Host–Guest Complexation. 6. The [2.2]Paracyclophanyl Structural Unit in Host Compounds[1,2]

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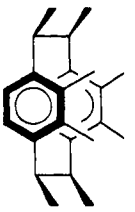
Abstract: Six new macrocyclic polyethers (**1–6**) have been prepared that incorporate the aryl groups of the [2.2]paracyclophane nucleus in the macroring system. Also prepared were four new macrocyclic polyethers (**7–10**) that incorporate *p*-phenylene units in the macroring. The appropriate phenols and polyethylene glycol chlorides or tosylates served as starting materials. Cycle **3** formed 1:2 complexes with *tert*-butylammonium thiocyanate (crystalline) and 1:1 complexes (crystalline) with hexamethylenediammonium or decamethylenediammonium hexafluorophosphate. Hosts **3, 5,** and **6** solubilized in $CDCl_3$ 2 mol of solid *t*-$BuNH_3^+(C_6H_5)_4B^-$ that were insoluble in the absence of cycle. The ^1H NMR spectra of these complexes provide evidence for their structures. Association constants of these hosts with Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, and *t*-$BuNH_3^+$ picrates in $CDCl_3$ at 24 °C are reported and discussed.

The rigid, layered structure of [2.2]paracyclophane with its 16 substitutable sites makes it an interesting unit for shaping host compounds for molecular complexation studies. Eight bonds generally point in one direction, and the other eight in the opposite direction. Incorporation of this unit into a macroring consumes two of these sites, and six remain which point in the general direction of the macroring. If the macrocycle is an assembly of groups for binding guest compounds, the remaining six sites might carry substituents that terminate in functional groups that provide for additional binding, valence control, and catalysis or chiral barriers. The [2.2]paracyclophanyl group possesses symmetry properties that are highly manipulatable through control of their substitution patterns.[3]

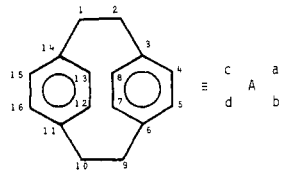


Eight semiconvergent sites of [2.2]paracyclophane

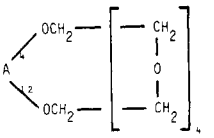
This paper reports the synthesis and a survey of the complexing properties of macrocyclic polyethers **1–6** which utilize in various possible pairs the aromatic bonding sites of [2.2]paracyclophane. For comparison, the four macrocyclic polyethers **7–10** were prepared which contain one or two *p*-phenylene units as part of the major ring system.

Synthesis

In the critical ring-closing reactions, no attempt was made to use high dilution nor to maximize yields. Diol **11**[4] with pentaethylene glycol and base gave **1.** The three tetraacetates **12–14** were prepared by a new method for preparing [2.2]paracyclophanes[5] which involved reducing the appropriate 3,6-bis(bromomethyl)benzenes with NaI in refluxing 2-butanone. The reaction probably goes through the *p*-xylylene intermediate formed by a 1,6-elimination, and the cycle formed by a 1,6 to 1,6-addition reaction as in the Winberg et al. method.[6] Tetraacetate **12** (20%) involved 3,6-bis(bromomethyl)catechol diacetate[7] as starting material, whereas **13** (25%) and **14** (5%) were separated from the mixture obtained when 2,5-bis(bromomethyl)hydroquinone diacetate[7] was reductively cyclized. The three cyclic tetraacetates were reduced with $LiAlH_4$, and the corresponding tetrols[8] were used directly



[2.2]Paracyclophane



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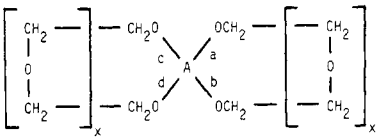
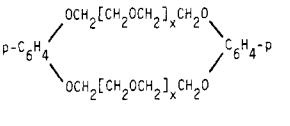
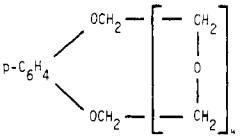




Comp.	a	b	c	d	x	Mp(°C)	Yield(%)		x	Mp(°C)	Yield(%)
2	4	5	15	16	3	192-193	6	7	2	96-97	7
3	4	5	15	16	4	157-158	14	8	3	93-94	8
4	4	12	7	15	3	118-119	3	9	4	67-69	7
5	4	12	7	15	4	121-122	25				
6	4	13	7	16	4	133-134	23				



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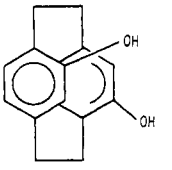
in the ring closures without characterization. Macrocyclic ethers **2–6** were prepared from these tetrols and tetraethylene glycol or pentaethylene glycol dichlorides or ditosylates under basic conditions that carefully excluded oxygen.

In the above synthesis of **2,** the cyclophane ring system was



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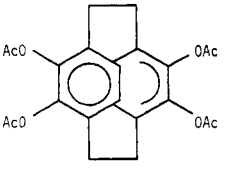

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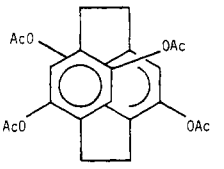

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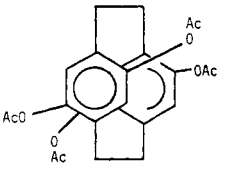

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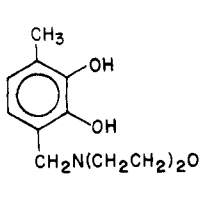
first assembled and then the macrocycle. In a second synthesis, the order was reversed. A Mannich reaction applied to 1,2-dihydroxy-3-methylbenzene gave **15** (83%), which with pentaethylene glycol dichloride and base gave **16** (35%). This substance was converted to its methiodide **17** whose derived



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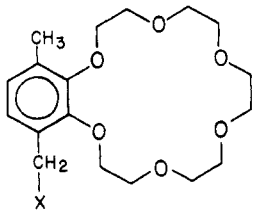


16, X = $N(CH_2CH_2)_2O$

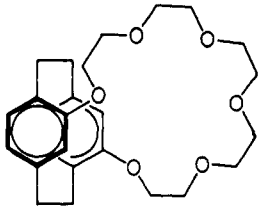
17, X = $\overset{+}{N}(CH_2CH_2)_2O\,I^-$, CH_3

quaternary ammonium hydroxide when heated[6] gave **2** (10%). The samples of **2** prepared by the two separate routes exhibited identical properties.

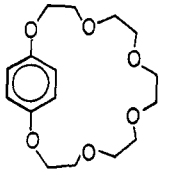
Macrocyclic polyethers **7–9** were prepared from hydroquinone and triethylene glycol, tetraethylene glycol, and pentaethylene glycol ditosylates, respectively. The dimeric products **7–9** moved slower on alumina chromatograms than the monomeric, of which only **10** was characterized.

Complexation

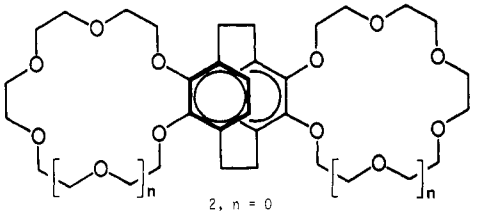
Symmetry Properties and Shapes of Hosts 1–10. The symmetry properties of the macrocyclic hosts are not only interesting in their own right, but also dictate the number of stereoisomeric complexes each might form with alkylammonium salts. Five different molecular point groups are represented by compounds **1–10,** which are formulated with their



1, C_2, chiral
nonsided



10, $C_{2v} = C_2 + 2\sigma$
achiral, nonsided



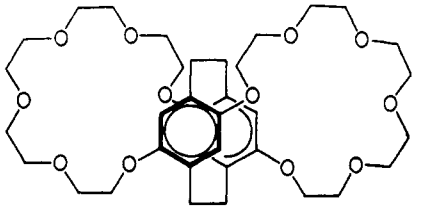
2, n = 0
3, n = 1

$C_{2h} = C_2 + \sigma$
achiral, sided

oxygens turned inward toward the holes. The point-group designations are placed under the formulas along with the symmetry elements.

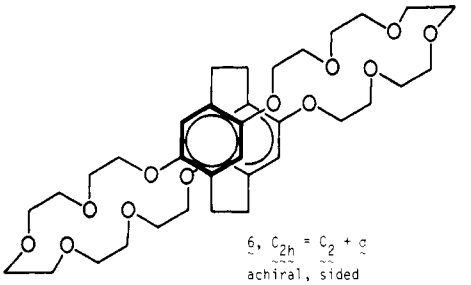
In ideal complexes with alkylammonium salts, the NH_3^+ groups bind the macrocyclic ethers, and the alkyl groups protrude roughly perpendicularly from the best planes of the oxygens. Interesting questions arise as to the structural relationships of complexes formed when complexation occurs on one vs. the other face of the host. Compounds **1** and **5** are chiral, but possess C_2 axes. When complexed with *1 mol* of an alkylammonium salt, the same complex is formed when complexation occurs from either of the two faces of **1,** or four faces of **5.** Thus hosts **1** and **5** are said to be "nonsided". The 1:1 complex of **5** has become "sided", since two isomers (diastereomers) can form upon complexation of the second ring (as well as the first). In the syn isomer, the alkyl groups protrude from the same, and in the anti isomer, from the opposite faces. Both isomers of the 2:1 complexes of **5** possess C_2 axes. The syn complex possesses one, and the anti complex possesses two. In principle, achiral host **8** can also form two diastereomeric complexes. Achiral hosts **3** and **6** can form two different 1:1 complexes and are therefore "sided". Three 2:1 achiral diastereomeric complexes are, according to principle, formable with **3** or **6** as hosts and achiral alkylammonium salts as guests.

Molecular models (Corey-Pauling-Koltun) of compounds **1–6** indicate that the methylene bridges and the transannular aryls of the [2.2]paracyclophane unit enforce conformations about the Ar-Ö-CH_2 bonds that place the CH_2 group roughly anti and the oxygen's electron pairs roughly syn to the transannular ring.[9] This conformation is further enforced by the ortho substituents in **3.** From the diameters of those graded spheres (ball bearings)[10] that could be inserted fully into the cycles in conformations in which the oxygens were turned inward and just contacting the spheres, the diameters of the holes were estimated as follows: for the ortho-substituted systems **2** and **3,** 2.05 and 2.65 Å, respectively; for the pseudo-ortho systems **1, 4,** and **5,** 3.05, 2.40, and 3.05 Å, respectively; for the

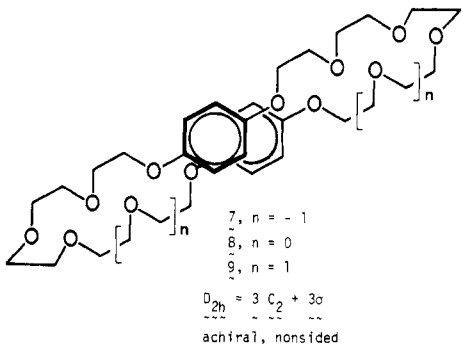


4, n = 0
5, n = 1

$D_2 = 3\,C_2$
chiral, nonsided



6, $C_{2h} = C_2 + \sigma$
achiral, sided



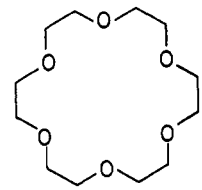
7, n = −1
8, n = 0
9, n = 1

$D_{2h} = 3\,C_2 + 3\sigma$
achiral, nonsided

pseudo-geminate system **6,** 2.9 Å. The cycles containing *p*-phenylene units, **7, 8,** and **9,** are more adaptable, but their ethylene glycol units are easily arranged in gauche semicircles of about 240–300°. The approximate hole diameters are for **7,** 1.3 Å; for **8,** 2.65 Å; for **9,** 3.3 Å. In CPK molecular models of complexes of hosts **1, 3, 5, 6, 8,** and **9,** the round holes and

their diameters in each macroring provide three alternate oxygens that potentially can form three linear O···HN^+ hydrogen bonds arranged in the form of a tripod. In the model complexes of **3** and **6**, three additional O···N^+ binding interactions, and in those of **1, 5, 8,** and **9**, only two such interactions, appear geometrically feasible. In the models of the latter complexes, the sixth oxygen misses contacting N^+ (by ~0.8 Å), because the hole is too large, or the place of the sixth oxygen has been taken by the two aryl groups arranged in parallel planes (complexes of **8**). The oxygens of cycle **2** are poorly arranged to complex alkylammonium salts, and the substance is a poor host, as are other macrocyclic ring systems containing only five oxygens.[11a]

Structures of Alkylammonium Complexes. The presence of aryl groups in the hosts and the potential presence of aryl groups in guests provide magnetic probes for information regarding the structures of complexes in solution. Table I records the ^1H NMR chemical shifts relative to Me_4Si of *t*-Bu protons in $CDCl_3$ of *t*-$BuNH_2$ and *t*-$BuNH_3^+SCN^-$ in the absence and presence of host compounds. The solutions studied in the absence of hosts were prepared by dissolution, and those prepared in the presence of host involved the extraction of D_2O solutions of *t*-$BuNH_3^+SCN^-$ with $CDCl_3$ solutions of host. In all cases that involved **1–10**, host concentrations [H] exceeded guest [G] by factors of at least 10. For comparison, the chemical shifts were also recorded with reference hosts **18, 19,** and **20**,[12] whose [G]/[H] ratios were 0.51, 0.22, and 0.03,



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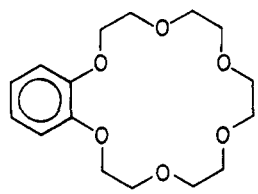

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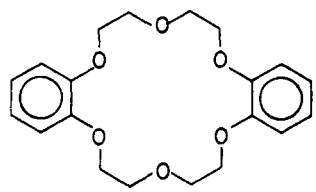

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respectively. With hosts **4, 7,** and **10,** too little salt was drawn into the organic layer for the chemical shifts to be identified.

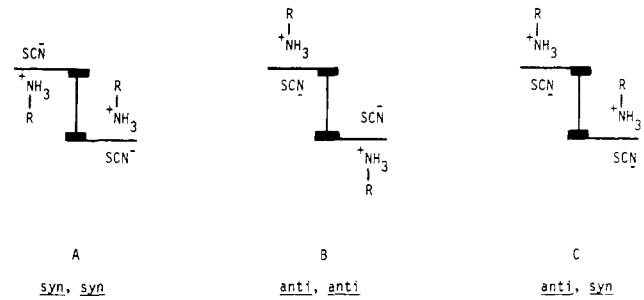
In CPK molecular models, about two of the *t*-Bu protons of the complex of benzo-18-crown-6 (**19**) and about four of the complex of dibenzo-18-crown-6 (**20**) overlap slightly the face of the benzene rings. In the ^1H NMR spectra, the averaged nine protons are moved *upfield* by the shielding cone of the benzene ring by 0.20 ppm in the complex of **19,** and by 0.48 ppm in the complex of **20.** In the complexes of the nonsided hosts **1** and **5** containing the pseudo-ortho [2.2]paracyclophane unit, the *t*-Bu protons are moved *downfield* by 0.10 and 0.11 ppm, respectively. In CPK models of these complexes, two of the *t*-Bu protons are close to and lie in the plane of one of the benzene rings and are therefore in the deshielding cone of that benzene ring.

Table I. Chemical Shifts in ^1H NMR Spectra in $CDCl_3$ at 24 °C of *t*-Bu Protons of *t*-$BuNH_3^+SCN^-$ Alone[a] and Complexed by Hosts[b]

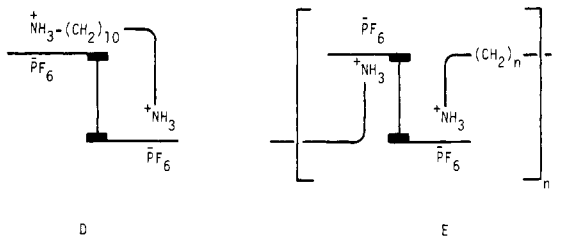
Host no.	δ ppm	Δδ ppm[c]	Host no.	δ ppm	Δδ ppm
None	1.49		**3**	1.48	−0.14
18	1.34	0	**5**	1.45	−0.11
19	1.14	0.20	**6**	1.44	−0.10
20	0.86	0.48	**8**	1.23	0.11
1	1.43	−0.10	**9**	1.21	0.13
2	1.51	−0.17			

[a] The chemical shift of the *t*-Bu protons of *t*-$BuNH_2$ are δ 1.15 ppm. [b] Varian HA-100 spectrometer. [c] Δδ = δ for complex of **18** minus δ complex in question.

In the complexes of hosts **2** and **3** containing the ortho [2.2]paracyclophane unit, the *t*-Bu protons are moved *downfield* by 0.14 and 0.11 ppm, respectively. Since **2** and **3** are sided, in principle the *t*-$BuNH_3^+$ can protrude from the macroring either anti or syn to the transannular benzene ring. The downfield shifts indicate that the syn structure dominates the complex. The antistructure should provide upfield chemical shifts of about 0.20 ppm as in the complex of benzo-18-crown-6. CPK models indicate that in the syn structures at least two *t*-Bu protons are close to lying in the plane of that aryl ring not bonded to the complexing macroring. Models also indicate that the syn structures are much more compact and somewhat more sterically compressed than the anti structures. Thus, the dominance of the syn structures must reflect the enforced orientations of the electron pairs of the aryloxy oxygens which point in the "syn direction". Because of the large predominance of host over guest concentration, the 1:1 complexes undoubtedly dominated the equilibria. However, a 2:1 crystalline complex of *t*-$BuNH_3^+SCN^-$ and **3** (mp 125–127 °C) was prepared in chloroform–ethyl acetate by mixing the host and guest.[9] The possible structures of this complex are formulated as A, B, and C. The NMR data indicate that isomer A should be the most stable in solution.



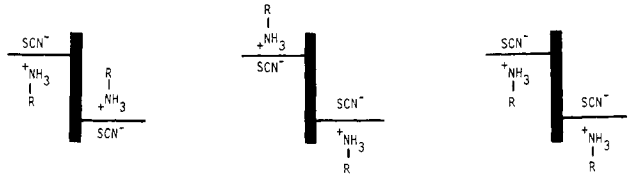
Crystalline complexes (1:1) of host **3** with hexamethylenediammonium dihexafluorophosphate and with decamethylenediammonium dihexafluorophosphate were formed when $CDCl_3$ solutions of **3** were shaken with D_2O solutions of the amine salts. These materials were insoluble in $CDCl_3$, so their ^1H NMR spectra were taken in CD_3CO_2D. The hexamethylene protons gave a complex multiplet centered at δ 1.40 ppm, and the decamethylene protons, a complex multiplet centered at δ 1.50 ppm. The hexamethylene complex must be polymeric since the hexamethylene chain is too short to span the distance between the two macrorings. The decamethylene chain *is long enough* (molecular models), but only if (1) the chain goes over the face of the benzene ring as in D, which should move the middle protons upfield; (2) the outside face



D E

of one macrocycle is complexed as in D. The small upfield shift of 0.10 ppm of the decamethylene (vs. the hexamethylene) is too small to attribute to structure D, and that complex too is probably polymeric.

Host **6,** which contains the pseudo-geminate [2.2]paracyclophane unit, is also sided. Its three possible isomeric complexes are formulated as F, J, and K. The *t*-Bu protons are

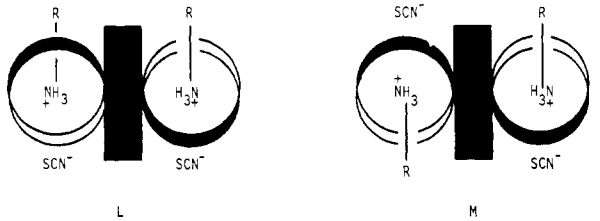


F J K

syn, syn anti, anti syn, anti

moved downfield by 0.10 ppm in the complex. In CPK models of the anti,anti complex, at least two protons lie in planes of the aryl rings. However, they are pushed by the methylene bridge to points too distant from the aryl rings to be in their deshielding cones, and no downfield shift is expected from the anti structures. The anti complexes can be constructed with models only with difficulty, for steric reasons. In contrast, the syn complexes are easily constructed, and two *t*-Bu protons are near to and lie in the planes of the aryl group. Thus, the downfield shift supports the less hindered syn structures for the complexes.

Hosts **3, 5,** and **6** each contain two sets of binding sites. Each compound in $CDCl_3$ was found to solubilize just 2 mol of solid *t*-$BuNH_3^+$ $B(C_6H_5)_4^-$. The two aryl protons of the pseudo-ortho host **5** were shifted from δ 6.18 ppm in the uncomplexed form to δ 5.90 ppm in the 2:1 complex. This upfield chemical shift of 0.28 ppm is attributed to the contacting of the ArH proton by three of the protons of the *t*-Bu group (CPK molecular models). This unique geometry is found in models of both of the two isomeric complexes (L and M). The 2:1 com-



L M

plexes of **3** and **6** gave ArH chemical shifts of δ 6.52 and 5.85, respectively, close to the respective values of δ 6.50 and 5.80 of the uncomplexed hosts. In none of the models of the isomeric complexes constructed from **3** and **6** were any of the ArH protons in contact with more than one *t*-Bu proton. Essentially no chemical shift was observed for the 2′-ArH's of 1′,3′-xylyl-18-crown-5 when it was complexed with *t*-$BuNH_3^+SCN^-$.[13b] In CPK models of that conformation of the complex consistent with the upfield shift of the *t*-Bu protons, the 2′-ArH proton is close to N^+, but distant from the *t*-Bu protons. There is no sterically compatible way to put the ArH proton of the complex of **5** in the shielding cone of an aryl group of $(C_6H_5)_4B^-$.

Complexation in $CDCl_3$ of chiral but racemic host **5** with 2 mol of racemic α-phenylethylammonium hexafluorophosphate (extraction method from D_2O–$NaPF_6$ solution) shifted the ArH protons of the host upfield 0.43 ppm to δ 5.75 (singlet). When 2 mol of optically pure salt of the *S* configuration were used, the ArH singlet of the host split into two singlets of equal intensities at δ 5.68 and 5.81 ppm. These singlets correspond to the chemical shifts of the two diastereomers formed in equal amounts. The upfield shift for one diastereomer was 0.50 ppm, and 0.37 ppm for the other. Apparently the ArH protons of the host are shielded by the phenyl group of the guest to different extents in the two diastereomeric complexes. This experiment exemplifies the use of a guest as a chiral shift reagent. It also identifies compounds **5** and **13** as racemates containing pseudo-ortho structures. Since tetraacetates **13** and **14** were made from the same starting materials, the experiment also identifies **6** and **14** as having pseudo-geminate structures.

Model cycles **8** and **9** containing two *p*-phenylene units (**8** and **9**) gave complexes with *t*-$BuNH_3^+SCN^-$ whose *t*-Bu protons were moved upfield 0.11 and 0.13 ppm, respectively, relative to those of the complex of 18-crown-6 (see Table I). Models (CPK) of the complexes of **9** indicate that all the conformations of the complexes of **5** and **6** are available, but none of them are enforced. In addition, several different conformations are available which allow the *t*-Bu protons to slightly overlap the faces of the benzene rings. These latter conformations appear to dominate the equilibrium mixture since the *t*-Bu protons are more in the shielding than in the deshielding cone of the aryl rings.

Complexation Constants. The association constants (K_a) of the Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, and *t*-$BuNH_3^+$ picrates with hosts **2, 3, 5, 6, 9,** and **21** (2,3-naphtho-18-crown-6)[13a] were measured in $CHCl_3$ at 24 °C making use of the H_2O extraction–ultraviolet absorption technique.[13b] Table II records the results.

Comparisons of K_a values for the NH_4^+ and *t*-$BuNH_3^+$ picrates are particularly instructive. Whereas **3** (containing six oxygens per assembly) binds NH_4^+ a factor of 200 better than **2** (containing five), **3** binds *t*-$BuNH_3^+$ only a factor of 2.4 better than **2.** This result suggests that NH_4^+ might be bound by three perfect hydrogen bonds in **3** and by imperfect bifurcated hydrogen bonds in **2,** and that *t*-$BuNH_3^+$ is bound by only two hydrogen bonds in both **2** and **3** for steric reasons. Host **3** binds NH_4^+ a factor of ~25 better than does **5,** whose enforced larger hole diameter provides at best three perfect NH···O but only two N^+···O interactions. Host **3** provides three of each kind. The free energy of binding NH_4^+ to **3** is about −9.03 kcal/mol, and NH_4^+ to **5,** about −7.15 kcal/mol. Thus, the deformation of **5** from a perfect arrangement costs about −1.9 kcal/mol in binding energy. As expected from CPK molecular model examination, **6** is a poorer binder of NH_4^+ than is isomer **3** by a factor of about 9. The hole of **6** is slightly enlarged, and the electron pairs turn inward, rather than toward one face, as in **3.** The free energy of binding NH_4^+ to **6** is about −7.8 kcal/mol, so **6** is between **3** and **5** as a host. As expected, **8** and **9** are poorly organized for binding either NH_4^+ or *t*-$BuNH_3^+$. The host, 2,3-naphtha-18-crown-6 (**21**), was included as a model compound, and binds NH_4^+ by a factor of about 2.8 better than does **3.** This factor is small and probably would be larger were it not for the enforced orientation of the electrons of the aryl oxygens toward one face in **3,** but not in **21,** where they are free to delocalize into the aryl ring.

A surprising feature of the data is how little the binding constants for *t*-$BuNH_3^+$ change with structure of the cyclophane hosts. Although steric effects would appear to be less important in the complex of **5** than in those of either **3** or **6,** K_a values differ by a maximum of a factor of ~3.2. This suggests that for all three hosts, steric effects allow formation of only two hydrogen bonds. The differences in free energy of com-

Table II. Association Constants (K_a) for Hosts with Picrate Salt Guests in $CHCl_3$ at 24 °C[a]

Host		K_a, $M^{-1} \times 10^{-3}$, values for guest picrate salts						
No.	Structure[b]	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	t-$BuNH_3^+$
2	*o*-PB-15-crown-5	15	1750	192	45	24	22	0.264
3	*o*-PB-18-crown-6	15	150	17 300[c]	≥2650[d]	390	4450	0.625
5	Pseudo-*o*-PB-23-crown-6	3.1	7.1	82	137	65	179	0.195
6	Pseudo-*gem*-PB-22-crown-6	4.3	25.2	1160	293	52	517	0.205
8	BP-34-crown-10	≲0.25	1.0	4.8	3.6	3.1	3.9	0.147
9	BP-40-crown-12	≲0.25	2.2	12.6	8.5	8.3	9.1	0.260
21	2,3-Naphtho-18-crown-6	22	1420	41 300	45 400	2920	12 500	434

[a] In determination of K_a values (ref 13b), the presence of two macrocycles per molecule was taken into account (all hosts but **21**) by working at molarities half those of the standard method (ref 13b) and using normalities of host compound instead of molarities in the calculations. [b] PB means [2.2]paracyclophane-bis, BP means bis-*p*-phenylene. [c] Precipitate formed after determination. [d] Precipitate formed during determination.

plexation for the three hosts toward NH_4^+ and t-$BuNH_3^+$ range from about −5.4 for **3** to −4 kcal/mol for **5.** The difference in values for **3** is large enough to indicate that chiral hosts based on **3** (e.g., 7,12-dimethyl-4,5,15,16-bis(18-crown-6)[2.2]paracyclophane) might show chiral recognition toward chiral guests of a magnitude that involves several kilocalories per mole difference in stabilities of diastereomeric complexes. Even a 3 kcal/mol difference out of the 6 would provide an enantiomer distribution contant (EDC)[14] of 160.

The K_a values for the metal picrates show interesting trends. All of the hosts give low values for Li^+. Host **2** containing 15-crown-5 assemblies provides K_a values higher by a factor of 10 for Na^+ than any of the other ions, presumably because of the better fit of the diameter of Na^+ (1.9 Å) to the diameter of the hole of **2** (2.05 Å).[15] Host **3** and model compound **21** both contain 18-crown-6 assemblies, and K^+ and Rb^+ provide the highest values for K_a. For example, K^+ is bound to **3** by a factor about 10^2 better than Na^+, again reflecting a match of diameters between host (2.65 Å) and guest (2.66 Å). Interestingly, the enlarged diameter of the oxygen assembly of the pseudo-ortho system **5** (~3.05 Å) nicely matches the 3.0 Å diameter of Rb^+, and **5** binds Rb^+ better than any of the other metal ions, but the factors are not large. The slightly enlarged model diameter of the macroring of the pseudo-geminate system **6** (~2.9 Å) best matches the 3.0 Å diameter of Rb^+, but the K_a value for Rb^+ is only about one-fifth of the value for K^+, whose diameter is about 2.66 Å. Thus, it is difficult for a ring to expand, but it can contract slightly by folding. Cycles **8** and **9** are relatively poor hosts for all the metal ions, presumably because of their lack of high organization. A comparison of the values of K_a for **6** and **9** toward K^+ illustrates the importance of high organization. The hosts differ only by the organizing and rigidifying extra ethylene bridges in **6.** These bridges increase K_a by a factor of about 10^2.

Experimental Section

General. All chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. All solvents were fractionally distilled. All ring-closing reactions were conducted in a N_2 atmosphere. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given in δ from internal tetramethylsilane with $CDCl_3$ as solvent. Spectra (^1H NMR) were recorded on Varian AR-60 or HA-100 spectrophotometers. Mass spectra were taken at 70 eV on an AEI Model MS-9 double-focusing mass spectrometer. Commercially available di-, tri-, and tetraethylene glycol were distilled through a 6-in. Vigreux column, and only the GLC-pure center fractions were used. Their tosylates were prepared as usual.[16] Ultraviolet measurements were made on a Beckman DU spectrophotometer. Anhydrous magnesium sulfate was used to dry organic layers from extractions. Gel permeation chromatography was performed on a 3/8 in. by 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.

4,5,15,16-Tetraacetoxy[2.2]paracyclophane (12). Into a refluxing solution of 70 g (0.47 mol) of sodium iodide in 1.6 L of 2-butanone was added by Soxhlet 20 g (0.53 mol) of 3,6-bis(bromomethyl)catechol diacetate.[7] The mixture was refluxed for a total of 42 h, cooled, and concentrated (40 °C, 30 mm) to 300 mL. To the crude reaction mixture were added 600 mL of saturated aqueous sodium bisulfite solution and 600 mL of $CHCl_3$. The two phases were stirred vigorously for 2 h, the layers were separated, and the aqueous layer was extracted with 200 mL of fresh $CHCl_3$. The organic extracts were dried and concentrated to 100 mL. The $CHCl_3$ solution was diluted with 600 mL of acetone, and 17 g (0.12 mol) of silver nitrate in 75 mL of water was added in a single portion. The mixture was stirred at 25 °C for 6 h, filtered, and concentrated (40 °C, 30 mm) to 200 mL. To the crude mixture was added $CHCl_3$ and water (400 mL of each), and the layers were separated. The aqueous layer was extracted with two 100-mL portions of $CHCl_3$ and the organic extracts were dried. The chloroform solution was concentrated to 75 mL and chromatographed on 200 g of silica gel made up in benzene. Elution of the column with benzene (1 L) and 2 L of benzene–chloroform (4:1 v) gave ~5 g of semisolid material. Crystallization of the material from 200 mL of chloroform–ethyl acetate (1:3) gave 2.3 g (20%) of a white solid, mp 340 °C dec. The ^1H NMR spectrum (60 MHz) in $CDCl_3$ gave δ 2.25 (s, 12, CH_3), 2.88 (m, 8 H, $ArCH_2$), 6.70 (s, 4 H, ArH). Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.37; H, 5.59.

4,7,12,15-Tetraacetoxy[2.2]paracyclophane (13) and 4,7,13,16-Tetraacetoxy[2.2]paracyclophane (14). These compounds were prepared by a procedure resembling that for the preparation of **12** except that 2,5-bis(bromomethyl)hydroquinone diacetate[7] (20 g) served as starting material. The crude product in 100 mL of $CHCl_3$ was chromatographed on 200 g of silica gel made up in benzene. Elution of the column with 1 L of benzene and 2 L of benzene–$CHCl_3$ (3:1 v) gave 8 g of a mixture of **13** and **14.** This material was crystallized from 200 mL of ethyl acetate–$CHCl_3$ to give 0.58 g (5%) of the pseudo-geminate tetraacetate (**14**) as colorless needles: mp 283–284 °C; ^1H NMR spectrum (60 MHz) δ 2.30 (s, 12 H, CH_3), 2.53–3.42 (m, 8 H, CH_2), 6.33 (s, 4 H, ArH). Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.41; H, 5.52.

The filtrates from the crystallization of **14** were allowed to evaporate at 25 °C and 2.9 g (25%) of the pseudo-ortho tetraacetate (**13**) crystallized: mp 263–264 °C; ^1H NMR spectrum (60 MHz) gave δ 2.30 (s, 12 H, CH_3), 2.40–3.30 (m, 8 H, CH_2), 6.55 (s, 4 H, ArH). Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.40; H, 5.37.

The structures of these isomeric tetraacetates (**13** and **14**) were differentiated by the fact that one was a racemate and the other a meso form, as demonstrated below in the complexation of their derived hosts **5** and **6.** Isomer **5** formed ^1H NMR detected diastereomeric complexes with optically pure α-phenylethylammonium hexafluorophosphate.

Isomeric Tetrahydroxy[2.2]paracyclophanes. Under nitrogen, 2.4 g (79 mmol) of 4,5,15,16-tetraacetoxy[2.2]paracyclophane (**12**) was extracted (Soxhlet) into a refluxing solution of 3 g (79 mmol) of $LiAlH_4$ in 250 mL of THF. After 18 h of reflux, the mixture was cooled and the excess reagent decomposed with ethanol. The mixture was stirred with 200 mL of 6 N HCl and 300 mL of ethyl ether. The layers were separated, and the aqueous phase was extracted four times with 150-mL portions of ether–THF (2:1 v). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 1.4 g (94%) of 4,5,15,16-tetrahydroxy[2.2]paracyclophane as a pink semisolid.[8] All of the above operations were conducted in deoxygen-

ated solvents under a blanket of nitrogen to prevent quinone formation. The tetraphenol was used in the next reactions without characterization or purification.

Similarly, from 3.1 g of 4,7,12,15-tetraacetoxy[2.2]paracyclophane (**13**) was formed 1.7 g (89%) of the corresponding tetrahydroxy compound as a pink oil,[8] which was used directly in the next reactions without characterization.

Similarly, from 0.8 g of 4,7,13,16-tetraacetoxy[2.2]paracyclophane (**14**) was formed 0.4 g (91%) of the corresponding tetrahydroxy compound as a pink semisolid,[8] which was used directly in the next reaction.

4,5,15,16-Bis(15-crown-5)[2.2]paracyclophane (2). To a solution of 1.0 g (3.7 mmol) of 4,5,15,16-tetrahydroxy[2.2]paracyclophane in 100 mL of 1-butanol under nitrogen was added 900 mg (16 mmol) of potassium hydroxide dissolved in 10 mL of water. The solution was heated to 100 °C and 1.8 g (7.8 mmol) of 1,11-dichloro-3,6,9-trioxaundecane in 30 mL of 1-butanol was added in a single portion. The solution was refluxed for 36 h, cooled, and concentrated (60 °C, 30 mm) to 25 mL. The crude reaction mixture was partitioned between CH_2Cl_2 and water, 300-mL portions of each. The layers were separated, and the aqueous phase was extracted with two fresh 100-mL portions of CH_2Cl_2. The organic extracts were dried and evaporated and the residue was dissolved in 15 mL of CH_2Cl_2. The solution was added to a neutral alumina (activity 1) column made up in benzene. Elution of the column with 500 mL of benzene, 1 L of benzene–ethyl ether (3:1 v), and 2 L of benzene–ethyl ether (1:1) gave small amounts of unidentified material. Further elution of the column with 3 L of ethyl ether and 99:1 (v) ethyl ether–ethanol (2 L) gave 120 mg (6%) of the desired product, mp 192–193 °C, after recrystallization from CH_2Cl_2–heptane. The mass spectrum gave M^+ *m/e* 588, and the 60-MHz ^1H NMR spectrum gave δ 2.40–3.30 (m, 8 H, $ArCH_2$), 3.30–4.20 (m, 32 H, OCH_2), and 6.45 (s, 4 H, ArH). Anal. Calcd for $C_{32}H_{44}O_{10}$: C, 65.29; H, 7.53. Found: C, 65.45; H, 7.59.

4,5,15,16-Bis(18-crown-6)[2.2]paracyclophane (3). To a solution of 4,5,15,16-tetrahydroxy[2.2]paracyclophane in 200 mL of 1-butanol under nitrogen was added 0.9 g (16 mmol) of potassium hydroxide in 10 mL of water. The stirred solution was heated to 80 °C and 2.2 g (8 mmol) of 1,14-dichloro-3,6,9,12-tetraoxatetradecane in 20 mL of 1-butanol was added in a single portion. The solution was refluxed for 24 h, cooled, and concentrated (50 °C, 30 mm) to 25 mL. The product **3** was isolated (as was **2**, see above) and crystallized from CH_2Cl_2–heptane: wt 0.35 g (14%); mp 157–158 °C; mass spectrum M^+ at *m/e* 676. The ^1H NMR spectrum (60 MHz) gave δ 2.40–3.25 (m, 8 H, $ArCH_2$), 3.32–4.20 (m, 40 H, OCH_2), 6.50 (s, 4 H, ArH). Anal. Calcd for $C_{36}H_{52}O_{12}$: C, 63.89; H, 7.74. Found: C, 63.80; H, 7.66.

3-Morpholinomethyl-6-methylcatechol (15). A mixture of 86 g (1 mol) of morpholine, 30 g (1 mol) of formaldehyde, and 250 mL of 2-propanol was refluxed until the solution was homogeneous (~10 min). To the cooled solution was added 124 g (1 mol) of 3-methylcatechol (Aldrich Chemical Co.) in 400 mL of 2-propanol over 15 min. The solution was refluxed for 15 min, cooled, and concentrated (30 mm, 25 °C) on a rotary evaporator. After distillation of about 100 mL of 2-propanol, the product crystallized from the cold reaction mixture. The solid was collected and washed with cold 2-propanol to give 185 g (83%) of a white solid, mp 132–134 °C, after drying at 25 °C. A single recrystallization from ethyl acetate gave an analytical sample of mp 134–135 °C, mass spectrum M^+ at *m/e* 223. The ^1H NMR spectrum (60 MHz) gave δ 2.20 (s, 3 H, $ArCH_3$), 2.50 (m, 4 H, $ArCH_2NCH_2$), 3.62 (s, 2 H, $ArCH_2$), 3.66 (m, 4 H, OCH_2), 6.42 (AB quartet, 2 H, ArH), 7.50 (broad s, 2 H, OH). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67. Found: C, 64.49; H, 7.74.

3-Morpholino-6-methylbenzo-18-crown-6 (16). To a solution of 22.3 g (100 mmol) of 3-morpholinomethyl-6-methylcatechol in 1.4 L of tetrahydrofuran under nitrogen was added 24 g (214 mmol) of potassium *tert*-butoxide. After the solution had stirred for 30 min at 25 °C, 29.0 g (107 mmol) of 1,14-dichloro-3,6,9,12-tetraoxatetradecane in 100 mL of tetrahydrofuran was added over 10 min. The mixture was stirred at 25 °C for 10 h and then refluxed for 6 h. The reaction mixture was cooled, filtered, and concentrated (40 °C, 30 mm) to 150 mL. The tetrahydrofuran solution was partitioned between CH_2Cl_2 (400 mL) and water (400 mL). The layers were separated and the aqueous phase was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were dried, concentrated to 75 mL, and chromatographed on 500 g of neutral alumina (activity 1) made up in benzene. Elution of the column with benzene (1 L), 9:1 (v) benzene–ethyl ether (1 L), and 2-L portions of benzene–ethyl ether mixtures (4:1, 1:1, and 1:4) gave small amounts of unidentified material. Further elution of the column with ethyl ether (3 L) and 99:1 (v) ethyl ether–ethanol (2 L) gave 15 g (35%) of **16** as a colorless oil, mass spectrum M^+ at *m/e* 425. The ^1H NMR spectrum (60 MHz) gave δ 2.20 (s, 3 H, $ArCH_3$), 2.44 (m, 4 H, $ArCH_2NCH_2$), 3.25–4.32 (m, 26 H, OCH_2 and $ArCH_2N$), 6.88 (AB quartet, 2 H, ArH). Anal. Calcd for $C_{22}H_{35}NO_7$: C, 62.10; H, 8.29. Found: C, 62.04; H, 8.20.

3-Morpholinomethyl-6-methylbenzo-18-crown-6 Methiodide (17). To a solution of 12.0 g (28 mmol) of **16** in 300 mL of ether–tetrahydrofuran (9:1 v) was added 12 g (85 mmol) of methyl iodide. After the mixture was stirred at 25 °C for 24 h, the solvent was decanted from the precipitated oil and the methiodide converted to the quaternary ammonium hydroxide without further purification. An analytical sample of the methiodide salt was obtained by drying a small sample of the precipitate at 165 °C (0.05 mm) for 12 h. Anal. Calcd for $C_{23}H_{38}INO_7$: C, 48.67; H, 6.76. Found: C, 48.81; H, 6.81.

4,5,15,16-Bis(18-crown-6)[2.2]paracyclophane (3). To a solution of 20 g (35 mmol) of 3-morpholinomethyl-6-methylbenzo-18-crown-6 methiodide in 250 mL of water under nitrogen was added 8.1 g (35 mmol) of silver oxide, and the mixture was stirred for 4 h at 25 °C. The solution was filtered and the filtrate added to 1 L of toluene containing 0.3 g of phenothiazine. The two-phase mixture was refluxed with vigorous stirring and the water azeotroped from the mixture using a Dean-Stark water separator attached to a reflux condenser. The water was removed over a period of 4 h and refluxing was then continued for 6 h. The toluene solution was cooled, filtered to remove polymer, and concentrated (50 °C, 30 mm) to 50 mL. The crude product was chromatographed on 300 g of neutral alumina (activity 1) made up in benzene. Elution of the column with 1 L of benzene, 2-L portions of 3:1 and 1:1 benzene–ethyl ether (by v), and 1 L of ethyl ether gave small amounts of unidentified material. Further elution of the column with 2 L of ethyl ether–ethanol (99:1 v) and 3 L of ethyl ether–ethanol (49:1) gave 1.2 g (10%) of **3** as a white solid, mp 156–157 °C, after recrystallization from CH_2Cl_2–heptane. The ^1H NMR spectrum and the R_f were identical with those of **3** prepared from 4,5,15,16-tetrahydroxy[2.2]paracyclophane (see above).

4,7,12,15-Bis(20-crown-5)[2.2]paracyclophane (4). To a solution of 900 mg (3.3 mmol) of 4,7,12,15-tetrahydroxy[2.2]paracyclophane in 150 mL of 1-butanol under nitrogen was added 790 mg (15 mmol) of potassium hydroxide in 10 mL of water. The solution was heated to 80 °C and 1.6 g (7 mmol) of 1,11-dichloro-3,6,9-trioxaundecane in 15 ml of 1-butanol was added in a single portion. The solution was refluxed for 40 h, cooled, and concentrated (60 °C, 30 mm) to 25 mL. The product (**4**) was isolated by the procedure used for **2** (see above), and was crystallized from CH_2Cl_2–heptane: wt 50 mg (3%); mp 118–119 °C; mass spectrum M^+ *m/e* 588. The ^1H NMR spectrum (60 MHz) gave δ 2.78 (m, 8 H, $ArCH_2$), 3.70 (m, 32 H, OCH_2), 6.12 (s, 4 H, ArH). Anal. Calcd for $C_{32}H_{44}O_{10}$: C, 65.29; H, 7.53. Found: C, 65.17; H, 7.55.

4,7,12,15-Bis(23-crown-6)[2.2]paracyclophane (5). To a solution of 1.8 g (6.6 mmol) of 4,7,12,15-tetrahydroxy[2.2]paracyclophane in 200 mL of THF under nitrogen was added 1.6 g (29 mmol) of potassium hydroxide in 20 mL of water. The solution was heated to 80 °C and 7.6 g (14 mmol) of pentaethylene glycol ditosylate in 30 mL of tetrahydrofuran was added in a single portion. The mixture was refluxed for 48 h, cooled, and concentrated (40 °C, 30 mm) to 30 mL. The product **5** was isolated by the same procedure used for **2**, and was recrystallized from CH_2Cl_2–heptane: wt 1.13 g (25%); mp 121–122 °C; mass spectrum M^+ *m/e* 676. The ^1H NMR spectrum (60 MHz) gave δ 2.38–3.30 (m, 8 H, $ArCH_2$), 3.38–4.30 (m, H, OCH_2), and 6.18 (s, 4 H, ArH). Anal. Calcd for $C_{36}H_{52}O_{12}$: C, 63.89; H, 7.74. Found: C, 63.77; H, 7.82.

4,7,13,16-Bis(22-crown-6)[2.2]paracyclophane (6). To a solution of 400 mg (1.5 mmol) of 4,7,13,16-tetrahydroxy[2.2]paracyclophane in 200 mL of THF under nitrogen was added 358 mg (6.4 mmol) of potassium hydroxide in 20 mL of water. The solution was heated to reflux and 1.7 g (3.2 mmol) of pentaethylene glycol ditosylate in 15 mL of tetrahydrofuran was added in a single portion. The mixture was refluxed for 48 h, cooled, and concentrated (40 °C, 30 mm) to 30 mL. The product, **6**, was isolated by the procedure used for **2**, and after crystallization from CH_2Cl_2–heptane amounted to 225 mg (23%), mp 133–134 °C, mass spectrum M^+ at *m/e* 676. The ^1H NMR spectrum (60 MHz) gave δ 2.60 (m, 4 H, $ArCH_2$), 3.60 (m, 4 H, $ArCH_2$), 3.80 (m, 40 H, OCH_2), 5.80 (s, 4 H, ArH). Anal. Calcd for

$C_{36}H_{52}O_{12}$: C, 63.89; H, 7.74. Found: C, 63.97; H, 7.73.

4,12-(23-Crown-6)[2.2]paracyclophane (1). To a solution of 4,12-dihydroxy[2.2]paracyclophane (**11**,[4] 800 mg, 3.3 mmol) in 100 mL of 1-butanol under nitrogen was added 392 mg (7 mmol) of potassium hydroxide dissolved in 5 mL of water. The solution was heated to 80 °C and 960 mg (3.5 mmol) of 1,14-dichloro-3,6,9,12-tetraoxatetradecane in 10 mL of 1-butanol was added in a single portion. The solution was refluxed for 24 h, cooled, and concentrated (60 °C, 30 mm) to 20 mL. The product, **1**, was isolated by the same procedure used for **2**, and after recrystallization from CH_2Cl_2–heptane amounted to 0.265 g (18%), mp 73–74 °C, mass spectrum M^+ *m/e* 442. The ^1H NMR spectrum (60 MHz) gave δ 2.90 (m, 8 H, $ArCH_2$), 3.70 (m, 20 H, OCH_2), and 6.02–6.50 (m, 6 H, ArH). Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.36; H, 7.52.

Bis(*p*-phenylene)-40-crown-12 (9) and *p*-Phenylene-20-crown-6 (10). Pentaethylene glycol ditosylate (54.6 g, 0.1 mol) in dioxane–1-butanol (3:2 v) was added to 450 mL of 1-butanol containing 14.7 g (0.115 mol) of *p*-hydroquinone and 9.1 g (0.228 mol) of sodium hydroxide in 10 mL of water stirred under a blanket of nitrogen. The mixture was refluxed for 19 h, cooled, filtered, and evaporated (40 mm) to give 30 g of residue, which was chromatographed on 900 g of alumina with ether as eluting solvent. Crystallization of the column eluate residue from benzene–hexane gave **9**: 2.2 g (7%); mp 67–69 °C; mass spectrum M^+ at *m/e* 624; gel permeation retention volume 128 mL; ^1H NMR (100 MHz) δ 3.2–3.8 (m, 16 H, CH_2OCH_2), 4.2 (m, 4 H, $ArOCH_2$), 6.9 (s, 4 H, ArH). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.53; H, 8.02.

The mother liquors from which **9** crystallized were evaporated, and the residue was submitted to gel permeation chromatography (retention volume 151 mL) to give 0.60 g (2%) of *p*-phenylene-20-crown-6 (**10**) as an oil, bp 120–130 °C (0.1 mm). The mass spectrum gave M^+ *m/e* 312, and the ^1H NMR spectrum (100 MHz) gave δ 3.2–3.8, 4.2 (m, 20 H, CH_2), 6.9 (s, 4 H, ArH). Anal. Calcd for $C_{32}H_{48}O_{12}$: C, 61.52; H, 7.74. Found: C, 61.53; H, 8.02.

Bis(*p*-phenylene)-34-crown-10 (8). Tetraethylene glycol ditosylate (50.2 g, 0.1 mol) was treated with *p*-hydroquinone and base exactly as in the preparation of **9**. After the solution had refluxed for 20 h, it was filtered and evaporated in vacuo to give 30 g of residue, which was chromatographed on 900 g of alumina with ether as eluting agent. The residue from the column eluate crystallized from hexane–benzene to give 2.1 g (8%) of **8**: mp 93.5–94 °C; mass spectrum M^+ *m/e* 536; ^1H NMR spectrum (100 MHz) δ 3.6–4.0 (m, 32 H, CH_2), 6.7 (s, 8 H, ArH); gel permeation retention volume 128 mL. Anal. Calcd for $C_{28}H_{40}O_{10}$: C, 62.67; H, 7.51. Found: C, 62.93; H, 7.50.

Bis(*p*-phenylene)-28-crown-8 (7). Triethylene glycol ditosylate (45.8 g, 0.1 mol) was treated with *p*-hydroquinone and base by the same procedure used to prepare **9**. From the reaction mixture was isolated 25 g of residue which was chromatographed on 800 g of alumina with ether as eluting agent. The residue from the chromatogram crystallized from benzene–ether to give 1.5 g (7%) of **7**: mp 95.5–96.5 °C; mass spectrum M^+ *m/e* 448; ^1H NMR spectrum (100 MHz) δ 3.6–4.0 (m, 24 H, CH_2), 6.7 (s, 8 H, ArH). Anal. Calcd for $C_{24}H_{32}O_8$: C, 64.27; H, 7.19. Found: C, 64.29; H, 7.12.

***tert*-Butylammonium Thiocyanate Complex of 4,5,15,16-Bis(18-crown-6)[2.2]paracyclophane (3).** To a solution of 50 mg (0.076 mmol) of **3** in 0.3 mL of $CHCl_3$ was added 20 mg (0.15 mmol) of solid *tert*-butylammonium thiocyanate. The homogeneous solution was diluted with 1.5 mL of ethyl acetate, stoppered, and allowed to stand at 25 °C for 24 h. The white, 2:1 complex (salt to cycle) that crystallized (56 mg, 80%) was collected, mp 125–127 °C. Anal. Calcd for $C_{47}H_{76}N_4O_{12}S_2$: C, 58.67; H, 8.15. Found: C, 57.45; H, 8.16.

Solubilization of Solid *tert*-Butylammonium Tetraphenylborate in Deuteriochloroform by Isomeric Hosts Containing [2.2]Paracyclophane Units and Two 6-Oxygen Macrocycles (3, 5, and 6). To a 30-mg sample of host in 0.3 mL of $CDCl_3$ was added *tert*-butylammonium tetraphenylborate in small portions with shaking. Each host solubilized 2 mol of salt (only), a fact confirmed by ^1H NMR integration (100 MHz) of the *tert*-butyl proton singlet against the aryl singlet of the host. The aryl protons of the bis-pseudo-ortho cycle (**5**) were shifted from δ 6.18 in the uncomplexed form to δ 5.90 ppm in the 2:1 complex. The aryl protons in the other two hosts were essentially unchanged in going from the free host to the complex.

Upon standing at 25 °C, the $CDCl_3$ solution containing **3** and 2 mol of t-$BuNH_3^+(C_6H_5)_4B^-$ deposited a white solid (mp 200 °C dec) which was redissolved in CD_3CN and identified (^1H NMR integration) as the 2:1 complex.

***tert*-Butylammonium Tetraphenylborate.** To a vigorously stirred solution of 3 g (0.03 mol) of *tert*-butylammonium chloride in 200 mL of H_2O was added 9.4 g (0.03 mol) of sodium tetraphenylborate in 250 mL of H_2O over 5 min. The suspension was stirred at 25 °C for 2 h, filtered, and dried at 50 °C (50 μ) to give 10.5 g (97%) of a white solid, mp 172–173 °C. Anal. Calcd for $C_{28}H_{32}BN$: C, 85.48; H, 8.22; N, 3.56. Found: C, 85.26; H, 8.11; N, 3.50.

Complexation of Bis-Pseudo-Ortho Paracyclophane Host 5 with α-Phenylethylammonium Hexafluorophosphate. A solution of 50 mg of **5** in 0.3 mL of $CDCl_3$ was shaken with 0.8 mL of D_2O 1.2 M in $NaPF_6$ containing 126 mg of racemic α-phenylethylammonium chloride. The $CDCl_3$ layer was separated, and the ^1H NMR spectrum (100 MHz) exhibited aryl proton singlets at δ 5.75, which represents a 0.43-ppm upfield shift over the position of those protons in the free host. When (*S*)-α-phenylethylammonium chloride was substituted for the racemic salt in the above experiment, two ArH singlets of equal intensity appeared at δ 5.68 and 5.81 ppm. One diastereomer gave a 0.5 ppm and the other a 0.37 ppm upfield shift.

Chemical Shifts of the ^1H NMR Spectra of the *tert*-Butyl Protons of the *tert*-Butylammonium Thiocyanate Complexes of Various Hosts. The ^1H NMR spectra of the *tert*-butyl protons of *tert*-butylamine and *tert*-butylammonium thiocyanate[13] in $CDCl_3$ at 24 °C were taken on a 100-MHz spectrophotometer on solutions prepared directly. The spectra of the complexes of **1–10** were taken on solutions prepared by extracting D_2O solutions at 24 °C of t-$BuNH_3^+SCN^-$ (0.30 mL, containing 39.5 mg (0.30 mmol) of salt) with $CDCl_3$ (0.60 mL containing 0.30 mmol of host). From the integrations of the *tert*-butyl protons vs. the ArH protons, the host to guest ratio was at least 10. With the complexes prepared from hosts **18–20**, the solutions were prepared by shaking 0.60 mL of $CDCl_3$ containing 0.0835 mmol of host with 1.6 mL of D_2O containing 21.2 mg (0.16 mmol) of *tert*-butylammonium thiocyanate at 24 °C. The guest to host ratios in these final $CDCl_3$ solutions were 0.51, 0.22, and 0.03 for hosts **18**, **19**, and **20**, respectively. Table I reports the chemical shifts.

Complex between Polymethylenediammonium Hexafluorophosphate Salts and 4,5,15,16-Bis(18-crown-6)[2.2]paracyclophane (3). To a solution of 50 mg of host **3** in 0.3 mL of $CDCl_3$ was added 0.8 mL of a D_2O solution (4 M in $LiPF_6$ and 2 M in hexamethylenediamine dihydrochloride). The mixture was shaken vigorously to give a cloudy solution which, after standing for 2 h at room temperature, deposited a white solid. The solid was collected and dried under vacuum at 25 °C to give 90 mg (94%) of material, mp 260–262 °C. An ^1H NMR spectrum of the complex in CD_3CO_2D exhibited a complex multiplet for the internal methylenes of the diamine salt which was centered at δ 1.50. Anal. Calcd for $C_{42}H_{70}N_2O_{12}P_2F_{12}$: C, 46.49; H, 6.50. Found: C, 47.39; H, 6.78.

To a solution of 65 mg of host **3** in 0.3 mL of $CDCl_3$ was added 0.8 mL of a D_2O solution (1.3 M in $LiPF_6$ and 0.7 M in decamethylenediamine dihydrochloride). A solid formed immediately after shaking the layers. The mixture was kept at 25 °C for 10 h and then filtered to give 123 mg (91%) of material, mp 240–242 °C, after drying under vacuum at 25 °C. An ^1H NMR spectrum of the complex in CD_3CO_2D exhibited a complex multiplet centered at δ 1.40 for the internal methylenes of the diamine salt. The complex dissolved in hot $(CD_3)_2SO$ (~30 mg in 0.30 mL), and the solution gave a spectrum consistent with uncomplexed host. When cooled, the solution deposited free host (**3**). The complex gave the following analysis. Anal. Calcd for $C_{46}H_{78}N_2O_{12}P_2F_{12}$: C, 48.42; H, 6.89. Found: C, 48.40; H, 7.15.

Complexation Constants. The association constants (K_a) of Table II were determined by the $CDCl_3$–D_2O extraction–UV picrate technique reported previously.[11b]

References and Notes

(1) This work was supported by a grant from the National Science Foundation, GP 33533X, and the U.S. Public Health Service, Research Grant GM 12640-12 from the Department of Health, Education and Welfare.

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Highly Modified Cysteine-Containing Antibiotics. Chemical Structure and Configuration of Nosiheptide

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Abstract: The complete structure of a metabolite with a strong antibiotic activity, isolated from *Streptomyces actuosus*, has been established by x-ray methods to be a polythiazole-containing product related to the structures of thiostrepton and siomycin A. The crystals are tetragonal, $C_{51}H_{43}N_{13}O_{12}S_6$, space group $I4_1$, with $a = 36.05$ and $c = 11.44$ Å. The structure has been solved by direct methods. The configurations of all asymmetric centers were established, and the general macrocycle ring conformation is discussed in terms of thiostrepton and peptide chains analogies.

Many strains of *Streptomyces* produce antibiotic substances containing thiazole rings and peptide residues. A tentative classification of such metabolites has been formalized by Berdy.[1] In this study, about 20 known structures were compiled and, among them, only two were found to contain more than four thiazole rings: thiostrepton[2] (from *S. azureus*), whose chemical formula has been mostly established by an x-ray analysis,[3] and siomycin A (from *S. sioyaensis*),[4] a close parent of the former, as deduced from ^{13}C NMR comparisons.[5] Moreover, the thiostrepton antibiotic group contains some other compounds like multhiomycin,[6] thiopeptin,[7] and sporangiomycin;[8] they have been included on the basis of similarities in antibacterial activity and physicochemical properties, but their complete structures have not hitherto been reported. In Figure 1 are shown the chemical formulas of two different compounds of the general thiazole-containing group: a complex one, thiostrepton, and the somewhat simpler althiomycin[9] (from *S. althioticus* and *S. matensis*). These two compounds have the structure of peptide chains highly modified by intense enzymatic oxidations or dehydrogenations. Gram-positive bacteria are very sensitive to all of these compounds while gram-negative species and yeasts are naturally resistant to these agents. The main characteristic of the antibiotics of this group is a very low toxicity, which is, however, associated with a low water solubility. These compounds so far have not found a place in medicine except thiostrepton itself, which is used for the treatment of bovine mastisis.

Thiazole rings encountered in these structures are actually stated to arise from a *D*-cysteine residue.[10] The unusual configuration of this precursor is deduced from the absolute configuration of the remaining asymmetric center in thiazole rings (when they are present), and from its quantitative isolation in the thiazoline hydrolysis.

In the present study, we wish to report the complete structure of nosiheptide, a new metabolite isolated from *S. actuosus*, with a strong in vitro activity and we shall discuss its particular conformation.

Initial studies, by biological cross resistance experiments, strongly suggested that nosiheptide belonged to the thiostrepton class. Intense degradative studies[12] led to the trial skeleton given in Figure 2.

Nosiheptide, as obtained by precipitation, is a yellowish powder. It crystallizes in ethyl acetate or acetic acid at low temperature (40 °C). The mass spectrum did not show the M^+ ion and, as the field desorption technique was not available, the final $C_{51}H_{43}N_{13}O_{12}S_6$ formula was mostly deduced from combustion analyses and ^{13}C, ^1H, and ^{15}N NMR spectrometric experiments.[13]

Nosiheptide is very sensitive to hydrolysis. The acid hydrolysis (HCl) gives several well-identified fragments (Figure 2), 1 mol of H_2S, 1 mol of L-threonine, and compounds **1, 2,** and **3.** On the other hand, alkaline hydrolysis liberates 4 mol of ammonia and the indolic fragment **4** is obtained after subsequent esterifications.

Using analogies between these products and those initially obtained by Bodansky et al.[14] in their thiostrepton degradations, the backbone given in Figure 2 was the state of the structure at the beginning of this x-ray determination. Five thiazole rings were recognized in these fragments but the sixth sulfur atom location could not be deduced from these studies and, furthermore, it was not possible to connect the indolic part **4** to the rest of the macrocycle. It is evident that if it is bridged in a similar way as in thiostrepton, it would possess shorter linkages, as no other usual amino acid than the L-threonine residue was detected in the degradative products (see Figure 1 for the tetrapeptidic chain of the quinaldic precursor in thiostrepton).

Experimental Section

Nosiheptide crystallizes in acetate-containing solvents, but gives