **15** eluted first (see method B for properties), then 4 g (98%) of 5-hydroxymethylfurfuryl vinyl ether as a slightly yellow oil: ^{1}H NMR ($CDCl_3$) 3.0 (s, 1, OH), 4.00 (d of d, 1, J_{AM} = 2, J_{AX} = 7 Hz, H trans to furfuryl ether), 4.23 (d of d, 1, J_{MA} = 2, J_{MX} = 14 Hz, H cis to furfuryl ether), 4.40, 4.56 (2s, 4, CH_2), 6.18 (m, 2, furyl CH), 6.40 (d of d, 1, J_{XA} = 7, J_{XM} = 14 Hz, H geminal to furfuryl ether).

Method B. Sodium hydride (0.75 g, 0.032 mol) was slowly added to 500 mL of DMF containing 4 g of chloro alcohol **23** (0.021 mol). The solution was stirred at 25 °C for 48 h, 500 mL of CH_2Cl_2 solution was added, and the solution was extracted with water to remove the DMF. The CH_2Cl_2 solution was dried, evaporated, and the residue (4.4 g) was purified by chromatography on alumina (120 g) with CH_2Cl_2 as eluent to give 1 g of the vinyl ether (28%) and 0.4 g of cycle **15** (11%) as a white solid: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) 3.57 (s, 8, OCH_2CH_2O), 4.44 (s, 8, CCH_2O), 6.20 (s, 4, CH); mass spectrum, molecular ion at *m/e* 308. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32;

H, 6.54. Found: C, 62.15; H, 6.69.

Method C. Ethylene glycol (3.1 g, 0.05 mol) was added to 500 mL of DMF containing 2.4 g of NaH (0.05 mol), and the mixture was stirred at 60 °C for 3 h. Then 4.1 g of dichloride **20** (0.025 mol) was added and heating was continued for 24 h. At this time another 2.4 g of NaH and another 4.1 g of dichloride **20** were added and heating was continued for another 68 h. The DMF was evaporated, the residue was dissolved in CH_2Cl_2, filtered, and the solvent was evaporated to give 11.2 g of black oil. Purification of the oil by chromatography (alumina, 300 g, CH_2Cl_2 as eluent) yielded first an intensely red fraction and then cycle **15** (0.2 g, 3%), whose spectral properties were identical with those described above.

The red fraction was purified by gel permeation chromatography to give a trace of intensely red unidentified oil and a yellow liquid (retention volumes 104 and 160 mL, respectively). The mass spectrum of the yellow liquid gave a molecular ion at *m/e* 220. The compound (**30**) displayed a temperature-dependent ^1H NMR spectrum, which was the key to its identity: 30 °C ($CDCl_3$) 2.0–3.5 (v br, non-Gaussian line, 4, CH_2), 6.14 and 6.17 (2 overlapping doublets, 2, $J_{32} = J_{67} = 3.4$ Hz, H-3 and H-6), 6.55 (d of d, 1, $J_{23} = 3.4$, $J_{21} = 0.7$ Hz, H-2), 6.77 (d, 1, $J_{12} = 0.7$ Hz, H-2), 6.88 (d, 1, $J_{76} = 3.4$ Hz, H-7). When the temperature was increased, the broadened peak became a sharp singlet at 2.60 (coalescence temperature = 30 °C, energy of activation = 13.9 kcal/mol).[17a] When the sample was cooled below 0 °C the broadened peak separated into an AB quartet, $V_A = 2.03$, $V_B = 3.23$, $J_{AB} = 10$ Hz. Conformational mobility in cyclophanes of this type has been previously noted.[14]

2,5-Bis(5′-tetrahydropyranyl-2′,5′-dioxapentyl)furan (24). Diol **19** (9.4 g, 0.0735 mol) was added to 400 mL of DMF containing 3.6 g of NaH (0.15 mol) and the solution was heated at 60 °C for 3 h. The tetrahydropyranyl ether of chloroethanol (24.8 g, 0.15 mol) in 100 mL of DMF was added and heating continued for 66 h. Another 12.4 g of the tetrahydropyranyl ether of chloroethanol (0.075 mol) and 1.8 g of NaH (0.075 mol) were added and heating continued for another 48 h. The solvent was distilled, the residue was dissolved in CH_2Cl_2, the solution was filtered, and the solvent evaporated to give 30 g of black oil, which was purified by chromatography (alumina, 1000 g, CH_2Cl_2 as eluent) to give 16.2 g of **24** (57%) as a colorless oil: ^1H NMR ($CDCl_3$) 1.4–1.8 (m, 16, tetrahydropyranyl CH_2), 3.3–4.0 (m, 8, OCH_2CH_2O), 4.44 (s, 4, CCH_2O), 4.6 (m, 2, tetrahydropyranyl CH), 6.21 6.21 (s, 2, furyl CH); mass spectrum, molecular ion at *m/e* 384.

2,5-Bis(2′,5′-dioxapentyl)furan (25). The pyranyl ether **24** (15.8 g, 0.0411 mol) was dissolved in 50 mL of CH_2Cl_2–50 mL of CH_3OH containing 1 mL of concentrated hydrochloric acid, and the solution was stirred (25 °C) for 1 h. Solid $NaHCO_3$ was added, the solution was filtered, and solvent evaporated to give 8.2 g of diol **25** (92%) as an oil: ^1H NMR ($CDCl_3$) 3.0 (s, 2, OH), 3.5 (m, 8, OCH_2CH_2O), 4.45 (s, 4, CCH_2O), 6.20 (s, 2 furyl CH); mass spectrum, molecular ion at *m/e* 216, and a very strong P − 2 peak at *m/e* 214.

***sym*-Bisfuranyl-18-crown-6 (15). Method D.** Diol **25** (8.2 g, 0.038 mol) was added to 400 mL of DMF containing 0.96 g of NaH (0.04 mol) and the mixture was heated at 60 °C for 3 h. Then dichloride **20** (3.3 g, 0.02 mol) was added and heating continued for 24 h. Then another 0.96 g of NaH and 3.3 g of dichloride **20** were added and heating was continued for another 200 h. The product was isolated as in method C to give 11.6 g of dark red oil, which was purified by chromatography (alumina, 300 g, CH_2Cl_2 as eluent) to give **15** (0.2 g, 2%) along with cyclophane **30** (ca. 0.5 g, 22%).

Bis-5,5′-formylfurfuryl Ether (26). As noted above, distillation of crude **18** gave only a 62% yield of pure **18.** Purification of the residue by chromatography (silica gel, CH_2Cl_2 as eluent) gave ether **26** (13%) as a white solid; mp 112–114 °C (lit. mp 112 °C);[11] ^1H NMR ($CDCl_3$) 4.63 (s, 4, CH_2), 6.56 (d, 1, $J = 3.5$ Hz, H-3), 7.21 (d, 1, $J = 3.5$ Hz, H-4), 9.62 (s, 1, CHO); mass spectrum, molecular ion at *m/e* 234. Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.63; H, 4.26. Alternatively, treatment of crude **18** in refluxing toluene with toluenesulfonic acid[11] gave dialdehyde **26** in 44% yield, after silica gel chromatography.

Bis-5,5′-(hydroxymethyl)furfuryl Ether (27). Dialdehyde **26** (7.8 g, 0.0033 mol) was added to 230 mL of absolute ethanol, sodium borohydride was added (2.5 g), and the mixture was stirred at 25 °C for 16 h. The solution was cooled, acidified with concentrated hydrochloric acid, solid sodium bicarbonate was *immediately* added, the mixture was filtered, and the solvent distilled. The residue was crystallized from $CHCl_3$ to give 7.5 g of diol **27** (98%) as a white solid: mp 92–93 °C; ^1H NMR (acetone-d_6) 3.0 (s, 2, OH), 4.42 (s, 4, CH_2OCH_2), 4.49 (s, 4, CH_2OH), 6.20 (d, 1, $J = 2.9$ Hz, H-4), 6.30 (d, 1, $J = 2.9$ Hz, H-3); IR ($CHCl_3$) 3330 (alcohol), 1025 (vinyl ether); mass spectrum, molecular ion at *m/e* 236. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.55; H, 6.07.

***unsym*-Bisfuranyl-18-crown-6 (11).** Diethylene glycol ditosylate (6.6 g, 0.016 mol) in 100 mL of THF was added to 200 mL of THF containing 3.7 g of diol **27** (0.0155 mol) and 4.05 g of *t*-BuOK (0.034 mol). The solution was stirred at 25 °C for 24 h, another 6.6 g of ditosylate was added, and the solution refluxed for 6 h. The solution was filtered and the solvent evaporated to give 7 g of residue, which was purified by chromatography (alumina, 300 g, CH_2Cl_2 as eluent) to give 1.7 g of cycle **11** (35%), which was recrystallized from CH_2Cl_2–pentane to give a white solid: mp 69–70 °C; ^1H NMR ($CDCl_3$) 3.64 (s, 8, OCH_2CH_2O), 4.48 (s, 8, CCH_2), 6.22 (AB quartet, $V_A = 6.20$, $V_B = 6.24$, $J_{AB} = 0.3$ Hz, 4, CH); mass spectrum, molecular ion at *m/e* 308. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.25; H, 6.36.

***unsym*-Bistetrahydrofuranyl-18-crown-6 (12).** Cycle **11** (0.1 g, 0.0003 mol) was added to 25 mL of THF containing ca. 100 mg of Raney nickel and the mixture was stirred at 25 °C under 1 atm hydrogen for 48 h. The mixture was filtered and the solvent evaporated to give 0.1 g of cycle **12** (~98%) as an oil: ^1H NMR ($CDCl_3$) 1.4–2.0 (m, 8, tetrahydrofuranyl CH_2), 3.4–4.0 (m, 16, all other CH_2), 4.1 (m, 4, tetrahydrofuranyl CH); mass spectrum, molecular ion at *m/e* 316; GLC retention time (270 °C) was 5.0 min. Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.73; H, 8.92. Found: C, 60.79; H, 8.73.

Trisfuranyl-18-crown-6 (13). Method A. Dichloride **20** (5.2 g, 0.0315 mol) in 100 mL of THF was added to 400 mL of THF containing 7.5 g of diol **27** (0.0315 mol) and 7.8 g of *t*-BuOK (0.07 mol). After stirring at 25 °C for 48 h, the solution was filtered and the solvent evaporated to give 10.7 g of dark red residue, which was purified by chromatography (silica gel, 230 g, CH_2Cl_2 as eluent) to give 1 g of solid, which was recrystallized from CH_2Cl_2–pentane to give cycle **13** (10%) as a white solid: mp 124–126 °C; ^1H NMR ($CDCl_3$) 4.47 (s, 12, CH_2), 6.27 (s, 6, CH); mass spectrum, molecular ion at *m/e* 330. Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.56; H, 5.65. Also recovered were cyclophane **30** (29%) and starting diol **27** (3.7 g, 50%).

Bis-5,5′-(chloromethyl)furfuryl Ether (28). Diol **27** was treated with thionyl chloride and lutidine[9a] to give crude **28** as a yellow oil (75%): ^1H NMR ($CDCl_3$) 4.5 (s, 4, $ClCH_2$), 4.6 (s, 4, OCH_2), 6.3 (s, 4, CH). Crude **28** was crystallized from CH_2Cl_2–pentane (−20 °C) to give a white solid, mp 34–35 °C. Both the solid and crude **28** rapidly (ca. 10 min) decomposed in moist air, and hence crude **28** was used immediately after preparation without purification.

Trisfuranyl-18-crown-6 (13). Method B. Dichloride **28** (1.5 g, 0.00545 mol) in 30 mL of DMF was added to 80 mL of DMF containing 0.7 g of diol **19** (0.00545 mol) and 0.33 g of NaH (0.0136 mol). The solution was stirred at 25 °C for 120 h, the solvent was distilled, the residue was dissolved in CH_2Cl_2, the solution was filtered, and the solvent distilled to give 1.5 g of residue. This material was purified by chromatography (silica gel, 50 g, CH_2Cl_2 as eluent) to give 0.72 g of cycle **13** (40%), whose properties were identical with those for **13** prepared by method A. When this reaction was conducted under the above conditions but with *t*-BuOK as base, the yield of cycle **13** was 35%, and much starting diol was recovered.

Tristetrahydrofuranyl-18-crown-6 (14). Method A. Trisfuranyl-18-crown-6 (**13**) (0.2 g, 0.0006 mol) was added to 20 mL of absolute ethanol containing ca. 100 mg of Raney nickel and the mixture was stirred at 25 °C under 1 atm of hydrogen for 12 h. The solution was filtered and the solvent evaporated to give 0.2 g of cycle **14** (~98%) as a colorless oil: ^1H NMR ($CDCl_3$) 1.8 (m, 12, tetrahydrofuryl CH_2), 3.5 (m, 12, all other CH_2), 4.2 (m, 6, CH); mass spectrum, molecular ion at *m/e* 342; GLC retention time (280 °C) 5.4 min. Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.16; H, 8.83. Found: C, 63.03; H, 8.91.

Bis-5,5′-(hydroxymethyl)tetrahydrofuranyl Ether (35). Diol **27** (3 g, 0.0126 mol) was dissolved in the minimum amount of absolute ethanol (ca. 5 mL) and added to 150 mL of ethyl acetate mixed with ca. 500 mg of Raney nickel. The mixture was stirred at 25 °C under 1 atm of hydrogen for 120 h. The mixture was filtered and the solvent evaporated to give 3 g of reduced diol **35** (~98%) as a colorless liquid: ^1H NMR ($CDCl_3$) 1.9 (m, 8, tetrahydrofuryl CH_2), 3.5 (m, 8, all other CH_2), 4.2 (m, 4, CH), 4.4 (s, 2, OH); mass spectrum, no molecular ion, but a strong P − 31 peak at *m/e* 215; GLC retention time (270 °C) 4.5 min; gel permeation retention volume 124 mL. Anal.

Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.01. Found: C, 58.74; H, 8.91. Alternatively, dialdehyde **26** (0.2 g, 0.0085 mol) was added to 25 mL of THF mixed with ca. 100 mg of Raney nickel and the mixture was stirred at 25 °C under 1 atm of hydrogen for 158 h. The solution was filtered and the solvent evaporated to give 0.2 g (~96%) of diol **35**, identical with **35** prepared above.

***cis*-Bis-2,5-(tosyloxymethyl)tetrahydrofuran (*cis*-34).** Diol *cis*-**33** was treated with *p*-toluenesulfonyl chloride in dry pyridine at 0 °C to give ditosylate *cis*-**34** (80%), whose properties were identical with those reported.[18]

Tristetrahydrofuranyl-18-crown-6 (14). Ditosylate *cis*-**34** (4.4 g, 0.01 mol) in 70 mL of DMF was added to 200 mL of DMF containing 2.46 g of diol *cis*-**35** and 0.6 g of NaH (0.025 mol). The solution was stirred at 25 °C for 144 h, the solvent was distilled, the residue was dissolved in CH_2Cl_2, the solution filtered, and the solvent evaporated. The crude residue formed a colloidal suspension when added to chloroform, and the ^1H NMR spectrum of the solution (CD_2Cl_2) indicated the presence of both **14** and sodium tosylate (approximately 2:1). The "complex" was dissolved in water and extracted with organic solvents: (a) with benzene, all material stayed in the aqueous phase; (b) with dichloromethane, both crown and the salt went into the organic phase; (c) with chloroform, only the crown went into the organic phase. The crude residue therefore was dissolved in 20 mL of water and extracted six times each with 40 mL of chloroform, the organic layer was dried, and the solvent evaporated. The residue (3.3 g) was purified by chromatography (alumina, 85 g, CH_2Cl_2 as eluent) to give 1.5 g of cycle **14** (44%), whose properties were identical with those of the same compound prepared by method A.

Monotetrahydrofuranyl-15-crown-5 (16) and *sym*-Bistetrahydrofuranyl-30-crown-10 (17). Triethylene glycol ditosylate (15 g, 0.032 mol) in 500 mL of THF was added to 1 L of THF containing 4.29 g of diol *cis*-**33** (0.0318 mol) and 7.3 g of *t*-BuOK (0.065 mol). The solution was stirred at 25 °C for 200 h, filtered, and the solvent was evaporated to give 7 g of residue, which was purified by chromatography (alumina, 200 g, CH_2Cl_2 as eluent) to give 2.4 g of a mixture of cycles **16** and **17** (3:1 by ^1H NMR, 23 and 8%, respectively). The mixture was purified by gel permeation chromatography to give **16** as an oil: ^1H NMR ($CDCl_3$) 1.9 (m, 4, tetrahydrofuryl CH_2), 3.5–3.8 (m, 16, all other CH_2), 4.1 (m, 2, CH); mass spectrum, molecular ion at *m/e* 246; gel permeation retention volume 135 mL; GLC retention time (250 and 300 °C) 4.5 and 1.5 min, respectively. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.01. Found: C, 58.49; H, 8.98.

Also isolated from the gel permeation chromatograph was cycle **17** as an oil: ^1H NMR ($CDCl_3$) 1.8 (m, 8, tetrahydrofuryl CH_2), 3.4–3.8 (m, 32, all other CH_2), 4.1 (m, 4, CH); mass spectrum, molecular ion at *m/e* 492; gel permeation retention volume 112.5 mL; GLC retention time (260 and 300 °C) 28 and 9.5 min, respectively. Anal. Calcd for $C_{24}H_{44}O_{10}$: C, 58.52; H, 9.01. Found: C, 58.25; H, 8.95.

1,4,7,10,13,16-Hexaoxa[16]paracyclophane (8), and 1,4,7,10,-13,16,23,26,29,32,35,38-Dodecaoxa[16.16]paracyclophane (43). Pentaethylene glycol ditosylate (54.6 g, 0.1 mol) in dioxane–butanol (60 mL–20 mL) was added to 450 mL of butanol containing 12.7 g of hydroquinone (0.115 mol) and 9.1 g of sodium hydroxide (0.228 mol) in 10 mL of water. After refluxing for 19 h, the solution was filtered and the solvent evaporated to give 30 g of residue, which was purified by chromatography (alumina, 900 g, ether as eluent) to give a mixture of cycles **8** and **43.** Cyrstallization of the mixture from benzene–hexane gave **43** as a white solid, 2.2 g (7%): mp 67–69 °C; ^1H NMR ($CDCl_3$) 3.6–4.1 (m, 40, CH_2), 6.7 (s, 8, CH); gel permeation retention volume 128 mL; mass spectrum, molecular ion at *m/e* 624. Anal. Calcd. for $C_{32}H_{48}O_{12}$: C, 61.52; H, 7.74. Found: C, 61.54; H, 7.54.

Further purification of the crude mother liquors by gel permeation chromatography gave cycle **8** as an oil, 0.62 g (2%): bp 120–130 °C (0.1 mm); ^1H NMR ($CDCl_3$) 3.2–3.8 (m, 16, CH_2OCH_2), 4.2 (m, 4, $ArOCH_2$), 6.9 (s, 4, CH); mass spectrum, molecular ion at *m/e* 312; gel permeation retention volume 151 mL. Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.53; H, 8.02.

1,4,7,10,13-Pentaoxacyclooctadecane (3).[6a] A mixture of 10.4 g (0.10 mol) of 1,5-pentanediol, 10.6 g (0.22 mol) of NaH, and 900 mL of DMF was stirred at 25 °C for 1 h. A solution of tetraethylene glycol ditosylate (50.2 g, 0.10 mol) in 100 mL of DMF was added, and the mixture was stirred for 6 days. The solvent was evaporated (20 mm) and the residue mixed with CH_2Cl_2 and water. The organic layer was washed with 5% hydrochloric acid and water, dried, and the solvent evaporated. The product was distilled at 135–140 °C (0.15 mm), weight 6.95 g (26%), and further purified by gel permeation chromatography, retention volume 155 mL: ^1H NMR ($CDCl_3$) 1.55 (s, 6, $CH_2CH_2CH_2$), 3.56 (m, 20, CH_2O); mass spectrum, molecular ion at *m/e* 263. Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.41; H, 9.90.

Cycle **3** formed a crystalline 1:1 complex[6a] with dimethyl acetylenedicarboxylate as did 18-crown-6 (see below): mp 63–64 °C, ^1H NMR ($CDCl_3$) 1.53 (br s, 6, $CH_2CH_2CH_2$), 3.53, 3.60 (s, s, 20, OCH_2), 3.78 (s, 6, OCH_3). Anal. Calcd for $C_{19}H_{32}O_9$: C, 56.42; H, 7.98. Found: C, 56.44; H, 8.09.

2,5,8,11,14,17-Hexaoxaoctadecane (1) To a solution of sodium methoxide (2.37 g, 0.044 mol) in methanol (200 mL) was added pentaethylene glycol ditosylate (22.6 g, 0.044 mol), and the mixture was heated at reflux for 48 h. The solvent was evaporated and the residue was shaken with water and CH_2Cl_2. The organic layer was washed with water, dried, the solvent was evaporated, and the residue was chromatographed on 500 g of alumina (pentane–ether) and distilled under high vacuum. The product was chromatographed on the gel permeation column (retention volume, 153 mL) to give 7.3 g (62%) of **1** as an oil, single peak by GLC: ^1H NMR ($CDCl_3$) 3.30 (s, 20, OCH_2), 3.43 (s, 6, OCH_3); mass spectrum, molecular ion at *m/e* 266. Anal. Calcd for $C_{12}H_{26}O_6$: C, 54.11; H, 9.84. Found: C, 53.89; H, 9.62.

Complex between 18-Crown-6 (2) and Dimethyl Acetylenedicarboxylate.[6c] A solution of 0.40 g (1.5 mmol) of ca. 85% pure **2** and 0.4 g (2.8 mmol) of dimethyl acetylenedicarboxylate in 5 mL of benzene was allowed to stand at 25 °C until half the solvent had evaporated (2 days). The 1:1 complex that separated was collected to give 0.32 g (50%) of material, mp 100–101 °C. An osmometric molecular weight determination of a 0.02 M solution of the complex in $CHCl_3$ gave an apparent molecular weight of 201. Anal. Calcd. for $C_{18}H_{30}O_{10}$: C, 53.19; H, 7.44. Found: C, 53.27; H, 7.53.

***m*-Xylyl-18-crown-5 (4).** To a solution of 1,3-bis(hydroxymethyl)-benzene[26] (5.52 g or 40 mmol, mp 54–57 °C) in 400 mL of dry DMF was added 9.43 g (84 mmol) of *t*-BuOK followed by 20.1 g (40 mmol) of tetraethylene glycol ditosylate in 100 mL of dry DMF. The mixture was stirred at 25 °C for 3 days. Evaporation of the solvent under vacuum gave a residue, which was shaken with a mixture of CH_2Cl_2 and 3% aqueous HCl. The organic layer was washed with water, dried, the solvent was evaporated, and the residue was chromatographed on silica gel with ether as eluting agent. The product (3.6 g or 30%) was crystallized from pentane to give prisms: mp 43–45 °C; ^1H NMR ($CDCl_3$) 3.73 (d, 16, OCH_2CH_2O), 4.65 (s, 4, $ArCH_2$), 7.1–7.3 (m, 3, ArH), 7.7–7.8 (s, 1, ArH); mass spectrum, molecular ion *m/e* 296. Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.00; H, 8.06.

***tert*-Butylammonium Thiocyanate.** To 20 g of *tert*-butylamine (0.294 mol) was carefully and slowly added 19 g of ammonium thiocyanate (0.25 mol). The mixture was heated at 85 °C until NH_3 evolution ceased (about 1 h). The cooled solid was recrystallized from 2.5 L of chloroform to give 23.7 g (72%) of salt, mp 124–125 °C. Anal. Calcd for $C_5H_{12}N_2S$: C, 45.43; H, 9.15; N, 21.20. Found: C, 45.41; H, 9.02; N, 21.09.

Determination of Distribution Constants (K_d). Chloroform (60 mL) was shaken at 24 °C for 1 min with 30 mL of water containing 3.950 g (30 mmol) of *tert*-butylammonium thiocyanate. The organic phase was very carefully separated and evaporated to give 3.0 mg (0.023 mmol) of *tert*-butylammonium thiocyanate. These results provided a value of $K_d = 3.8 \times 10^{-4}$ M^{-1}.

An exact duplication of the above experiment except that the extraction was performed at 0 °C provided 10.0 mg (0.076 mmol) of salt in the organic phase and $K_d = 1.26 \times 10^{-3}$ M^{-1}.

Extraction Experiments. Scale A. The host compound (0.0835 mmol) was dissolved in 0.60 mL of $CDCl_3$ and the solution was used to extract 1.6 mL of D_2O containing 21.2 mg (0.16 mmol) of *t*-$BuNH_3SCN$ at 24 °C for 1 min. The phases were allowed to separate (30–60 min), and each phase was pipetted into an NMR tube and its integrated spectrum obtained. The layers were then pipetted back together, cooled to 0 °C, and the procedure repeated. The guest-to-host molar ratios in the $CDCl_3$ phase (R) were calculated from the integral of the $(CH_3)_3C$ peak of the salt and the total integral of the cycle. Less than 0.5% of the total host used was detected in the aqueous layer at either temperature except when 18-crown-6 (**2**) was employed. At 24 °C, 15% of the **2** used was in the aqueous layer at equilibrium. At 0 °C, 12% was in the aqueous layer at equilibrium. The R values

obtained for all hosts are recorded in Table I. Those for **2** as host are corrected for the amount of host found in the D_2O layer at equilibrium.

Extraction Experiments. Scale B. The host compound (0.0835 mmol) was dissolved in 0.60 mL of $CDCl_3$ and used to extract 0.6 mL of D_2O containing 31.6 mg (0.24 mmol) of *t*-$BuNH_3SCN$ at 24 and 0 °C. Otherwise the procedure was identical with that for scale A. Table I records the results.

Extraction Experiments. Scale C. The host compound (0.0835 mmol) was dissolved in 0.60 mL of $CDCl_3$ (a 0.139 M solution) and used to extract 0.30 mL of D_2O containing 39.5 mg (0.3 mmol) of *t*-$BuNH_3SCN$ at 24 and 0 °C. Otherwise the procedure was identical with that for scale A. Table I records the results.

Determination of Distribution Constants (K_d). Two methods were used to determine K_d values defined in eq 4. The first involved a conductometric and the second a spectroscopic method.

A. Conductometric Method. A glass conductivity cell with platinized platinum electrodes (cell constant = 0.356 cm^{-1}) was used in conjunction with a Phillips measuring bridge (PR 9530). All conductivity measurements were made at 23.8 ± 0.2 °C. High purity water with a conductivity of $(1.2 \pm 0.3) \times 10^{-6}$ Ω^{-1} cm^{-1} was used for all measurements. The solvents D_2O and $CDCl_3$ from Stohler Isotope Chemicals were used directly. The conductivity cell was calibrated for *t*-$BuNH_3SCN$ concentrations with a least-squares fitted standardization curve obtained by measurement of the conductivities of seven standard solutions ranging in concentration from 0 to 40×10^{-5} M (correlation coefficient = 0.999 92). Measured conductivities ranged from 1.1×10^{-6} to 40×10^{-6} Ω^{-1} cm^{-1}. The deviations in the measured conductivity of pure water indicated a lower limit of detectability of salt of approximately 0.5×10^{-5} M.

Values of K_d were determined as follows. To 25 mL of a 1.0 M D_2O solution of *t*-$BuNH_3SCN$ contained in a separatory funnel was added 50 mL of $CDCl_3$. The mixture was shaken vigorously at 23.8 ± 0.2 °C and the phases were allowed to separate for 24 h. The $CDCl_3$ layer was carefully drawn off and extracted with 50 mL of high purity water. The conductivity of this aqueous extract was then measured, and the concentration of the salt in the extract read off the calibration curve. Since K_d is very low valued, essentially all the salt initially extracted into the chloroform layer was extractd into the second water layer. Furthermore, a trivial amount of salt in the original water layer was removed by extraction into the $CDCl_3$ layer. The above procedure was applied to three successive $CDCl_3$ extractions of the same original aqueous solution of *t*-$BuNH_3SCN$ and the three $CDCl_3$ layers were separately extracted into three aqueous solutions whose salt concentrations were determined from their conductivities. The K_d values calculated from the concentrations of the salt in the three final aqueous solutions were 6.4×10^{-5}, 3.4×10^{-5}, and 2.3×10^{-5} M^{-1} the average of which was $(4.0 \pm 2) \times 10^{-5}$ M^{-1}. The same extraction procedure was repeated in a cold room at 0 °C and the extractions of the $CDCl_3$ layers with water were performed at 23.8 ± 0.2 °C and the concentrations of salt determined by conductivity. In two extractions from the same salt solution, K_d values of 3.4×10^{-5} and 2.0×10^{-5} M^{-1} were obtained to give an average value of $(2.7 \pm 0.7) \times 10^{-5}$ M^{-1}.

In a control experiment, 25 mL of salt-free D_2O was extracted with 25 mL of $CDCl_3$, which in turn was extracted with 25 mL of conductivity water. The conductivity of the final aqueous solution was $(1.3 \pm 0.2) \times 10^{-6}$ Ω^{-1} cm^{-1}, identical within error of the original conductivity water.

B. Spectroscopic Method. Fluorescamine (Fluram) was obtained from Hoffmann-La Roche, Inc., Nutley, N.J., and was recrystallized four times from dichloromethane–ether prior to use. SpectrAR grade acetone (Mallinckrodt) was distilled through a Vigreux column prior to use. All chemicals used in the preparation of the borate buffer were AR grade (Mallinckrodt) and the D_2O solvent (Stohler Isotope Chemicals) was used directly. The $CDCl_3$ was purified by passage through a column of EM Reagents neutral alumina activity grade I immediately prior to use. High purity water refers to water purified by a large commercial unit, including submicron filtration, reverse osmosis, and deionization, and had a conductivity of $(1.2 \pm 0.3) \times 10^{-6}$ Ω^{-1} cm^{-1}. It was used throughout the analysis. All glassware except the syringes were cleaned by immersion in hot 35% nitric acid (steam bath) for at least 4 h, carefully rinsed with distilled water, soaked in distilled water for 8–10 h, rinsed with high purity water, and air dried. Fluorescence measurements were performed with a Spex Fluorolog photon counting fluorimeter at 25 °C. The excitation wavelength was 386 nm, and the emission wavelength was 472 nm.

The fluorescence method[27] was used to analyze for *t*-$BuNH_2$. To a 20-mL culture tube were added 1.5 mL of borate buffer[28] and 1.8 mL of a *t*-$BuNH_3SCN$ solution in high-purity water. The concentration of the stock solution of borate buffer (0.1 M) was such that the final solution (3.0 mL) contained the amine in 0.05 M borate buffer at pH 8.8. While this solution was vigorously agitated on a vortex-type mixer, 1.0 mL of a freshly prepared fluorescamine solution (14 mg of fluorescamine in 50 mL of acetone) was added rapidly with a glass syringe. The fluorescence of the resulting mixture was then read on the fluorimeter. The fluorescence developed within minutes and thereafter remained constant for at least 8 h. For each run, a separate standardization curve was obtained from five standard *t*-$BuNH_3Cl$ solutions ranging in concentration from 0.29×10^{-5} to 5.7×10^{-5} M and a blank. Plots obtained from the six points gave least-squares lines with correlation coefficients ranging from 0.997 to 0.9998. Deviations in the measured values of the blank for seven separate standard curves indicate a lower limit of detectability by this method of $\sim 0.05 \times 10^{-5}$ M.

Values of K_d were measured as follows. To a 40-mL centrifuge tube fitted with an aluminum foil cap was added 5 mL of a 1.0 M solution of *t*-$BuNH_3SCN$ in D_2O. To this solution was added 10 mL of $CDCl_3$. The phases were mixed vigorously on a vortex mixer for 20 s, separated by centrifugation for 15 min. Most of the aqueous phase was withdrawn carefully via syringe and the volume noted (~4.6 mL). A 5-mL aliquot of the $CDCl_3$ phase was then withdrawn via syringe, great care being taken not to contaminate the $CDCl_3$ layer with any of the aqueous phase. This $CDCl_3$ solution was added to another centrifuge tube and extracted with 5 mL of high-purity water (vortex mixer) and centrifuged. Approximately 3 mL of the resulting aqueous extract was removed with a disposable pipet and used in 1.5-mL portions for the above spectroscopic analysis. In runs where multiple analyses on the same original D_2O–salt solution were performed, the D_2O–salt solution recovered (see above) was injected into a centrifuge tube, twice its volume of $CDCl_3$ was added (always >7 mL), and the procedure repeated. For each analysis, 5 mL of the $CDCl_3$ phase was withdrawn and reextracted with 5 mL of high purity water.

As a check on the reextraction procedure, two solutions of *t*-$BuNH_3ClO_4$ in $CDCl_3$ were prepared, one of 6.0×10^{-5} M and the other of 3.0×10^{-5} M. Extraction of 5 mL of these solutions with high-purity water followed by spectroscopic analysis of the aqueous extract gave values of 6.2×10^{-5} and 3.6×10^{-5} M amine, respectively. These results indicate a valid estimate of the salt concentrations in the $CDCl_3$ phase can be made by the distribution–reextraction process.

Blanks (consisting of aqueous phases obtained exactly as above except salt was omitted from the original D_2O phase) were analyzed for each run. In 14 analyses, a mean value of 0.116×10^{-5} M was obtained, with a standard deviation of 0.10×10^{-5} M. The origin of this blank fluorescence is presumably due to impurities in the D_2O or $CDCl_3$. This blank fixes a lower limit for estimation of salt concentration at $\sim 0.3 \times 10^{-5}$ M.

Three runs were made to determine the K_d of the *t*-$BuNH_3SCN$ at 24 °C. All values were corrected for the fluorescent blanks. The first run gave a value of 6.7×10^{-5} M^{-1}. In run 2, multiple analyses gave K_d values of 7.8×10^{-5} M^{-1} for the first and 5.3×10^{-5} M^{-1} for the second extraction. In run 3, multiple extractions gave 8.1×10^{-5}, 6.7×10^{-5}, and 5.7×10^{-5} M^{-1}. These six values were averaged to give $(6.7 \pm 1.0) \times 10^{-5}$ M^{-1} by the fluorescent method at 24 °C. As a crude check for possible partitioning of an equilibrium amount of unprotonated amine into the $CDCl_3$ phase, the final salt solution from run 3 was treated with a drop of concentrated HCl to give a pH of ~1. Extraction of this acidified solution gave $K_d = 2.6 \times 10^{-5}$ M^{-1}. However, an H_2S odor developed, and the value was not used. The somewhat higher values obtained by the fluorescent method may be due to a small equilibrium concentration of free amine present in both the aqueous and chloroform layer, but the agreement between the conductometric and spectrometric methods is within experimental error of one another. The two together gave results satisfactory for our purposes.

The same extraction and separation procedures were repeated in a cold room at −3 °C. In one run with three multiple extractions, K_d values of 3.1×10^{-5}, 1.3×10^{-5}, and 1.4×10^{-5} M^{-1} were obtained and were averaged to give $(1.9 \pm 0.7) \times 10^{-5}$ M^{-1} at −3 °C.

The values of K_d used in the calculations of the paper were the average of those obtained by conductivity and by spectroscopy, namely

5.2×10^{-5} M^{-1} at 24 °C and 2.3×10^{-5} M^{-1} at 0 °C. These values are obviously only approximate.

References and Notes

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Gas-Phase Nucleophilic Displacement Reactions

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Abstract: Displacement reactions of each of a variety of anionic nucleophiles reacting with each of a variety of neutrals have been studied by pulsed ion cyclotron resonance (ICR) spectroscopy. Rate constants for these reactions are interpreted in terms of a three-step reaction sequence. RRKM calculations are used to obtain information about the energy of transition states. The origin of the barrier to reaction in solution is discussed.

Bimolecular nucleophilic substitution (S_N2) reactions have been one of the most widely studied families of reactions in chemistry. For many years they were the favorites of physical organic chemists. The history of their study closely parallels and is sometimes responsible for the development of ideas such as structure-reactivity relationships, linear free energy relationships, steric inhibition, kinetics as a probe of mechanism, stereochemistry as a probe of mechanism, and solvent effects. Since the basic properties of the mechanism have been well-known for a long time; they are discussed in detail in most physical organic chemistry texts and other books as well.[1-5]

$$X^- + RY \rightarrow Y^- + RX$$

The reaction was first recognized to be first order in both nucleophile (X^-) and substrate (RY) by Hughes, Ingold, and co-workers.[6] It is thus distinct from the first-order S_N1 process, which involves dissociation of the substrate into a carbonium ion (R^+) and anion (Y^-) in the rate-determining first step. The S_N2 reaction was envisioned as proceeding in one step, with formation of the new bond occurring synchronously with cleavage of the old bond. The reaction has been shown to give inversion of configuration at the site of attack, implying backside attack at carbon. As a result, the rate of the reaction is very sensitive to steric hindrance to backside attack. Alkyl groups attached to the carbon under attack greatly inhibit the reaction.

In addition to the structure of the substrate, the nature of the nucleophile and leaving group affect the overall reaction rate. Many attempts have been made to correlate nucleophilicity, which is a kinetic property of a nucleophile measured by its rate constant for an S_N2 reaction, with thermodynamic properties such as basicity, polarizability, and redox potential. These attempts have generally failed except for nucleophiles of related structure, such as substituted phenoxide ions. The overall rates of S_N2 reactions have been found to be strongly solvent dependent. Often the rate of a reaction will increase by orders of magnitude on switching from a protic solvent such as methanol to a dipolar aprotic one such as DMSO. Winstein even found that the nucleophilic order of the halides in protic solvents ($I^- > Br^- > Cl^- > F^-$) was reversed in acetone solvent.[7]