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Host-Guest Complexation. 40. Synthesis and Complexation of Macrocyclic Hosts Containing Cyclic Ureas, Anisyls, and Steric Barriers[1]

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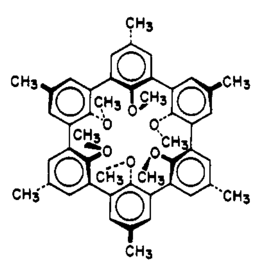
The synthesis and complexing properties of eight new macrocyclic hosts are described. These hosts contain three cyclic urea and two anisyl units as binding sites combined with one of the following: a *m*-xylylene, an aryl bromide, an aryl ester, or biphenyl units substituted to provide potential steric barriers to complexation with bulky guests. The association constants and free energies of complexation of alkali metal cations and ammonium and alkylammonium ions in $CDCl_3$ saturated with H_2O were determined by the extraction method. Substitution for the hydrogen in the X-position of **3** with Br or CO_2CH_3 groups generally decreased the binding of alkali metal cations by 0 to 2 kcal mol^{-1}. A crystal structure of the Na^+ complex of macrocycle **5** containing the aryl ester bridging unit shows that the carbonyl of the ester hydrogen-bonds a water molecule, which in turn ligates Na^+. Incorporation of steric barriers into the bridging *m*-xylylene units provides hosts which discriminate in binding $MeNH_3^+$ and $(CH_3)_3CNH_3^+$ by up to 2.5 kcal mol^{-1}.

Recently, we have reported that the strong and selective alkali cation-complexing properties of spherands,[2] such as **1**, could be modified by the addition of extra ring mem-



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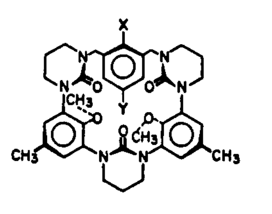

2, X = OMe, Y = Me

bers[3] or by the replacement of some of the anisyl modules with other units.[4] Macrocyclic hosts which possess three cyclic urea units, such as **2**, exhibit strong binding[4a] and rapid rates of complexation and decomplexation.[5] In CPK molecular models the cyclic ureas project their carbonyl oxygens toward the binding cavity in much the same orientation as the anisyls provide for their ether oxygens. In addition to being an intrinsically better ligand for alkali metal cations than is the anisyl ether oxygen, the urea carbonyl is a much stronger hydrogen bond acceptor.[6] The cyclic urea unit provides more access to the binding cavity by guests that hydrogen bond to the host. Indeed, **2** was shown to be the most powerful complexing agent for alkylammonium ions synthesized to date.[4a] Compounds such as **2**, to which were bonded some of the catalytic groups of chymotrypsin (primary hydroxyl and imidazole), were demonstrated to be effective partial transacylase enzyme mimics.[7]

Because of the powerful binding of these cyclic urea-containing hosts of alkali metal and alkylammonium ions, chiral analogues should provide good candidates for study as catalysts or enantioselective binders of amino acids or esters. Such hosts require steric barriers located close to their binding sites. This paper reports the synthesis and complexation properties of eight new macrocycles, **3**–**10**,

(1) We warmly thank the U.S. Public Health Service for Grant 12640 and the National Science Foundation for Grant CHE 81-09532 for support of this work.

(2) (a) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Brown, S. B.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 3645–3657. (b) Cram, D. J.; Lein, G. M. *Ibid.* **1985**, *107*, 3657–3668.

(3) Cram, D. J.; deGrandpre, M. P.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3286–3292.

(4) (a) Cram, D. J.; Dicker, I. B.; Lauer, M.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7150–7167. (b) Katz, H. E.; Cram, D. J. *Ibid.* **1984**, *106*, 4977–4987. (c) Artz, S. P.; Cram, D. J. *Ibid.* **1984**, *106*, 2160–2170. (d) Lein, G. M.; Cram, D. J. *Ibid.* **1985**, *107*, 448–455.

(5) Anthonsen, T.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 414–416. Compound **5** in this paper mistakenly contains a methyl group in the 5-position of the bridging 1,3-xylyl group. The correct structure is that of **3** in the present paper.

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

(7) (a) Cram, D. J.; Katz, H. E.; Dicker, I. B. *J. Am. Chem. Soc.* **1984**, *106*, 4987–5000. (b) Cram, D. J.; Lam, P. Y.-S.; Ho, S. P. *Ibid.* **1986**, *108*, 839–841.

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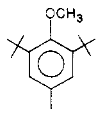
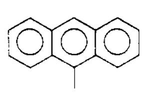
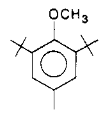
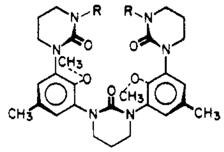
Chart I. Structures of Hosts and Differentiation in Host-Guest Binding Involving $MeNH_3^+$ and t-$BuNH_3^+$

hosts			host differentiation of guests		guest differentiation of hosts, GDH[c]	
no.	X	Y	HDG[a]	DEF[b]	$MeNH_3^+$	t-$BuNH_3^+$
2	OMe	Me	1.3	0.09	−0.6	−0.4
3	H	H	1.1	0.08	0	0
4	Br	H	1.3	0.11	1.8	2.0
5	CO_2Me	H	1.2	0.09	1.0	1.1
6		H	1.7	0.14	1.8	2.4
7		H	1.4	0.15	4.3	4.6
8	H	t-Bu	0.7	0.06	2.0	1.6
9	Br	t-Bu	1.3	0.10	0.8	1.0
10		t-Bu	2.5	0.19	0.9	2.3

[a] $[(-\Delta G°(MeNH_3^+) - (-\Delta G°(t\text{-}BuNH_3^+))]$ = HDG, kcal mol^{-1}. [b] $[(-\Delta G°(MeNH_3^+) - (-\Delta G°(t\text{-}BuNH_3^+))]/-\Delta G°(MeNH_3^+)$ = DEF, or differentiation efficiency factor. [c] $[(-\Delta G°(HH)) - (-\Delta G°(XY))]$ = GDH, kcal mol^{-1}.

which contain various functional groups or steric barriers substituted as X and Y of **2**. Chart I indicates their structures and the experimental section contains their systematic names.

Syntheses. The synthesis of **11** has been reported.[4a] Methylation of **11** with NaH–THF–CH_3I gave **12** (32%),

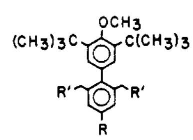


11, R = H

12, R = CH_3

needed as a noncyclic model. Cycles **3**–**10** were prepared by treating the appropriate *m*-bis(bromomethyl)benzene derivatives with the bis(anion) of **11** after deprotonation with NaH–THF.[4a] The yields for the ring closures given in parentheses refer to isolated analytically pure decomplexed macrocyclic host. Reaction of **11** with 1,3-bis(bromomethyl)benzene gave **3** (32%); with 2-bromo-1,3-bis(bromomethyl)benzene[8] gave **4** (6%); with methyl 2,6-bis(bromomethyl)benzoate[8] gave **5** (3%); with 2,6-bis(bromomethyl)-3′,5′-bis(1,1-dimethylethyl)-4′-methoxy-1,1′-biphenyl (**13**) gave **6** (8%); with 9-[2,6-bis(bromomethyl)phenyl]anthracene (**21**) gave **7** (17%); with 1,3-bis(bromomethyl)-5-(1,1-dimethylethyl)benzene[9] (**18**) gave **8** (19%); with 2-bromo–1,3-bis(bromomethyl)-5-(1,1-dimethylethyl)benzene (**19**) gave **9** (19%); and with 2,6-bis(bromomethyl)-4,3′,5′-tris(1,1-dimethylethyl)-4′-methoxy-1,1′-biphenyl (**14**) gave **10** (4%).

The syntheses of the new xylylene dibromides used in the above ring closures are outlined. Reaction of 2-bromo-1,3-dimethyl-5-(1,1-dimethylethyl)benzene[10] (**22**) with NBS–CCl_4 gave 2-bromo-1,3-bis(bromomethyl)-5-(1,1-dimethylethyl)benzene, **19** (10%). The Grignard reagent of 2-bromo-1,3-dimethylbenzene (**23**) in ether was coupled with 5-bromo-1,3-bis(1,1-dimethylethyl)-2-methoxybenzene[11] (**24**) with $Ni(acac)_2$ as catalyst[12] to give **15** (52%). Analogously, the Grignard reagent of 2-bromo-1,3-dimethyl-5-(1,1-dimethylethyl)benzene (**22**) was coupled[12] with **24** to provide **16** (38%). Treatment of **15** with NBS–CCl_4 gave **13** (44%). Unfortunately, similar attempts to brominate **16** gave a bad mixture of products, hydrolysis of which with $NaHCO_3$–H_2O–CH_3CN provided diol **17** (24%). When treated with HBr–$CHCl_3$, **17** gave the desired dibromide, **14** (86%). The Grignard reagent from 2-bromo-1,3-bis(methoxymethyl)benzene[13] (**25**) was added by a conventional procedure[14] to anthrone to give **20** (25%). Treatment of **20** with HBr–$CHCl_3$ gave **21** (72%).



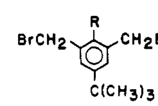
13, R = H, R′ = Br

14, R = $(CH_3)_3C$, R′ = Br

15, R = H, R′ = H

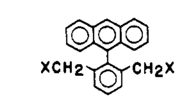
16, R = $(CH_3)_3C$, R′ = H

17, R = $(CH_3)_3C$, R′ = OH



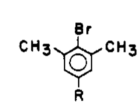
18, R = H

19, R = Br



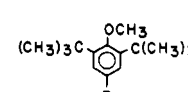
20, X = OCH_3

21, X = Br



22, R = $(CH_3)_3C$

23, R = H



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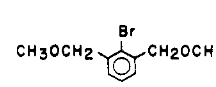

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Free Energies of Binding and Association Constants. The free energies of binding ($-\Delta G°$) and association constants (K_a) of hosts **3**–**12** binding the alkali metal and the ammonium picrates in $CDCl_3$ saturated with H_2O were determined at 25 °C by the extraction method.[15,4c]

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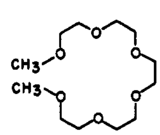
Table I. Binding Free Energies ($-\Delta G°$) of Hosts for Picrate Salt Guests at 25 °C in $CDCl_3$ Saturated with D_2O

host	$-\Delta G°$ [a] or K_a [b]	guest cation							
		Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	$MeNH_3^+$	t-$BuNH_3^+$
2	$-\Delta G°$	12.1	15.3	15.5	14.2	13.1	14.4	14.4	13.1
3	$-\Delta F°$	13.4	15.4	15.5	13.3	14.3	13.9	13.8	12.7
4	$-\Delta G°$	13.1	13.5	13.3	12.8	12.6	12.8	12.0	10.7
5	$-\Delta G°$	13.3	14.3	14.2	13.6	13.2	13.6	12.8	11.6
6	$-\Delta G°$	12.8	12.8	13.6	13.5	13.8	13.1	12.0	10.3
7	$-\Delta G°$	10.7	10.8	10.5	10.0	10.9	10.3	9.5	8.1
8	$-\Delta G°$	12.5	13.5	13.3	12.6	12.2	12.5	11.8	11.1
9	$-\Delta G°$	12.8	14.6	14.2	13.6	14.8	13.8	13.0	11.7
10	$-\Delta G°$	12.8	15.0	14.8	13.2	16.6	13.9	12.9	10.4
11	$-\Delta G°$	–	6.6	6.9	–	–	6.9	–	–
12	$-\Delta G°$	–	6.1	6.3	–	–	6.2	–	–
26	$-\Delta G°$	–	<5.0	<5.0	–	–	<4.5	–	–
27	$-\Delta G°$	5.9	8.3	10.8	9.6	8.3	9.5	7.5	6.9
28 [c]	$-\Delta G°$	10.2	9.9	10.1	9.5	9.4	7.0	7.4	8.6
2	K_a	7.2×10^8	1.6×10^{11}	2.2×10^{11}	1.4×10^{10}	3.9×10^9	3.5×10^{10}	3.5×10^{10}	4.5×10^9
3	K_a	6.9×10^9	2.0×10^{11}	2.3×10^{11}	5.7×10^9	3.1×10^{10}	1.6×10^{10}	1.3×10^{10}	2.1×10^9
4	K_a	3.9×10^9	9.8×10^9	6.4×10^9	2.8×10^9	1.9×10^9	2.9×10^9	7.6×10^8	7.2×10^7
5	K_a	6.3×10^9	3.3×10^{10}	2.4×10^{10}	1.0×10^{10}	4.9×10^9	1.0×10^{10}	2.3×10^9	4.5×10^8
6	K_a	2.5×10^9	2.4×10^9	1.1×10^{10}	9.2×10^9	1.4×10^{10}	6.3×10^9	7.1×10^8	3.9×10^7
7	K_a	8.2×10^7	9.6×10^7	5.6×10^7	2.0×10^7	1.0×10^8	3.6×10^7	8.6×10^6	8.4×10^5
8	K_a	1.7×10^9	1.1×10^{10}	8.0×10^9	2.1×10^9	1.1×10^9	1.8×10^9	1.6×10^8	1.4×10^8
9	K_a	2.5×10^9	5.0×10^{10}	3.0×10^{10}	1.2×10^{10}	8.2×10^{10}	1.8×10^{10}	3.5×10^9	4.5×10^8
10	K_a	2.4×10^9	1.1×10^{11}	6.7×10^{10}	4.2×10^9	2.3×10^{12}	1.7×10^{10}	3.4×10^9	4.7×10^7
11	K_a		7.0×10^4	1.2×10^5			1.1×10^5		
12	K_a		3.1×10^4	4.4×10^4			3.7×10^4		
26	K_a		$<4.2 \times 10^3$	$<4.2 \times 10^3$			$<1.8 \times 10^3$		
27	K_a	2.2×10^4	1.2×10^6	8.6×10^7	1.1×10^7	1.3×10^6	9.9×10^6	3.3×10^5	1.1×10^5
28 [c]	K_a	3.0×10^7	1.8×10^7	2.9×10^7	9.0×10^6	8.0×10^6	1.4×10^5	2.7×10^5	2.0×10^6

[a] In mol^{-1}. [b] In kcal mol^{-1}. [c] Binding values for alkali metal ions refer to 2:1 complexes (ref 17).

Solutions of Li, Na, K, Rb, Cs, NH_4, $MeNH_3$, and t-$BuNH_3$ picrates in H_2O (0.001 M) were extracted into $CDCl_3$ in the absence and presence of host (0.001 M). The concentrations of host and guest were 0.015 M for the determinations involving **11** and **12**. The hosts and their complexes are soluble essentially only in the $CDCl_3$ phase. The binding of piperidinium by **9** was determined by the same kind of extractive technique.[4b] The $-\Delta G°$ and K_a values were calculated from absorbances of the picrate ion in both the aqueous and organic layers, and the averages of these two determinations are shown in Table I. The $-\Delta G°$ values determined from each phase were usually within 0.4 kcal mol^{-1} of one another. The $-\Delta G°$ and K_a values for host **2** for pentaglyme (**26**), 2,3-naphtho-18-crown-6 (**27**),[16] and host **28**[17] (**2** lacking the three methoxy and three p-methyl groups) are included in Table I for comparison purposes.



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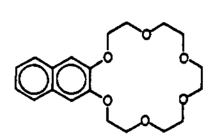

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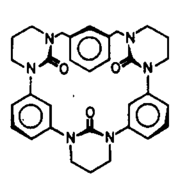

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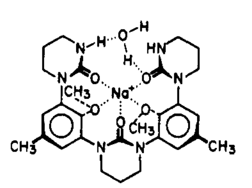

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Discussion

The binding properties of the nonmacrocyclic hosts are discussed in the first section. The crystal structures of several complexes are compared in the second section. Correlations between the structures and binding characteristics toward the alkali metal and ammonium ions are discussed in the third section. The fourth section compares the conformations of the hosts before and after complexation. Section 5 treats steric control of structural recognition in complexation of alkylammonium ions. In section 6 the rates of complexation and decomplexation of **9** with t-$BuNH_3$ picrate are discussed.

Binding Properties of Nonmacrocyclic Hosts. The nonmacrocyclic hosts **11** and **12** possess three cyclic urea and two anisyl oxygens that offer five potential binding sites for guests. These podands[18] complex Na^+, K^+, and NH_4^+ ions with $-\Delta G°$ values that range from 6.1 to 6.9 kcal mol^{-1}. Pentaglyme **26**, which also contains five binding sites, is below the detection limits of complexation by the picrate extraction method (about 5 kcal mol^{-1}). Based on precedents,[18a,19] we estimate **26** binds in the 3 to 4 kcal mol^{-1} range. Thus podands **11** and **12** are stronger binders by 2–3 kcal mol^{-1} than their polyether counterpart (**26**).

Host **11** is a slightly stronger binder (by approximately 0.6 kcal mol^{-1}) than **12**. From inspection of molecular models, methylation of the terminal nitrogens appears not to sterically or electronically impede complexation. Methylation would, however, eliminate any role that H-

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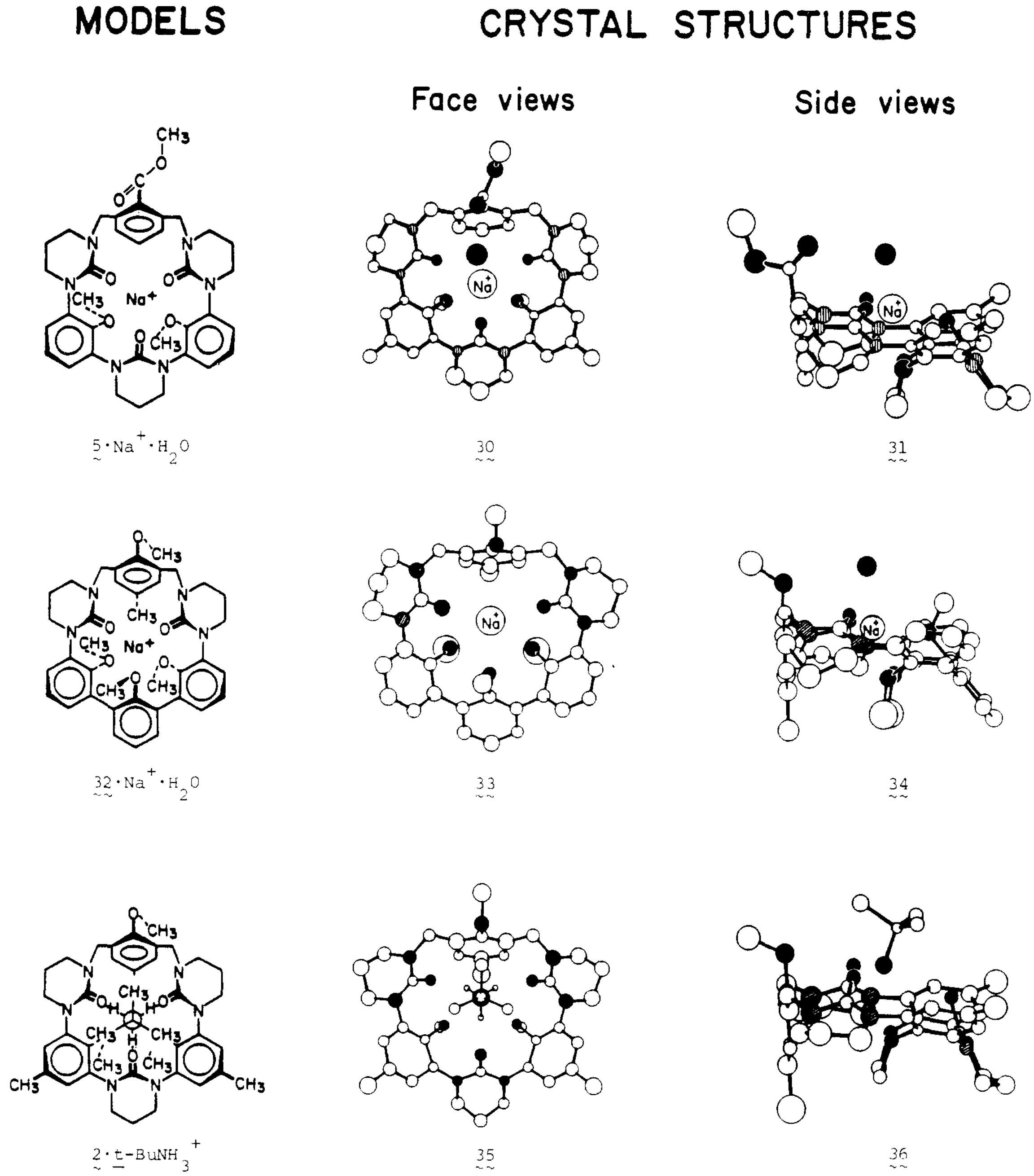
Chart II



bonding plays in holding the nitrogen ends of the podand together during complexation. Although direct H-bonding from one terminal urea to the other terminal urea in **11** appears unlikely, a water-mediated H-bond such as that shown in **29** is possible. Evidence supporting H-bonding of some kind by the terminal N–H groups of **11** upon complexation may be found in the pronounced shift (from 4.95 to 6.10 ppm) and broadening of their resonance in the ^{1}H NMR spectrum caused by addition of sodium picrate. The uptake of only 1 equiv of sodium picrate by a $CDCl_3$ solution of **11** suggests the formation of a 1:1 host–Na^+ complex.

Crystal Structures of Complexes of Macrocycles. In CPK molecular models of host **5**, it is possible without apparent strain to generate a binding conformation for the alkali metal ions in which the ester's carbonyl group cooperates with the three cyclic urea and two anisyl oxygens in directly coordinating the metal ion. A crystal structure of **5**·NaOH·H_2O was determined, two views of which are depicted in **30** and **31**. These structures are compared with those of complexes **32**·Na^+ and **2**·*t*-$BuNH_3^+$ reported earlier.[4a] Host **32** resembles **2** except that the cyclic urea unit of **2** at 6 o'clock has been replaced by the nearly isosteric anisyl unit in **32** (Chart II).

Although a detailed account of the crystal structure **5**·NaOH·H_2O is not given here, a few interesting features are discussed. Like **32**·Na^+, **5**·Na^+ crystallizes with a mole of ligating water whose oxygen occupies one of the six binding sites that surround the metal ion. In **30–31**, the six ligating sites have an average Na^+ to O distance of 2.49 Å. If we assume the oxygens have the usual covalent diameter of 2.80 Å, the effective diameter of the Na^+ is 2.18 Å, comparable to the Na^+ diameter of 2.32 Å in **33–34**. The distances of the three urea oxygens to the Na^+ in **30–31** are 2.48, 2.44, and 2.29 Å, those of the two anisyl oxygens are 2.69 and 2.63 Å, and that of the water is 2.42 Å. These distances locate the Na^+ 0.19 Å below the best plane defined by the 20-atom ring members of the macrocycle to provide a nesting structure. The angle of tilt of the plane of the CH_2ArCH_2 group in **30–31** with respect to the best plane of the macroring is 112°, slightly greater than the corresponding angles in **33–34** (107°) and in **35–36** (104°). The average dihedral angle between the anisyl planes and the bound cyclic urea best planes in **30–31** is 116°, as compared to 118° in **33–34** and 111° in **35–36**.

The general correspondence between structures suggested by CPK model examination and the crystal structures is remarkably good except for the interposition of a water molecule between the Na^+ and the carbonyl group of the ester in **30–31** ($Na^+{\cdot}OH_2{\cdot}O{=}C$). Interestingly, a similarly located water molecule is found in **33–34**, and in the crystal structure of **32**$\cdot Cs^+ \cdot H_2O$ as well.[4a]

Correlations between Structures of Cyclic Hosts and Binding Free Energies of the Alkali Metal Ions. Cyclic hosts **2–10** are comprised of 20-membered rings containing three cyclic urea and two anisyl units. The $-\Delta G°$ values for complexation by **2–10** of the alkali metal cations typically range from 10 to 15 kcal mol^{-1}. Most of these values are about 5–7 kcal mol^{-1} greater than those for the lipophilic chorand, 2,3-naphtho-18-crown-6 (**27**).[16] The superior binding power of the hemispherands as compared to the chorands is attributed mainly to the fact that the modules of the former are more preorganized for binding in the free hosts than are those of the more flexible latter hosts (principle of preorganization).[20] This effect appears to outweigh others, such as the availability of six oxygens in the chorand vs. five oxygens in the hemispherands, or the differences in intrinsic binding abilities of the cyclic urea, CH_2OCH_2, or $ArOCH_3$ oxygens.

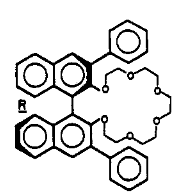
Cyclic hosts **2–6** and **8–10** are remarkably similar in their abilities to bind Li^+, Na^+, K^+, Rb^+, Cs^+, and NH_4^+ ions (Table I). The maximum difference observed for any host–guest combination is $\Delta(\Delta G°) = 4.5$ kcal mol^{-1} ($-\Delta G°$ for **10**$\cdot Cs^+$ of 16.6 vs. $-\Delta G°$ for **2**$\cdot Li^+$ of 12.1 kcal mol^{-1}). The maximum difference for any of these eight hosts binding a particular guest is $\Delta(\Delta G°)$ is 4.4 kcal mol^{-1} ($-\Delta G°$ for **10**$\cdot Cs^+$ of 16.6 vs. $-\Delta G°$ for **8**$\cdot Cs^+$ of 12.2 kcal mol^{-1}). The other differences range from a high of 2.2 kcal mol^{-1} for K^+ to a low of 1.6 kcal mol^{-1} for Rb^+. As usual,[4a] the $-\Delta G°$ values for each of the eight hosts binding Rb^+ and NH_4^+ were essentially the same ($(\Delta(\Delta G°)_{av.} < 0.3$ kcal mol^{-1}). The maximum difference for any of these six guests binding a particular host is $\Delta(\Delta G°) = 3.8$ kcal mol^{-1} ($-\Delta G°$ for **10**$\cdot Cs^+$ of 16.6 vs. $-\Delta G°$ for **10**$\cdot Li^+$ of 12.8 kcal mol^{-1}). The other differences range from a high of 3.4 kcal mol^{-1} for **2** to a low of 1.0 kcal mol^{-1} for **6**. Thus, this class of hosts shows very low structural recognition in complexing the alkali metal and ammonium ions. Molecular models of these hosts suggest that the three carbonyl groups of the cyclic urea units and the two anisyl oxygens can easily adapt by rotations about their N–Ar bonds to the different space occupation requirements of these six guests. This ability to undergo adjustments in cavity size is not affected in a major way by the X and Y substituents on the *m*-xylylene group bridging the two cyclic urea modules, which suggests these substituents play little direct role in binding these essentially spherical guests.

Host **7** contains the bulky 9-anthracyl group attached in the X-position of the *m*-xylylene bridging module. This host binds the six guests with $-\Delta G°$ values that vary only from a low of 10.0 to a high of 10.9 kcal mol^{-1}. The average $-\Delta G°$ value is 2 to 4 kcal mol^{-1} below the average value for any of the other hosts. In molecular models of **7** and its complexes, one benzene ring of the anthracene stands above the open face of the binding site occupied by the water in the crystal structures **31** and **34**. We interpret the lower $-\Delta G°$ values for **7** as being due to steric inhibition of water ligation of the complexed alkali metal and ammonium ions. Notice that such ligation in **5** and **32** complexes appears to be stabilizing.

Conformations of the Hosts and Complexes. Spectral studies (^1H NMR) of **2–5** in $CDCl_3$ at 27 °C indicate that significant differences exist in the uncomplexed conformational states of these molecules. The ^1H NMR spectrum of **2** showed it to be a mixture of four conformers equilibrating slowly on the ^1H NMR time scale.[4a] Free hosts **4** and **5** both exist in two conformations which equilibrated slowly on the ^1H NMR time scale. Unlike the others, hosts **3** and **8**, exhibited broad signals which sharpened upon cooling. These two hosts are unique among **2–10**, and it appears that the conformers of **3** and **8** interconvert more rapidly than those of the other hosts. In **3** and **8**, X is hydrogen, whereas in the other hosts, X is a bulky group. We conclude that the conformers of **3** and **8** interconvert via a simple ring flip of the bridging *m*-xylylene unit. In hosts **2**, **4–7**, **9**, and **10**, this process is impeded by the substituent in the X-position of the bridging unit. In the latter hosts, the interconversions of conformers probably occur by successive rotations of each of the arylmethoxy and cyclic urea units through the middle of the cavity. All conformations of free hosts **3–10** interconvert rapidly on the human time scale.

Additions of guests to solutions of hosts **2–10** provided ^1H NMR spectra for single symmetrical complexes. The conformation adopted by **2**$\cdot t\text{-}BuNH_3^+$ and **5**$\cdot Na^+ \cdot H_2O$ in their crystal structures probably represents the solution phase conformation of all of the complexes of **2–10**.

Steric Control of Structural Recognition in Complexation of Alkylammonium Ions. Tripod binding of alkylammonium ions by chorand hosts provides complexes that are highly structured.[21] Introduction of the chiral binaphthyl units into hosts such as **37** and **38** provided



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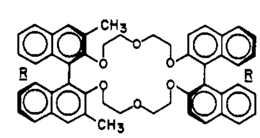

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systems that were enantioselective in their complexation of amino ester and amino acid salts by factors as high as 22 for **37**[22] and 31 for **38**.[23] The *chiral efficiency* of such systems was defined as $(\Delta G°_A - \Delta G°_B)/\Delta G°_A$ in which $\Delta G°_A$ and $\Delta G°_B$ were the free energies of complexation by **37** or **38** of the more and less bound enantiomeric amino acid or ester salts, respectively, at 0 °C in $CDCl_3$ saturated with water. The highest chiral efficiency observed for **37** involved $C_6H_5CH(CO_2H)NH_3ClO_4$ and was 0.30, whereas that for **38** involved $C_6H_5CH(CO_2CH_3)NH_3PF_6$ and was 0.32.[24] Our inability to obtain higher chiral recognition by encumbering the chorand hosts with larger steric barriers was attributed to the intrinsically low binding free

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energies of these hosts ($-\Delta G°_A$ values of 4 to 5.6 kcal mol^{-1}). As the steric barriers increased, highly structured tripod binding gave way to relatively unstructured dipodal binding and chiral recognition was lost. This hypothesis was supported by the observation that piperidinium picrate containing only the potential for dipodal binding gave $-\Delta G°$ values about two-thirds that for alkylammonium picrates capable of tripodal binding.[4b] These trends suggest that if chiral recognition with $-\Delta(\Delta G°)$ values as high as 4 or 5 kcal mol^{-1} is to be realized, $-\Delta G°_A$ values in the 14 kcal mol^{-1} range would be required with chiral efficiency factors of about 0.3.

The tris(urea) hosts **2–10** bind $MeNH_3^+$ ions with $-\Delta G°$ values that range from a low of 9.5 to a high of 14.4 kcal mol^{-1}. Chorand hosts **37** and **38** provide values of 6.2[22] and 4.4 kcal mol^{-1},[24] respectively. The tris(urea) host **28**, similar to **2–10** but stripped of the anisyl methoxyl X and Y substituents, complexes NH_4^+, $MeNH_3^+$, and t-$BuNH_3^+$ with $-\Delta G°$ values of only 7.0, 7.4, and 8.6 kcal mol^{-1}, respectively. Thus, only the tris(urea)–bis(anisyl) host binding site appears to complex strongly enough to suggest its ultimate application to chiral recognition studies involving amino acids and esters.

In the present study, steric barriers of increasing size were introduced into the X- and Y-positions of **2** to determine the point at which nonbonded interactions between host and guest provided maximum structural recognition of $MeNH_3^+$ over t-$BuNH_3^+$ ions. Crystal structures **35** and **36** indicate that X-substituents potentially contact the hydrogens of the alkyl groups of the guest. Molecular model examinations suggest that as the Y-substituents increase in bulk, the angle of tilt between their aryl plane and the best plane of the macrocycle should decrease due to nonbonded repulsions between the hydrogens of the Y-substituent and the OCH_3 groups on the noncomplexing face of the host. Accordingly, the X-substituent is pressed closer to the alkyl substituent of bound alkylammonium guests and becomes a more effective steric barrier.

The $-\Delta G°$ values for **2–10** binding $MeNH_3^+$ and t-$BuNH_3^+$ (Table I) were used to evaluate this approach. Parameters that measure structural differentiation in complexation are defined as follows. Values of $[(-\Delta G°(MeNH_3^+) - (-\Delta G°(t\text{-}BuNH_3^+))]$ measure the extent to which a *host differentiates* between *guests* (HDG). Values of $[(-\Delta G°(MeNH_3^+)) - (-\Delta G°(t\text{-}BuNH_3^+))]/\Delta G°(MeNH_3^+)$ measure the *differentiation efficiency factor* (DEF). Values of $[(-\Delta G°(HH)) - (-\Delta G°(XY))]$ measure the extents to which a *guest differentiates* between *hosts* (GDH). The standard host is **3** (in which X = Y = H) to which the other hosts with other X and Y substituents are compared. The guest which differentiates between hosts is either $MeNH_3^+$ or t-$BuNH_3^+$. Chart II records the values of these parameters.

The HDG parameter values (kcal mol^{-1}) increase with changes in X and Y as follows: X = H, Y = t-Bu, 0.7; X = Y = H, 1.1; X = CO_2CH_3, Y = H, 1.2; X = Br, Y = H, 1.3; X = OCH_3, Y = CH_3, 1.3; X = Br, Y = t-Bu, 1.3; X = 9-anthracyl, Y = H, 1.4; X = 4-CH_3O-3,5-(t-Bu)$_2C_6H_2$, Y = H, 1.7; X = 4-CH_3O-3,5-(t-Bu)$_2C_6H_2$, Y = t-Bu, 2.5. The differentiation efficiency factor (DEF) increases in a similar order from a low of 0.06 for X = H and Y = t-Bu to a high of 0.19 for X = 4-CH_3O-3,5-(t-Bu)$_2C_6H_2$ and Y = t-Bu. Hosts **8**, **3**, **4**, **5**, **2**, and **9** fall in one class with DEF values of 0.06–0.11. The sum of the steric requirements of the X and Y groups involved is hardly enough to be felt for these hosts. Hosts **6** and **7** constitute a second class, whose DEF values are 0.14 and 0.15, respectively. Here the respective X groups (4-CH_3O-3,5-(t-Bu)$_2C_6H_2$ and 9-anthracyl) are large enough to depress somewhat the binding of t-$BuNH_3^+$. In **6** and **7**, Y = H, which allows the steric barriers to pivot away from the alkyl group of the guest. Host **10** with X = 4-CHO-3,5-(t-Bu)$_2C_6H_2$ and Y = t-Bu is in a class by itself with a DEF factor of 0.19. In models, **10** appears to be very rigid, and better preorganized for binding than most of the more flexible hosts. As overall complexing agents for all eight guests, **2**, **3**, and **10** are the best binders. They are also the hosts whose X and Y groups best balance one another in their steric requirements.

The question remains whether **6**, **7**, and **10**, whose X groups offer the most steric inhibition to complexing t-$BuNH_3^+$, are forced into dipodal binding with this guest. The $-\Delta G°$ values for the three hosts are 10.3, 8.1, and 10.4 kcal mol^{-1}, respectively. Measurement of the enforced dipodal binding of **9** with piperidinium picrate gave $-\Delta G°$ = 7.3 kcal mol^{-1} (K_a = 2.5 × 10^5 M^{-1}). This value is close enough to the 8.1 kcal mol^{-1} for **7** binding t-$BuNH_3^+$ to suggest that the steric barrier with X = 9-anthracyl imposes dipodal binding on complex **7**·t-$BuNH_3^+$. The values for **6**·t-$BuNH_3^+$ and **10**·t-$BuNH_3^+$ are high enough to suggest that tripodal binding is retained. Molecular models (CPK) with tripodal binding in these latter complexes can be constructed, but are very compact.

Of the parameter that measures the ability of a guest to differentiate between hosts (GDH, kcal mol^{-1}), only values for **2** (X = OCH_3, Y = CH_3) were negative (−0.6 for $MeNH_3^+$ and −0.4 for t-$BuNH_3^+$, Chart I). This fact correlates with the electron-releasing character of these substituents. The others range from 0.8 to 4.6. The values of GDH for $MeNH_3^+$ and t-$BuNH_3^+$ are close to one another throughout the series except for **6** (X = 4-CH_3O-3,5-(t-Bu)$_2C_6H_2$, Y = H), and particularly for **10** (X = 4-CH_3O-3,5-(t-Bu)$_2C_6H_2$, Y = t-Bu). The GDH value for $MeNH_3^+$ complexing **6** is 1.8 and for t-$BuNH_3^+$ is 2.4, whereas the value for $MeNH_3^+$ binding **10** is 0.09 and for t-$BuNH_3^+$ binding **10** is 2.3 kcal mol^{-1}. Interestingly, the GDH values for $MeNH_3^+$ and t-$BuNH_3^+$ binding **7** (9-anthracyl) are 4.3 and 4.6 kcal mol^{-1}, respectively. This suggests that possibly both $MeNH_3^+$ and t-$BuNH_3^+$ complex **7** with only dipodal binding.

Rate Constants for Complexation and Decomplexation. The rate constants at 25 °C for decomplexation (k_{-1}) of **9** (X = Br, Y = t-Bu) with *tert*-butylammonium picrate in $CDCl_3$ saturated with H_2O were determined by the ^1H NMR line-shape analysis method at various temperatures.[5] From k_{-1} and the K_a value for complexation (Table I), the complexation rate constant (k_1) was calculated. The value of k_{-1} (1.9 × 10^2 s^{-1}) for decomplexation is approximately a factor of only three lower than for hosts **2** and **3**, whereas the value of k_1 (8.6 × 10^{10} mol^{-1} s^{-1}) is a factor of 16 to 36 lower than that for **2** and **3**.[5] Spectral evidence (^1H NMR) shows that several conformations of hosts **2**, **3**, and **9** are eliminated by complexation with t-$BuNH_3^+$, a process which undoubtedly involves desolvation of the host by H_2O. The slower rate of complexation associated with **9** probably reflects a slower rate of conformational reorganization for this more sterically encumbered host than for the less hindered hosts **2** and **3**.

Experimental Section

General. Dry Et_2O and THF were prepared by distilling from sodium benzophenone ketyl prior to use. Oil-free sodium hydride was prepared by stirring a 50% mineral oil dispersion of NaH with pentane 3 times in a Buchner funnel. Chromatography was performed with E. Merck silica gel, particle size 0.063–0.200 mm (gravity column) or 0.040–0.063 mm (medium-pressure column).

Preparative thin-layer chromatography was performed on E. Merck glass plates (2.0 mm layer thickness, silica gel). Columns for gel permeation chromatography were 20 ft by 0.25 in. i.d. aluminum tubing packed with 100 Å Styragel (Waters). A separate column was used for complexed and decomplexed hosts. Elution of the columns was carried out with doubly distilled CH_2Cl_2 at a flow rate of approximately 4 mL min^{-1} and a back pressure of 400–600 psi. Melting points below 240 °C were recorded on a Thomas-Hoover and those above 240 °C on a Mel-Temp apparatus. All melting points are uncorrected. Hosts were dried (140 °C, 5×10^{-5} mm, 24–48 h) prior to elemental analysis or complexation studies. Mass spectra were recorded at the indicated voltage and probe temperature on an AE-1 Model MS-9 spectrometer. The mass spectra of complexed hosts sometimes exhibited a peak corresponding to free host but more commonly exhibited higher mass peaks. In the case of Na^+ complexes, M + 8 peaks were observed. Presumably, under the conditions of mass spectroscopic analysis, the counterion displaces a methyl of one of the arylmethoxy units. The sodium salt (loss of 15 and a gain of 23 mass units) of the demethylated host then gives the M + 8 parent mass peak. The fact that the KBr complex of host 8 exhibits an M + 24 peak (M + 39 − 15) supports this interpretation. Nuclear magnetic resonance spectra were recorded on a Bruker WP-200 spectrometer (200 MHz) except where noted that a Varian T-60 spectrometer (60 MHz) was employed. $CDCl_3$ was the solvent throughout. Chemical shifts are δ-values reported in parts per million. Internal tetramethylsilane at 0.00 ppm or $CHCl_3$ at 7.24 ppm was used as the reference resonance. The methylene protons connecting the bridging aryl unit and the cyclic urea units were observed to give an AB pattern in the ^1H NMR spectrum of the host molecules. Signals for the inner and outer protons of the methylene are typically found in the ranges 3.4–4.0 ppm and 4.5–5.5 ppm. The geminal coupling constant for these protons is usually between 14 and 16 Hz. The specific assignments of these two sets of proton resonances are not made. The 3.4–4.0 ppm range also contains signals due to the methylene protons of the cyclic urea units. Consequently, this region generally exhibits very complicated envelopes of resonances. The exact positions of the AB patterns were established by homonuclear decoupling experiments. Ultraviolet measurements were made with a Gilford Model 252 photometer utilizing a Beckman DU monochromator. All hosts were detected by their strong and lasting absorption of iodine vapor when a developed thin-layer chromatogram was placed in an iodine chamber. Thin-layer chromatography was conducted on silica gel precoated plastic sheets (E. Merck, thickness 0.2 mm), and the sheets were developed in 80% CH_2Cl_2, 20% EtOH. Bands corresponding to hosts darken within seconds after placement in the chamber and retain their color for 5–30 hours. Bands corresponding to unreacted 11 or oligomeric products from the ring closure reactions also darken, but the color fades much more quickly. The reason for this strong absorption of iodine by the hosts is not clear; however, there is ample literature precedent for the reversible formation of iodine complexes.[25]

1,3-Bis[2-methoxy-3-*N*-(tetrahydro-2-pyrimidinonyl)-5-methylphenyl]tetrahydro-2-pyrimidinone (11). Compound 11 was prepared according to literature methods.[4a] In the ring closure reactions of 11, more satisfactory results were obtained with material which was chromatographed (silica gel; 20% EtOH, 80% CH_2Cl_2) and thoroughly dried. Compound 11 is hygroscopic. Anal. Calcd for $C_{28}H_{36}N_6O_5$: C, 62.67; H, 6.76. Found: C, 57.92; H, 6.22. Found after drying (160 °C, 48 h, 0.05 mm): C, 62.30; H, 6.55. ^1H NMR: δ 1.99–2.10 (m, 4 H, NCH_2CH_2), 2.2–2.3 (m, 2 H, NCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.41 (m, 4 H, NCH_2CH_2), 3.55 (m, 4 H, NCH_2CH_2), 3.73 (m, 4 H, NCH_2CH_2), 3.81 (s, 6 H, OCH_3), 4.95 (br s, 2 H, NH), 6.95 (d, J = 2 Hz, 2 H, ArH), 7.03 (d, J = 2 Hz, 2 H, ArH).

The binding of alkali cations by 11 is too weak to prepare $CDCl_3$ solutions of complexed host by stirring with aqueous solutions of guests. A sodium picrate complex was prepared by allowing a $CDCl_3$ solution of 11 to stand over solid sodium picrate for 2 days. The salt is absorbed directly from the solid phase. This process is slow and may be accelerated by sonication. In the ^1H NMR spectrum of partially complexed 11, only time-averaged signals of free and complexed 11 are observed. Sodium picrate complex: ^1H NMR δ 1.85–2.00 (m, 4 H, NCH_2CH_2), 2.10–2.30 (m, 2 H, NCH_2CH_2), 2.20 (s, 6 H, $ArCH_3$), 3.00–4.00 (m, 12 H, NCH_2CH_2), 3.76 (s, 6 H, OCH_3), 6.10 (very br s, 2 H, NH), 6.84 (br s, 2 H, ArH), 6.92 (br s, 2 H, ArH), 8.8 (s, 2 H, ArH).

36,38-Dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6-(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (3). A suspension of 0.67 g of 11 (1.2 mmol) and 1.2 g of NaH (oil-free, 25 mmol) in 500 mL of dry THF was refluxed for 4 h under N_2 and cooled to −78 °C. A solution of 0.35 g of 1,3-bis(bromomethyl)benzene (α,α′-dibromo-*m*-xylene, Aldrich, 1.3 mmol) in 10 mL of dry THF was syringed into the mixture, and the reaction was allowed to warm to 25 °C over 10 h. Water (10 mL) was added, and the solvent was removed under reduced pressure. The residue was partitioned between 30 mL of CH_2Cl_2 and 20 mL of H_2O containing 2 g of NaBr. The mixture was stirred for 60 min, and 2 drops concentrated HCl were added to break the emission. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to leave a solid. This solid was purified by gel chromatography (Styragel 100 Å, CH_2Cl_2) to yield the NaBr complex of 3. After recrystallization from CH_2Cl_2/toluene, 0.47 g (51%) of the pure NaBr complex of 3 was obtained. This material was decomplexed by dissolving 0.10 g in CH_3OH and refluxing, and then adding enough H_2O to replace the CH_3OH which was allowed to evaporate. Upon cooling, the solution deposited the free cycle as a powder. After recrystallization of the powder from CH_2Cl_2/toluene, 53 mg (32%) of pure 3 remained, mp (decomposition) 230 °C: ^1H NMR δ 2.00–2.50 (m, 12 H, $ArCH_3$ and NCH_2CH_2), 3.00–3.95 (m, 20 H, $ArOCH_3$, NCH_2CH_2 and $ArCH_2N$), 5.80 (br s, 2 H, $ArCH_2N$), 6.75–7.70 (m, 8 H, ArH); MS (16 eV), *m/e* 638 (M^+). Anal. Calcd for $C_{36}H_{42}N_6O_5 \cdot H_2O$: C, 65.83; H, 6.75. Found: C, 65.63; H, 7.17.

^1H NMR of 3·NaBr: δ 2.20–2.45 (m, 6 H, NCH_2CH_2), 2.27 (s, 6 H, $ArCH_3$), 3.70 (s, 6 H, $ArOCH_3$), 3.55–4.05 (m, 14 H, NCH_2CH_2 and $ArCH_2N$), 4.60 ($^1/_2$ AB, J = 15 Hz, 2 H, $ArCH_2N$), 6.86 (s, 4 H, ArH), 7.16 (s, 1 H, ArH), 7.35 (d, J = 10 Hz, 2 H, ArH), 7.53 (t, J = 10 Hz, 1 H, ArH). MS (16 eV): *m/e* 638 (M^+). Anal. Calcd for $C_{36}H_{42}N_6O_5 \cdot NaBr$: C, 58.29; H, 5.71. Found: C, 58.11; H, 5.79.

34-Bromo-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (4). A suspension of 0.7 g of 11 (1.3 mmol, dried as above) and 1.7 g of NaH (oil-free, 35 mmol) in 800 mL of dry THF was refluxed for 5 h under N_2 and then cooled to −78 °C. A solution of 0.45 g of 2-bromo-1,3-bis(bromomethyl)benzene[8] (1.3 mmol) in 18 mL of dry THF was syringed into the mixture, and the reaction was allowed to warm to 25 °C over 15 h. The reaction was stirred at 25 °C for 24 h and then refluxed for 2 h. The reaction was neutralized with 5% aqueous HCl. The solvent was removed under reduced pressure to precipitate a gum which was purified by chromatography (silica gel; 10% CH_3OH, 90% CH_2Cl_2) to give solid complexed cycle. This solid was taken up in CH_2Cl_2 and washed 3 times with distilled water. The CH_2Cl_2 layer was dried by passing through filter paper and then evaporated to leave 58 mg of pure decomplexed 4 (6%), decomposition starts at 230 °C, mp approximately 280 °C: ^1H NMR δ 1.95–2.40 (m, 12 H, NCH_2CH_2 and $ArCH_3$), 2.88 (s, 3 H, OCH_3), 3.20–4.20 (m, 15 H, NCH_2CH_2 and $ArOCH_3$), 3.91 and 4.95 (AB, J = 16 Hz, 2 H, $ArCH_2N$), 3.65 and 5.50 (AB, J = 16 Hz, 2 H, $ArCH_2N$), 6.60–7.80 (m, 7 H, ArH); MS (70 eV, 270 °C), *m/e* 716 (M^+, ^{79}Br). Anal. Calcd for $C_{36}H_{41}O_5N_6Br$: C, 60.00; H, 5.76. Found: C, 60.25; H, 5.84.

^1H NMR of 4·cesium picrate: δ 2.1–2.4 (m, 6 H, NCH_2CH_2), 2.24 (s, 6 H, $ArCH_3$), 3.3–4.2 (m, 18 H, NCH_2CH_2 and $ArOCH_3$), 3.72 and 5.35 (AB, J = 16 Hz, 4 H, $ArCH_2N$), 6.86 (s, 2 H, ArH), 6.90 (s, 2 H, ArH), 7.42 (d, J = 8 Hz, 2 H, ArH), 7.57 (t, J = 8 Hz, 1 H, ArH), 8.75 (s, 2 H, ArH).

^1H NMR of 4·NaBr: δ 2.1–2.6 (m, 6 H, NCH_2CH_2), 2.25 (s, 6 H, $ArCH_3$), 3.6–4.1 (m, 12 H, NCH_2CH_2), 3.72 (s, 6 H, $ArOCH_3$), 3.78 and 5.26 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 6.85 (s, 4 H, ArH), 7.36 (d, J = 8 Hz, 2 H, ArH), 7.62 (t, J = 8 Hz, 1 H, ArH).

34-Carbomethoxy-36,38-dimethoxy-4,14-dimethyl-33,35,37-trioxo-1,7,11,17,21,29-hexaazaheptacyclo-

(25) (a) Le Goaller, R.; Handel, H.; Labbe, P.; Pierre, J.-L. *J. Am. Chem. Soc.* **1984**, *106*, 1694–1698. (b) Herbstein, F. H.; Schwotzer, W. *Ibid.* **1984**, *106*, 2367–2373.

[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6-(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (5). A suspension of 0.7 g of 11 (1.3 mmol, dried as above) and 1.7 g of NaH (oil-free, 35 mmol) in 800 mL of dry THF was refluxed for 5 h under N_2 and then cooled to -78 °C. A solution of 0.44 g of methyl 2,6-bis(bromomethyl)benzoate[8] (1.3 mmol) in 20 mL of dry THF was syringed into the mixture, and the reaction was allowed to warm to 25 °C over 15 h. Aqueous HCl (5%) was added until the solution was neutralized. The solvent was removed under reduced pressure to initially precipitate a gum and finally a white powder. The powder (0.2 g) was dissolved in 15 mL of CH_2Cl_2 and washed 4 times with 150 mL of distilled water. The CH_2Cl_2 was evaporated to leave a solid which was purified by gel chromatography (Styragel 100 Å, CH_2Cl_2) to give 25 mg of pure decomplexed 5 (3%). ^{1}H NMR δ 1.90–2.40 (m, 12 H, NCH_2CH_2 and $ArCH_3$), 2.85–4.10 (m, 23 H, $ArCH_2N$, NCH_2CH_2, $ArOCH_3$, and $COOCH_3$), 4.90 ($^1/_2$ AB, J = 16 Hz, 1.2 H, $ArCH_2N$), 5.35 ($^1/_2$ AB, J = 16 Hz, 0.8 H, $ArCH_2N$), 6.7–7.8 (m, 7 H, ArH); IR (KBr) 1724 cm^{-1} (ester), 1647 cm^{-1} (urea); MS (70 eV, 200 °C), m/e 696 (M^+). Anal. Calcd for $C_{38}H_{44}O_7N_6$: C, 65.40; H, 6.36. Found: C, 65.46; H, 6.18.

An ^{1}H NMR spectrum of host 5 partially complexed with sodium picrate shows separate signals for free and complexed cycle with no averaging of signals. Sodium picrate complex: ^{1}H NMR δ 2.1–2.4 (m, 6 H, NCH_2CH_2), 2.24 (s, 6 H, $ArCH_3$), 3.40–4.05 (m, 12 H, NCH_2CH_2), 3.50 (s, 6 H, $ArOCH_3$), 3.80 (s, 3 H, $COOCH_3$), 3.96 and 4.55 (AB, J = 16 Hz, 4 H, $ArCH_2N$), 6.85 (s, 4 H, ArH), 7.35 (d, J = 8 Hz, 2 H, ArH), 7.55 (t, J = 8 Hz, 1 H, ArH), 8.78 (s, 1 H, ArH). IR of 5·NaBr in KBr: 1728 cm^{-1} (ester) and 1643 cm^{-1} (urea).

X-ray quality crystals of 5·NaOH·H_2O were grown by dissolving a sample of the NaBr complex in CH_3OH and refluxing for 4 h. Water was added to replace the CH_3OH which was allowed to evaporate. Cooling of the solution gave an oily residue, which, on standing for 3 days, redissolved in the mother liquor and then crystallized. The ^{1}H NMR spectrum of the crystals indicated that they were of Na^+ complexed cycle. Mass spectral analysis showed only a peak for the uncomplexed cycle. A positive flame test for Na^+ was observed. Elemental analysis could not be correlated with any reasonable formula. Anal. Calcd for $C_{38}H_{44}O_7N_6$·NaOH: C, 61.95; H, 6.16. Found (attempt 1): C, 47.43; H, 5.62; Found (attempt 2): C, 51.56; H, 5.77. A crystal structure determination indicated that the composition was $C_{38}H_{44}O_7N_6$·NaOH·XH_2O where X is at least six. There is uncertainty because of disorder in the crystal lattice.

Compound 5·NaOH·H_2O crystallized in the triclinic system in space group $P\bar{1}$. Unit cell dimensions are a = 8.783 (3), b = 15.925 (7), c = 18.746 (7) Å, α = 99.48 (3), β = 102.72 (3), γ = 106.38 (3), V = 2381 (2) Å^3, Z (the number of molecules in the unit cell) = 2. Measurements were taken at ambient temperature on a Syntex P$\bar{1}$ diffractometer using Mo Kα radiation. The structure was solved by direct methods.

4′-Methoxy-2,6-dimethyl-3′,5′-bis(1,1-dimethylethyl)-1,1′-biphenyl (15). The Grignard reagent from 12.5 g (68 mmol) of **23** was prepared by refluxing it in 50 mL of dry Et_2O with 2.38 g of Mg for 2 h under N_2. This solution was cannulated dropwise into a solution of 23.0 g of 5-bromo-1,3-bis(1,1-dimethylethyl)-2-methoxybenzene (**24**)[11] (62 mmol) in 100 mL of dry Et_2O containing 0.2 g of anhydrous Ni(acac)$_2$. The solution was refluxed for 2 h and then cooled to 25 °C. After quenching the reaction with 5% aqueous HCl, the aqueous layer was extracted with Et_2O. The combined Et_2O layers were dried ($MgSO_4$) and evaporated to leave an oil. This oil was purified by chromatography (medium pressure, silica gel, cyclohexane) to give 10.5 g (52%) of **15** as an oil which solidified after standing for 20 h. An analytical sample (0.8 g) was prepared by recrystallization of 2.1 g of the above product from 20 mL of CH_3OH, mp 69–71 °C: ^{1}H NMR (60 MHz) δ 1.44 (s, 18 H, C(CH_3)$_3$), 2.12 (s, 6 H, $ArCH_3$), 3.80 (s, 4 H, $ArCH_2$), 7.12 (s, 2 H, ArH), 7.20 (br s, 3 H, ArH); MS (70 eV, 180 °C), m/e 324 (M^+). Anal. Calcd for $C_{23}H_{32}O$: C, 85.13; H, 9.94. Found: C, 85.20; H, 9.99.

2,6-Bis(bromomethyl)-3′,5′-bis(1,1-dimethylethyl)-4′-methoxy-1,1′-biphenyl (13). A mixture of 1.3 g of **15** (3.8 mmol), 1.35 g of NBS (7.6 mmol), 0.1 g of AIBN (Alfa), and 30 mL of CCl_4 was refluxed for 1 h. The mixture was filtered, and the solvent was removed from the filtrate under reduced pressure to leave an oil which crystallized on standing for 20 h. Recrystallization of the material from 20 mL of CH_3OH gave 0.8 g of pure **13** (44%), mp 93–97 °C: ^{1}H NMR δ 1.46 (s, 18 H, C(CH_3)$_3$), 3.76 (s, 3 H, OCH_3), 4.22 (s, 4 H, $ArCH_2$), 7.21 (s, 2 H, ArH), 7.35 (AB_2 pattern,[26] J = 8 Hz, 2 H, ArH), 7.46 (AB_2 pattern,[26] J = 8 Hz, 1 H, ArH); MS (70 eV, 220 °C), m/e 480 (M^+, ^{79}Br). Anal. Calcd for $C_{23}H_{30}OBr_2$: C, 57.28; H, 6.27. Found: C, 57.31; H, 6.24.

34-[3,5-Bis(1,1-dimethylethyl)-4-methoxyphenyl]-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo-[27.3.1.1^{2,6}.1^{7,21}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6-(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (6). A suspension of 0.51 g of 11 (0.96 mmol, dried as above) and 1.2 g of NaH (oil-free, 21 mmol) in 800 mL of dry THF was refluxed for 20 h under N_2 and then cooled to −78 °C. A solution of 0.46 g of **13** (0.96 mmol) in 40 mL of dry THF was cooled to −78 °C and cannulated into the reaction mixture. The reaction was allowed to warm to 25 °C over 15 h. Water was added cautiously until hydrogen evolution stopped. The solvent was removed under reduced pressure, and the residue was partitioned between 300 mL of CH_2Cl_2 and 300 mL of water containing 17 g of NaBr. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated to give 0.79 g of powder. This powder was dissolved in 2 mL of $CHCl_3$, and Et_2O was added (approximately 3 mL) to the cloud point. The solution was then cooled to 0 °C gradually. Crystals of the pure 6·NaBr formed (0.174 g, 19%). The crystals were dissolved in 50 mL of $CHCl_3$ and washed with 500 mL of distilled water. Evaporation of the $CHCl_3$ layer left 60 mg of pure 6 (8%), dec 290–320 °C without melting: ^{1}H NMR δ 1.33 (s, 9 H, C(CH_3)$_3$), 1.41 (s, 9 H, C(CH_3)$_3$), 1.70–2.30 (m, 12 H, NCH_2CH_2 and $ArCH_3$), 3.08 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.40–4.10 (m, 12 H, NCH_2CH_2), 3.91 and 4.76 (AB, J = 15 Hz, 2 H, $ArCH_2N$), 3.65 and 5.30 (AB, J = 15 Hz, 2 H, $ArCH_2N$), 6.60–7.50 (m, 9 H, ArH); MS (70 eV, 350 °C), m/e 856 (M^+). Anal. Calcd for $C_{51}H_{64}O_6N_6$·H_2O: C, 70.00; H, 7.60. Found: C, 69.94; H, 7.49. ^{1}H NMR of 6·NaBr: δ 1.26 (s, 9 H, C(CH_3)$_3$), 1.39 (s, 9 H, C(CH_3)$_3$), 2.10–2.40 (m, 6 H, NCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.55 and 4.54 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 3.60–4.10 (m, 12 H, NCH_2CH_2), 3.69 (s, 3 H, OCH_3), 3.81 (s, 6 H, OCH_3), 6.72 (d, J = 2 Hz, 1 H, ArH), 6.84 (s, 4 H, ArH), 7.33–7.43 (m, 3 H, ArH), 7.61 (t, 1 H, J = 8 Hz, ArH). MS (70 eV, 340 °C): m/e 864 (M + 8 ion). Anal. Calcd for $C_{51}H_{64}O_6N_6$·NaBr: C, 63.81; H, 6.72. Found: C, 63.80; H, 6.68.

2-Bromo-1,3-bis(bromomethyl)-5-(1,1-dimethylethyl)-benzene (19). A mixture of 32.38 g of 2-bromo-1,3-dimethyl-5-(1,1-dimethylethyl)benzene,[10] **18** (134 mmol), 52.47 g of NBS (295 mmol), 2.5 g of AIBN (Afla), and 300 mL of CCl_4 was refluxed for 2 h. The reaction mixture was filtered, and the solvent was removed from the filtrate under reduced pressure to leave an oil which slowly crystallized. Repeated recrystallization from hexane failed to give pure product. Approximately half of the product mixture was purified by medium pressure chromatography (silica gel, cyclohexane) to yield 1.4 g of pure **19** (10%), mp 75–80 °C. An analytical sample was prepared by sublimation (70 °C, 0.6 mm): ^{1}H NMR (60 MHz), δ 1.35 (s, 9 H, C(CH_3)$_3$), 4.75 (s, 4 H, $ArCH_2$), 7.55 (s, 2 H, ArH); MS (70 eV, 180 °C), m/e 396 (M^+, ^{79}Br). Anal. Calcd for $C_{12}H_{15}Br_3$: C, 36.13; H, 3.79. Found: C, 36.19; H, 3.74.

34-Bromo-25-(1,1-dimethylethyl)-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}-.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27-(34)-nonaene-33,35,37-trione (9). A suspension of 0.7 g of 11 (1.3 mmol) and 1.7 g of NaH (oil-free, 35 mmol) in 800 mL of dry THF was refluxed for 10 h under N_2 and then cooled to −78 °C. A solution of 0.55 g of **19** (1.4 mmol) in 30 mL of dry THF at −78 °C was cannulated into the mixture, and the reaction was allowed to warm to 25 °C over 15 h. The mixture was refluxed for 3 h, cooled to 25 °C, and H_2O was added cautiously until hydrogen evolution stopped. The solvent was removed under reduced pressure, and the residue was partitioned between 200 mL of CH_2Cl_2 and 100 mL of H_2O containing 10 g of NaBr. After stirring for 30 m, 2 drops of concentrated HCl were added to break the

(26) Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. *Organic Structural Analysis*; Macmillan: New York, **1976**, pp 78–79.

emulsion. The aqueous layer was extracted with 100 mL of CH_2Cl_2, and the combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to leave a solid. This solid was purified by gel chromatography (Styragel 100 Å, CH_2Cl_2) to give 0.41 g (36%) of solid which was mainly cycle complexed with NaBr. This material was decomplexed by dissolving in 2 mL of CH_2Cl_2 and vortexing 5 times with 18 mL of distilled H_2O, each time centrifuging to break the emulsion. Evaporation of the CH_2Cl_2 layer left 0.25 g of decomplexed cycle, which was purified by gel chromatography (Styragel 100 Å, CH_2Cl_2) to give 0.1 g of pure decomplexed **9** (10%), mp (with decomposition) 220–230 °C: ^{1}H NMR δ 1.20–1.36 (m, 9 H, $C(CH_3)_3$), 1.95–2.30 (m, 12 H, NCH_2CH_2 and $ArCH_3$), 3.00–4.20 (m, 20 H, NCH_2CH_2, $ArOCH_3$, and $ArCH_2N$), 4.85 ($^1/_2$ AB, J = 14 Hz, 0.6 H, $ArCH_2N$), 5.05 ($^1/_2$ AB, J = 14 Hz, 0.6 H, $ArCH_2N$), 5.58 ($^1/_2$ AB, J = 14 Hz, 0.6 H, $ArCH_2N$), 6.70–7.70 (m, 6 H, ArH); MS (70 eV, 280 °C), m/e 772 (M^+). Anal. Calcd for $C_{40}H_{49}N_6O_5Br$: C, 62.09; H, 6.38. Found: C, 62.16; H, 6.39. MS of **9**·NaBr (70 eV, 300 °C): m/e 780 (M + 8 ion). ^{1}H NMR of **9**·sodium picrate: δ 1.36 (s, 9 H, $C(CH_3)_3$), 2.20–2.45 (m, 6 H, NCH_2CH_2), 2.28 (s, 6 H, $ArCH_3$), 3.50–4.10 (m, 12 H, NCH_2CH_2), 3.50 (s, 6 H, $ArOCH_3$), 3.77 and 5.30 (AB, J = 14 Hz, 4 H, $ArCH_2N$), 6.90 (br s, 4 H, ArH), 7.26 (s, 2 H, ArH), 8.75 (s, 2 H, ArH).

An ^{1}H NMR spectrum of host **9** partially complexed with cesium picrate exhibits separate signals for free and complexed cycle with no averaging of signals. ^{1}H NMR of **9**·cesium picrate: δ 1.32 (s, 9 H, $C(CH_3)_3$), 2.10–2.40 (m, 6 H, NCH_2CH_2), 2.29 (s, 6 H, $ArCH_3$), 3.46 (s, 6 H, $ArOCH_3$), 3.40–4.10 (m, 12 H, NCH_2CH_2), 3.76 and 5.40 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 6.89 (s, 2 H, ArH), 6.91 (s, 2 H, ArH), 7.36 (s, 2 H, ArH), 8.75 (s, 2 H, ArH).

^{1}H NMR of **9**·ammonium picrate: δ 1.32 (s, 9 H, $C(CH_3)_3$), 2.15–2.40 (m, 6 H, NCH_2CH_2), 2.27 (s, 6 H, $ArCH_3$), 3.54 (s, 6 H, $ArOCH_3$), 3.50–4.20 (m, 12 H, NCH_2CH_2), 3.75 and 5.48 (AB, J = 14 Hz, 4 H, $ArCH_2N$), 6.10 (very br s, 4 H, NH_4^+), 6.89 (s, 2 H, ArH), 6.92 (s, 2 H, ArH), 7.38 (s, 2 H, ArH), 8.75 (s, 2 H, ArH).

^{1}H NMR of **9**·methylammonium picrate: δ 1.30 (s, 9 H, $C(CH_3)_3$), 2.00 (br s, 3 H, $CH_3NH_3^+$), 2.10–2.40 (m, 6 H, NCH_2CH_2), 2.28 (s, 6 H, $ArCH_3$), 3.50 (s, 6 H, $ArOCH_3$), 3.40–4.20 (m, 12 H, NCH_2CH_2), 3.80 and 5.50 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 6.90 (br s, 3 H, NH_3^+), 6.89 (s, 2 H, ArH), 6.92 (s, 2 H, ArH), 7.39 (s, 2 H, ArH), 8.75 (s, 2 H, ArH).

^{1}H NMR of **9**·*tert*-butylammonium picrate: δ 0.90 (br s, 9 H, $(CH_3)_3CNH_3^+$), 1.32 (s, 9 H, $C(CH_3)_3$), 2.25 (s, 6 H, $ArCH_3$), 2.20–2.40 (m, 6 H, NCH_2CH_2), 3.47 (s, 6 H, $ArOCH_3$), 3.40–4.10 (m, 12 H, NCH_2CH_2), 3.80 and 5.49 (AB, J = 14 Hz, 4 H, $ArCH_2N$), 6.92 (s, 4 H, ArH), 7.34 (s, 2 H, ArH), 8.93 (s, 2 H, ArH). No signal for the NH_3^+ protons could be identified.

In the presence of 2 equiv of *tert*-butylammonium picrate the spectrum was identical with that described above except that at 27 °C, the signals for the guest were broadened significantly; i.e., there was slow exchange between free and complexed states.[5] The exchange could be slowed by cooling to −53 °C to produce sharp signals in the ^{1}H NMR spectrum for all protons. The host resonances were practically identical with those reported above. Complexed *tert*-butylammonium ion exhibited resonances at 0.77 ppm (s, 9 H, CH_3) and 6.75 ppm (br s, 3 H, NH_3^+). Free *tert*-butylammonium ion exhibited the normal resonances of 1.40 (s, 9 H, CH_3) and 7.88 (br s, 3 H, NH_3^+). These peak assignments are in accord with literature values.[27]

^{1}H NMR of **9**·piperidinium picrate: δ 1.32 (s, 9 H, $C(CH_3)_3$), 1.20–1.40 (m, 6 H, $N^+CH_2CH_2CH_2$), 2.10–2.50 (m, 10 H, NCH_2CH_2 and $N^+CH_2CH_2CH_2$), 2.33 (s, 6 H, $ArCH_3$), 3.28 (s, 6 H, $ArOCH_3$), 3.45–4.10 (m, 12 H, NCH_2CH_2), 3.71 and 5.34 (AB, J = 14 Hz, 4 H, $ArCH_2N$), 6.88 (s, 2 H, ArH), 6.92 (s, 2 H, ArH), 7.28 (s, 2 H, ArH), 7.50 (br s, 2 H, NH_2^+), 8.75 (s, 2 H, ArH).

4′-Methoxy-2,6-dimethyl-4,3′,5′-tris(1,1-dimethylethyl)-1,1′-biphenyl (16). The Grignard reagent was prepared from 38.85 g of **22**[10] (160 mmol) by refluxing it in 200 mL of dry Et_2O with 8 g of Mg and 0.5 mL of ethylene dibromide under N_2 for 5 h. The resulting slurry was cannulated dropwise into a solution of 37.95 g of 5-bromo-1,3-bis(1,1-dimethylethyl)-2-methoxybenzene[11] (**24**) (130 mmol) in 100 mL of dry Et_2O containing 2 g of anhydrous $Ni(acac)_2$. The reaction began to reflux, and reflux was maintained for 9 h. Another 0.5 g of anhydrous $Ni(acac)_2$ was added, and reflux was continued for 5 h. The reaction was quenched with 100 mL of 5% aqueous HCl. The Et_2O layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to leave an oil. This oil was purified by chromatography (silica gel, hexanes) to give 18.85 g (38%) of **16** as an oil which solidified on standing for 20 h, mp 87–89 °C: ^{1}H NMR (60 MHz) δ 1.35 (s, 9 H, $C(CH_3)_3$), 1.42 (s, 18 H, $C(CH_3)_3$), 2.08 (s, 6 H, $ArCH_3$), 3.75 (s, 3 H, OCH_3), 7.05 (s, 2 H, ArH), 7.17 (br s, 2 H, ArH); MS (70 eV, 230 °C), m/e 380 (M^+). Anal. Calcd for $C_{27}H_{40}O$: C, 85.20; H, 10.59. Found: C, 85.02; H, 10.44.

2,6-Bis(bromomethyl)-4,3′,5′-tris(1,1-dimethylethyl)-4′-methoxy-1,1′-biphenyl (14) and 2,6-Bis(hydroxymethyl)-4,3′,5′-tris(1,1-dimethylethyl)-4′-methoxy-1,1′-biphenyl (17). A mixture of 10.6 g of **16** (28 mmol), 10.3 g of NBS (57 mmol), 0.55 g of AIBN, and 400 mL of CCl_4 was refluxed for 30 min. The reaction was filtered and the solvent was removed from the filtrate under reduced pressure to leave a very viscous oil containing **14**. All attempts to purify the product by crystallization or chromatography failed. Therefore, the following procedure was used to isolate pure **14**. The oil (9.07 g, approximately 16 mmol of the mixture) was dissolved in 150 mL of CH_3CN. Saturated aqueous $NaHCO_3$ (150 mL) solution and 100 mL of water were added, and the mixture was refluxed for 25 h. More saturated aqueous $NaHCO_3$ (100 mL) and CH_3CN (100 mL) were added. Reflux was continued for 25 h. The CH_3CN was removed under reduced pressure, and the remaining aqueous solution was extracted twice with 100 mL Et_2O. The Et_2O layer was dried (Na_2SO_4) and evaporated to leave a foam. This foam was purified by chromatography (silica gel, CH_2Cl_2) to give 1.7 g of pure diol **17** as a foam (24%), mp 87–89 °C. ^{1}H NMR (60 MHz) δ 1.34 (s, 9 H, $C(CH_3)_3$), 1.40 (s, 18 H, $C(CH_3)_3$), 3.75 (s, 3 H, OCH_3), 4.20 (s, 4 H, $ArCH_2$), 4.20 (br s, 2 H, OH), 7.08 (s, 2 H, ArH), 7.50 (br s, 2 H, ArH); MS (70 eV, 230 °C), m/e 412 (M^+). Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77. Found: C, 78.58; H, 9.65.

Diol **17** (1.70 g, 3.2 mmol) was dissolved in 250 mL of $CHCl_3$, and HBr gas was bubbled into the solution for 15 min. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to leave an oil which was passed through a short column of silica gel with cyclohexane as the mobile phase. Evaporation of the solvent left 1.9 g of **14** as an oil which solidified to a waxy solid on standing for several months (86%), mp 95–105 °C: ^{1}H NMR (60 MHz) δ 1.35 (s, 9 H, $C(CH_3)_3$), 1.46 (s, 18 H, $C(CH_3)_3$), 3.76 (s, 3 H, OCH_3), 4.25 (s, 4 H, $ArCH_2$), 7.25 (s, 2 H, ArH), 7.50 (s, 2 H, ArH); MS (70 eV, 180 °C), m/e 536 (M^+, ^{79}Br). Anal. Calcd for $C_{27}H_{38}OBr_2$: C, 60.23; H, 7.11. Found: C, 60.21; H, 7.02.

34-[3,5-Bis(1,1-dimethylethyl)-4-methoxyphenyl]-25-(1,1-dimethylethyl)-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (10). A suspension of 0.7 g of **11** (1.3 mmol, dried as above) and 1.7 g of NaH (oil-free, 35 mmol) in 800 mL of dry THF was refluxed for 9 h under N_2 and then cooled to −78 °C. A solution of 0.7 g of **14** (1.3 mmol) in 16 mL of dry THF was cooled to −78 °C and cannulated into the reaction. The reaction was allowed to warm to 25 °C over 15 h and then refluxed for 3 h. After cooling to 25 °C, water was added cautiously until hydrogen evolution stopped. Removal of the solvent under reduced pressure left a solid which was partitioned between 200 mL of CH_2Cl_2 and 100 mL of water containing 10 g of NaBr. After the mixture had stirred for 30 min, 0.2 mL of concentrated HBr was added to break the emulsion. The aqueous layer was extracted with 100 mL of CH_2Cl_2, and the combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to leave 1.39 g of solid. This solid was purified by gel chromatography (Styragel 100 Å, CH_2Cl_2) to give 0.6 g of a solid which was dissolved in 2 mL of CH_2Cl_2 and precipitated with 200 mL of Et_2O 4 times. This left 0.1 g of material which was mainly NaBr complex. This solid was dissolved in 4 mL of CH_2Cl_2 and vortexed 6 times with 16 mL of distilled water in a centrifuge tube, each time centrifuging to separate the layers. The CH_2Cl_2 layer was evaporated to leave 40 mg of pure decomplexed host **10** (4%), decomposition 210–240 °C: ^{1}H NMR δ 1.30 (s, 9 H, $C(CH_3)_3$), 1.37 (s, 9 H, $C(CH_3)_3$), 1.43

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(s, 9 H, $C(CH_3)_3$, 2.00–2.60 (m, 6 H, NCH_2CH_2), 2.15 (s, 3 H, $ArCH_3$), 2.28 (s, 3 H, $ArCH_3$), 3.19 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.40–4.10 (m, 14 H, NCH_2CH_2 and $ArCH_2N$), 4.71 ($^1/_2$ AB, J = 15 Hz, 1 H, $ArCH_2N$), 5.25 ($^1/_2$ AB, J = 15 Hz, 1 H, $ArCH_2$), 6.70–8.00 (m, 8 H, ArH); MS (70 eV, 290 °C), m/e 912 (M^+). Anal. Calcd for $C_{55}H_{72}O_6N_6{\cdot}H_2O$: C, 70.94; H, 8.01. Found: C, 70.76; H, 7.93.

^{1}H NMR of **10**·NaBr: δ 1.20 (s, 9 H, $C(CH_3)_3$), 1.36 (s, 9 H, $C(CH_3)_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 2.27 (s, 6 H, $ArCH_3$), 2.10–2.40 (m, 6 H, NCH_2CH_2), 3.50–4.10 (m, 12 H, NCH_2CH_2), 3.58 and 4.50 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 3.64 (s, 6 H, OCH_3), 3.67 (s, 3 H, OCH_3), 6.68 (d, J = 2 Hz, 1 H, ArH), 6.87 (s, 4 H, ArH), 7.33 (s, 2 H, ArH), 7.53 (d, J = 2 Hz, ArH). MS (70 eV, 290 °C): m/e 920 (M + 8 ion).

^{1}H NMR of **10**·methylammonium picrate: δ 1.35 (s, 9 H, $C(CH_3)_3$), 1.36 (s, 9 H, $C(CH_3)_3$), 1.39 (s, 9 H, $C(CH_3)_3$), 1.88 (br s, 3 H, $CH_3NH_3^+$), 2.10–2.40 (m, 6 H, NCH_2CH_2), 2.28 (s, 6H, $ArCH_3$), 3.50–4.10 (m, 14 H, NCH_2CH_2 and $ArCH_2N$), 3.63 (s, 6 H, OCH_3), 3.68 (s, 3 H, OCH_3), 5.05 ($^1/_2$ AB, J = 15 Hz, 2 H, $ArCH_2N$), 6.61 (s, 1 H, ArH), 6.90 (br s, 3 H, NH_3^+), 6.92 (s, 4 H, ArH), 7.41 (s, 2 H, ArH), 7.95 (s, 1 H, ArH), 8.78 (s, 2 H, ArH).

25-(1,1-Dimethylethyl)-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (8). A suspension of 0.7 g of **11** (1.3 mmol, dried as above) and 1.7 g of NaH (oil-free, 35 mmol) in 800 mL of dry THF was refluxed for 5 h under N_2 and then cooled to −78 °C. A solution of 0.42 g of 1,3-bis(bromomethyl)-5-(1,1-dimethylethyl)benzene[9] (**18**) (1.3 mmol) in 18 mL of dry THF was syringed into the mixture, and the reaction was allowed to warm to 25 °C over 15 h. The reaction was stirred at 25 °C for 24 h and then refluxed for 2 h. The reaction was neutralized with 5% aqueous HCl. The solvent was removed under reduced pressure to precipitate a gum. This gum was purified by chromatograhy (silica gel; 10% CH_3OH, 90% CH_2Cl_2) to give solid complexed cycle. This solid was dissolved in CH_2Cl_2 and washed 3 times with distilled water. The CH_2Cl_2 layer was dried by passing through filter paper and then evaporated to leave 173 mg of pure **8** (19%), mp 210–215 °C. The ^{1}H NMR spectrum of noncomplexed **8** exhibited very broad signals at 25 °C. These signals sharpened upon cooling to 2 °C or upon addition of a guest: ^{1}H NMR (2 °C) δ 1.31 (s, 9 H, $C(CH_3)_3$), 1.90–2.50 (m, 12 H, NCH_2CH_2 and $ArCH_3$), 3.20–4.10 (m, 19 H, NCH_2CH_2, $ArCH_2N$, and $ArOCH_3$), 3.54 and 5.60 (AB, J = 15 Hz, 2 H, $ArCH_2N$), 5.75 ($^1/_2$ AB, J = 15 Hz, 1 H, $ArCH_2N$), 6.8–7.4 (m, 7 H, ArH); MS (70 eV, 280 °C), m/e 694 (M^+). Anal. Calcd for $C_{40}H_{50}O_5N_6$: C, 69.14; H, 7.25. Found: C, 68.79; H, 7.27.

^{1}H NMR of **8**·sodium picrate (27 °C): δ 1.32 (s, 9 H, $C(CH_3)_3$), 2.1–2.4 (m, 6 H, NCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.51 (s, 6 H, $ArOCH_3$), 3.40–4.05 (m, 14 H, NCH_2CH_2 and $ArCH_2N$), 4.62 ($^1/_2$ AB, J = 14 Hz, 2 H, $ArCH_2N$), 6.85 (br s, 5 H, ArH), 7.28 (s, 2 H, ArH), 8.75 (s, 2 H, ArH). NaBr complex: MS of **8**·NaBr (70 eV, 290 °C) 694 and 702 (M^+ and M + 8 ion); of **8**·KBr (70 eV, 290 °C) 694 and 718 (M^+ and M + 24 ion).

^{1}H NMR of **8**-cesium picrate (27 °C): δ 1.32 (s, 9 H, $C(CH_3)_3$), 2.1–2.4 (m, 6 H, NCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.52 (s, 6 H, $ArOCH_3$), 3.4–4.0 (m, 12 H, NCH_2CH_2), 3.84 and 4.60 (AB, 4 H, J = 13 Hz, $ArCH_2$), 6.86 (br s, 5 H, ArH), 7.27 (s, 2 H, ArH), 8.75 (s, 2 H, ArH).

9-[2,6-Bis(methoxymethyl)phenyl]anthracene (20). The Grignard reagent of 2-bromo-1,3-bis(methoxymethyl)benzene[13] (**25**) was prepared by refluxing 5.8 g of **25** (24 mmol) in 200 mL of dry THF with 1.15 g of Mg and 0.2 mL of ethylene dibromide for 6 h under N_2. A solution of 4.36 g of anthrone in 60 mL of THF was added, and reflux was continued for 13 h. Aqueous 6 M HCl was added, and the mixture was boiled for 1 min. The solution was cooled to 25 °C and extracted 3 times with 100 mL of Et_2O. The combined Et_2O layers were dried ($MgSO_4$) and evaporated to give 6.8 g of a solid. Crystallization from 25 mL of absolute EtOH gave a product which was further purified by chromatography (medium pressure, silica gel, CH_2Cl_2) to give 1.93 g of pure **20** (25%), mp 118–119 °C. ^{1}H NMR (60 MHz) δ 2.95 (s, 6 H, OCH_3), 3.80 (s, 4 H, $ArCH_2$), 7.40–7.80 (m, 9 H, ArH), 8.00–8.25 (m, 2 H, ArH), 8.5 (br s, 1 H, ArH); MS (70 eV, 200 °C), m/e 342 (M^+). Anal. Calcd for $C_{24}H_{22}O$: C, 84.18; H, 6.48. Found: C, 84.24; H, 6.52.

9-[2,6-Bis(bromomethyl)phenyl]anthracene (21). In a 500-mL flask was placed 1.62 g of **20** (4.7 mmol) and 200 mL of $CHCl_3$. HBr gas was bubbled vigorously through the reaction for 8 h. Aqueous saturated $NaHCO_3$ was added to the reaction and the $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to leave a residue. This residue was purified by chromatography (medium pressure, silica gel; 50% cyclohexane, 50% $CHCl_3$) to give 1.48 g of pure **21** (72%), mp 132–134 °C: ^{1}H NMR (60 MHz) δ 3.95 (s, 4 H, $ArCH_2$), 7.30–7.90 (m, 9 H, ArH), 8.10–8.30 (m, 2 H, ArH), 8.65 (br s, 1 H, ArH); MS (70 eV, 220 °C), m/e 438 (M^+, ^{79}Br). Anal. Calcd for $C_{22}H_{16}Br_2$: C, 60.03; H, 3.66. Found: C, 60.07; H, 3.77.

34-(9-Anthracenyl)-36,38-dimethoxy-4,14-dimethyl-1,7,11,17,21,29-hexaazaheptacyclo[27.3.1.1^{2,6}.1^{7,11}.1^{12,16}.1^{17,21}.1^{23,27}]octatriaconta-2,4,6(38),12,14,16(36),23,25,27(34)-nonaene-33,35,37-trione (7). A suspension of 0.7 g of **11** (1.3 mmol, dried as above) and 2.05 g of NaH (oil-free, 42.7 mmol) in 800 mL of dry THF was refluxed for 20 h under N_2 and then cooled to −78 °C. A solution of 0.58 g of **21** (1.3 mmol) in 20 mL of dry THF was cooled to −78 °C and cannulated into the mixture. The reaction was allowed to warm to 25 °C over 15 h and then refluxed for 2 h. Water was added cautiously until hydrogen evolution stopped. The solvent was removed under reduced pressure, and the residue was partitioned between 200 mL of CH_2Cl_2 and 100 mL of H_2O containing 4 g of NaBr. Evaporation of the CH_2Cl_2 layer left 1.07 g of solid. Purification by gel chromatography (Styragel 100 Å, CH_2Cl_2) was made difficult by the facile loss of ions on the column. The material isolated from the column was dissolved in 30 mL of CH_2Cl_2 and washed twice with 100 mL of distilled water. Evaporation of the CH_2Cl_2 layer left a solid which was dissolved in 2 mL of CH_2Cl_2. Ethyl acetate (approximately 2 mL) was added until the cloud point was reached. The solution was cooled at 0 °C for 10 h to precipitate 0.21 g of decomplexed fluorescent host **7** (17%), decomposition without melting 235–255 °C. The ^{1}H NMR spectrum of decomplexed **7** is very complicated. There are two envelopes of resonances from 1.5–4.8 ppm and from 6.6–8.5 ppm. MS (16 eV, 320 °C), no parent peak was observed and only decomposition fragments were detected. Presumably the high-probe temperature decomposed the entire sample. Anal. Calcd for $C_{50}H_{50}N_6O_5{\cdot}1.5H_2O$: C, 71.32; H, 6.34. Found: C, 71.30; H, 5.94.

^{1}H NMR of **7**·sodium picrate: δ 2.10–2.50 (m, 6 H, NCH_2CH_2), 2.28 (s, 6 H, $ArCH_3$), 3.30 and 5.21 (AB, J = 15 Hz, 4 H, $ArCH_2N$), 3.30–4.15 (m, 12 H, NCH_2CH_2), 3.88 (s, 6 H, OCH_3), 6.80 (s, 2 H, ArH), 6.90 (s, 2 H, ArH), 7.25–7.60 (m, 7 H, ArH), 7.80–8.10 (m, 4 H, ArH), 8.50 (s, 1 H, ArH), 8.82 (s, 2 H, ArH): MS of **7**·NaBr (70 eV, 320 °C): m/e 814 and 822 (M^+ and M + 8 ion).

1,3-Bis[2-methoxy-3-*N*-(3-methyltetrahydro-2-pyrimidinonyl)-5-methylphenyl]tetrahydro-2-pyrimidinone (12). In a 500 mL flask was placed 0.6 g of **11** (1.1 mmol), 300 mL of dry THF, and 2 g of NaH (oil-free, 42 mmol). The mixture was refluxed for 5 h under N_2 and then cooled to −78 °C. Iodomethane (0.15 mL, 2.4 mmol) was added, and the reaction allowed to warm to 25 °C. Another 0.05 mL of iodomethane (0.8 mmol) was added, and the reaction was refluxed for 2 h. Water was added cautiously, and the solvent was removed under reduced pressure to leave a tan oil. This oil was partitioned between 100 mL of water and 200 mL of CH_2Cl_2. The aqueous layer was extracted with 100 mL of CH_2Cl_2, and the combined CH_2Cl_2 layers were dried ($MgSO_4$) and evaporated to give 0.66 g of crude **12**. This product (0.1 g) was purified by preparative thin-layer chromatography (silica gel; 20% EtOH, 80% CH_2Cl_2) to give 0.03 g of pure **12** (32%), mp 100–150 °C. This compound is hygroscopic. ^{1}H NMR: δ 2.00–2.15 (m, 4 H, NCH_2CH_2), 2.15–2.30 (m, 2 H, NCH_2CH_2), 2.26 (s, 6 H, $ArCH_3$), 3.00 (s, 6 H, NCH_3), 3.39 (m, 4 H, NCH_2CH_2), 3.58 (m, 4 H, NCH_2CH_2), 3.72 (m, 4 H, NCH_2CH_2), 3.84 (s, 6 H, OCH_3), 6.93 (d, J = 2 Hz, 2 H, ArH), 7.01 (d, J = 2 Hz, 2 H, ArH). MS (70 eV, 220 °C): m/e 564 (M^+). Anal. Calcd for $C_{30}H_{40}N_6O_5$: C, 63.81; H, 7.14; Found: C, 61.31; H, 7.05. Found after drying (100 °C, 48 h, 0.05 mm): C, 63.80; H, 7.15.

Registry No. **2**, 83604-23-3; **3**, 99922-07-3; **3**·NaBr, 104463-86-7; **4**, 104463-67-4; **4**·Cs picrate, 104487-38-9; **4**·NaBr, 104463-87-8; **5**, 104463-68-5; **5**·Na picrate, 104463-89-0; **5**·NaOH, 104463-90-3; **6**, 104463-69-6; **6**·NaBr, 104463-91-4; **7**, 104487-35-6; **7**·Na picrate, 104463-93-6; **8**, 104463-70-9; **8**·Na picrate, 104463-95-8; **8**·Cs picrate,

104487-40-3; **9**, 104463-71-0; **9**·NaBr, 104463-96-9; **9**·Cs picrate, 104463-98-1; **9**·NH_4 picrate, 104463-82-3; **9**·$MeNH_3$ picrate, 104463-83-4; **9**·$BuNH_3$ picrate, 104463-84-5; **9**·piperidinium picrate, 104463-85-6; **10**, 104463-72-1; **10**·NaBr, 104487-41-4; **10**·$MeNH_3$ picrate, 104487-36-7; **11**, 83604-32-4; **11**·Na picrate, 104464-00-8; **12**, 104463-73-2; **13**, 104463-74-3; **14**, 104463-75-4; **15**, 104463-76-5; **16**, 104463-77-6; **17**, 104463-78-7; **18**, 64726-28-9; **20**, 104463-79-8; **21**, 104463-80-1; **22**, 5345-05-1; **23**, 576-22-7; **24**, 1516-96-7; **25**, 65654-53-7; **26**, 1191-87-3; **27**, 17454-52-3; **28**, 104463-81-2; **29**, 104463-99-2; **37**, 75640-58-3; **38**, 53938-62-8; MeI, 74-88-4; Li picrate, 18390-55-1; Na picrate, 3324-58-1; K picrate, 573-83-1; Rb picrate, 23296-29-9; Cs picrate, 3638-61-7; NH_4 picrate, 131-74-8; $MeNH_3$ picrate, 6032-31-1; *t*-$BuNH_3$ picrate, 38188-68-0; 1,3-bis(bromomethyl)benzene, 626-15-3; 2-bromo-1,3-bis(bromomethyl)benzene, 25006-88-6; methyl 2,6-bis(bromomethyl)benzoate, 56263-51-5; anthrone, 90-44-8.

Electrosynthesis of 1,2-Dithiolane 1-Oxides from Substituted 1,3-Dithianes

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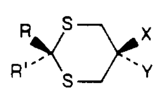
Controlled potential oxidation of a variety of 5-substituted 2-*tert*-butyl-1,3-dithianes in wet acetonitrile, using an undivided electrochemical cell, provide 4-substituted 1,2-dithiolane 1-oxides selectively and in good yields. Adsorption to the electrode surface of the platinum anode, rendering it passive in the electrolysis of these sulfur-containing compounds is a solvable problem. Although acid-sensitive *O*-trimethylsilyl ethers are cleaved under the reaction conditions, *O*-*tert*-butyldimethylsilyl ethers only suffer cleavage to a modest extent, and an ethylene ketal moiety suffers little, if any, cleavage.

Anodic oxidation of dithioacetals and ketals has been studied in detail.[1] Electrochemical oxidation of substituted 1,3-dithianes directly,[2] as well as indirectly[3] via redox catalysis with tri-*p*-tolylamine, affords carbonyl compounds in high yield under mild conditions. Such methodology has been recommended for the unmasking of the carbonyl compound protected in the 1,3-dithiane system.[2,3] The initial papers reported that the sulfur-containing products of oxidation of 1,3-dithianes (**1**, X = Y = H) were 1,2-dithiolane (**2**, R = H) and a sulfur-containing polymer, probably $[S(CH_2)_3S]_n$, but the yield of 1,2-dithiolane was not given.[1d,2a] The mechanistic implications of these



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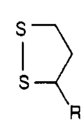

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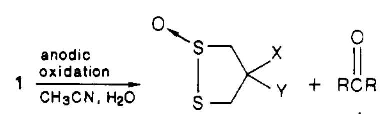
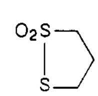
products were commented upon, but use of this method for synthesizing 1,2-dithiolanes was not explored. Very recently, Porter et al.[2b] published a detailed study on the sulfur-containing products obtained by constant current electrolysis of a variety of dithioacetals and dithioketals. Only products from chain contraction, i.e., products in which the carbonyl compound masked in the starting material had been released, were observed. The products included disulfides, thiolsulfinates, and thiolsulfonates. This paper reports our finding that controlled potential electrolysis of substituted 1,3-dithianes in aqueous acetonitrile provides a synthetically useful route to substituted and unsubstituted 1,2-dithiolane 1-oxides as shown in eq 1.



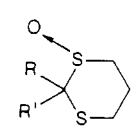
3 **4** (1)

Results and Discussion

Despite expectations based on previous reports, no 1,2-dithiolane (**2**, R = H) was isolated from the anodic oxidation of 1,3-dithiane (**1**, R = R′ = X = Y = H). After controlled potential electrolysis, a mixture of products was obtained, not including 1,2-dithiolane, from which 1,2-dithiolane 1-oxide (**3**, X = Y = H)[4] was isolated in 20% yield, 1,2-dithiolane 1,1-dioxide (**5**) in 6% yield, and 1,3-dithiane 1-oxide (**6**, R = R′ = H)[5] in 22% yield. Porter



5



6

and co-workers[2b] reported the formation of thiosulfinates and thiolsulfonates analogous to **3**, X = Y = H, and **5**, respectively, on anodic oxidation of dithioacetals and ketals. However, they reported that sulfoxides or sulfones derived from the dithioacetals and -ketals were not formed in contrast to sulfoxide formation on anodic oxidation of phenyl sulfides[6] and our isolation of 1,3-dithiane 1-oxide

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