Synthesis and Complexation Properties of New Unsymmetrical Cryptands

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Twelve novel unsymmetrical cryptands (1–12) containing various units (methylene, 2-methylenylpropylene, pyridine-2,6-diyldimethylene, *o*- and *m*-xylylene) each in two bridges have been synthesized by a one-step cyclization procedure. These cryptands were obtained by treating tetraalcohols 15–17, obtained from diethanolamine and diglycolyl dichloride followed by reduction or from diethanolamine and the appropriate oligoethylene glycol dichloride or ditosylate, with methylene chloride, 3-chloro-2-(chloromethyl)-1-propene, α,α'-dibromo-*o*-xylene, α,α'-dibromo-*m*-xylene, and 2,6-pyridinediyldimethyl ditosylate. Cryptands 7 and 11, containing two acetal functions, were obtained in yields of 59 and 40%, respectively. Bis(2-methylenepropylene)-bridged cryptand 4 was independently synthesized by another method. Complexation properties of nearly all of these cryptands with the alkali metal cations were studied by an NMR technique. Some of the results were verified by a calorimetric titration technique. Cryptands 5 and 9, containing a 2,6-pyridinediyldimethylene unit in two bridges, and 11, containing a methylene unit in two bridges, showed high selectivity for potassium over sodium ions by factors ranging from 40 to 200. Bisacetal-containing cryptand 7 exhibited high selectivity for sodium over potassium ions with a selectivity factor of over 1000.

Introduction

Macropolycyclic polyethers are promising chelating agents and have been studied extensively.[1,2] Since Lehn and co-workers first synthesized a series of cryptands (macrobicyclic polyethers)[3] and studied their complexation properties,[4] many reports on the synthesis and properties of the cryptands have been published.[5–16] Some molecules similar to the cryptands but with carbon bridgehead atoms were found to have good selectivity for sodium over potassium ions.[17,18] Schiff base-containing molecules similar to the cryptands and containing aromatic[19–22] and heteroaromatic[21,22] bridges were prepared for complexation of the transition metal ions. Cryptands containing aromatic subcyclic rings,[23,24] a pyridine[23–27] and other heteroaromatic subcyclic rings[27–29] in their bridges also have been syn-

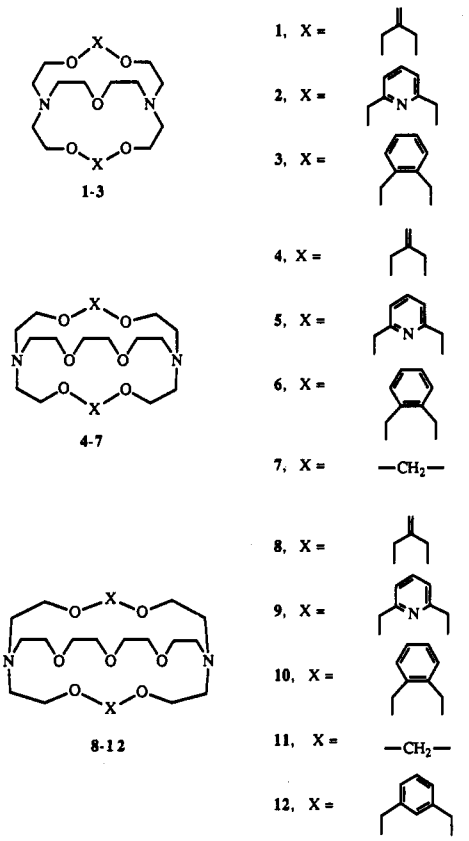

Figure 1. New cryptands (macrobicyclic polyethers) (1–12).

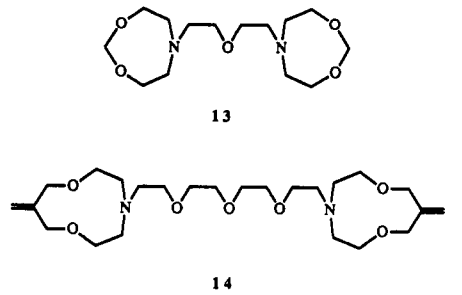

Figure 2. Bis-crown ethers 13 and 14.

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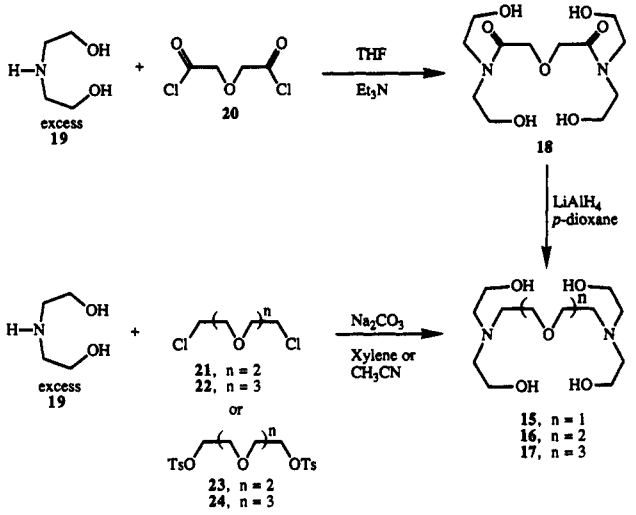
Scheme I. Preparation of Tetraalcohols 15–17



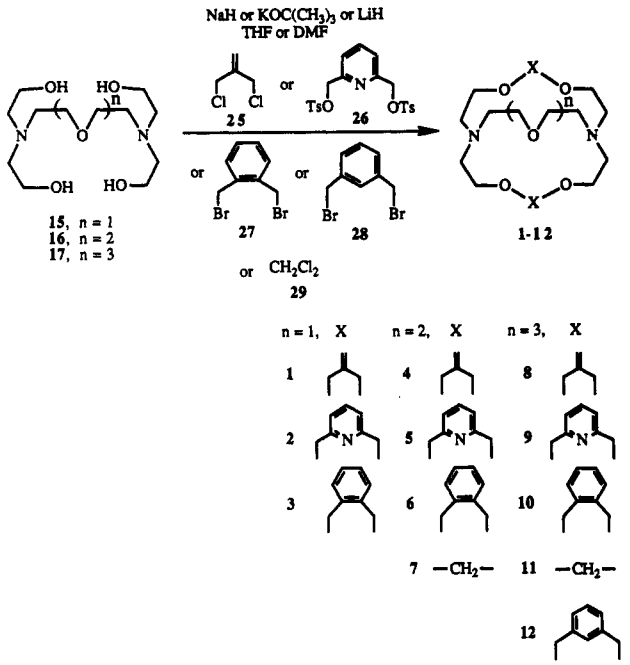
thesized. Functionalized cryptands have been prepared,[30,33] and some of them were attached to polymers for the separation of metal ions.[33,34]

Most of the reported cryptands have been prepared via the diazo-crown by a multistep process. A one-step method was used to prepare symmetrical aromatic ring-containing cryptands[25,26] and unsymmetrical cryptands which have no aromatic subcyclic units.[35] The many methods for preparing cryptands have been reviewed.[36]

The cryptands form thermodynamically stable complexes with a variety of metal ions.[2] Because of their superior complexing abilities as compared to the macromonocyclic crown ethers, the cryptands have been used for isotopic separations, in the transport and separation of a variety of ions, as phase-transfer catalysts, and for other purposes.[2,5–7,28,34,37] However, the selectivity of the cryptands for one metal ion over another is not sufficient to meet the requirements for many industrial separations. New preorganized molecules such as the unsymmetrical cryptands are needed to help find molecules with improved selectivities for certain cations.

In this paper, we present a one-step synthesis of 12 new unsymmetrical cryptands containing various units in two of their bridges (1–12, see Figure 1) from readily available tetraalcohol starting materials. A preliminary report of this work has been published.[38] New bis-crown ethers 13

Scheme II. Synthesis of Cryptands (Macrobicyclic Polyethers) 1–12



and 14 (Figure 2) also were prepared. The complexing properties of most of these cryptand ligands with the alkali metal ions are reported. Three solid complexes of cryptand 4 with some inorganic salts were isolated.

Results and Discussion

Tetraalcohols 15–17, the starting materials for the preparation of these new cryptands, were prepared by two routes (Scheme I). Treatment of diglycolyl dichloride (20) with an excess amount of diethanolamine (19) in the presence of triethylamine gave diamido tetraalcohol 18. The triethylamine hydrochloride salt was easily removed by dissolving 18 in cooled DMF. 18, without characterization, was reduced to tetraalcohol 15 in an overall yield of 68% by treatment with lithium aluminum hydride. 15 has been reported in three patents.[39] Tetraalcohols 16 and 17 were prepared in 90% yields by treating an excess amount of 19 with dichlorides 21 and 22, respectively, in refluxing xylene (Scheme I). 16 and 17 also were prepared from ditosylates 23 and 24 in acetonitrile, but in low yields. 16 and 17 have been reported previously using a similar method.[40]

Twelve new cryptands (1–12) containing different bridges were synthesized by a one-step cyclization of tetraalcohols 15–17 with two dichlorides, a ditosylate and two dibromides (25–29) (Scheme II). Treatment of dichloride 25 with tetraalcohols 15–17 gave bis(2-methylenepropylene)-bridged cryptands 1, 4 and 8, respectively. Similarly, the reaction of 2,6-pyridinediyldimethyl ditosylate (26) or α,α'-dibromo-*o*-xylene (27) with tetraalcohols 15–17 gave bis(2,6-pyridineyldimethylene)-bridged cryptands 2, 5, and 9 or bis(*o*-xylylene)-bridged cryptands 3, 6, and 10, respectively. Bis(*m*-xylylene)-bridged cryptand 12 was prepared from α,α'-dibromo-*m*-xylene (28) and tetraalcohol 17. The bismethylene-bridged cryptands 7

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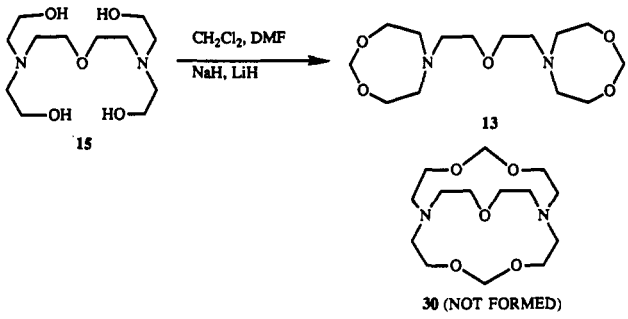
Scheme III. Formation of Bis-crown Ether 13

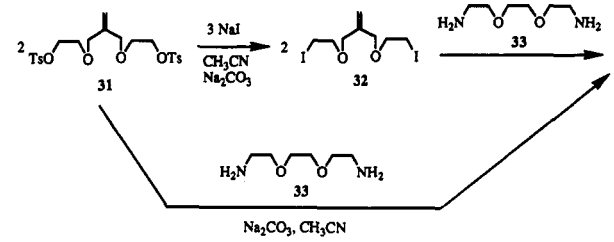


and 11 (containing two acetal functions) were synthesized in yields of 59% and 40% by treating methylene dichloride (29) with tetraalcohols 16 and 17, respectively. Cryptands 1–3 were obtained using a mixture of LiH and NaH as the base. Cryptands 4–10 and 12 were synthesized using NaH as the base and 11 was obtained using KO-*t*-C_4H_9 as the base in the presence of Cs_2CO_3. Both THF and DMF were used as solvents in these reactions. Acetal-containing cryptands like 7 and 11 have not been reported. These acetal-containing cryptands were obtained in much higher yields than most of the other cryptands shown in Scheme II. Cryptands 1 and 4 were obtained in yields of 28% and 37%, respectively. Cryptand 6, first obtained in a 9% yield, was produced in an optimized yield of 55%. The yields for most of the other cryptands were not optimized. This one-step cyclization method is a simple and convenient route to the unsymmetrical cryptands so we believe this route is better than the more complicated procedures. All of these cryptands were characterized by their IR, ^1H and ^{13}C NMR, and MS spectra and by their combustion analyses.

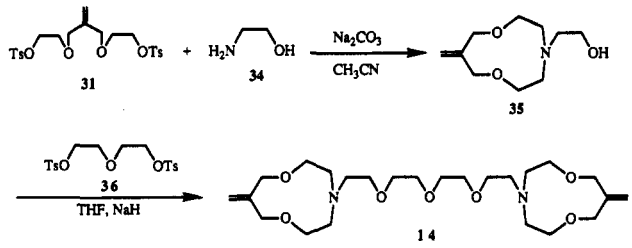
The same procedure for the preparation of bismethylene-bridged cryptands 7 and 11 was used in an attempt to prepare bismethylene-bridged cryptand 30 (Scheme III). Cryptand 30 was not formed; however, bis(aza-8-crown-3) 13 was produced in a 28% yield. The structure of bis-crown 13 was confirmed by its spectral and combustion analyses. 13 has the same molecular weight as expected cryptand 30. However, their NMR spectra and TLC properties are not expected to be the same. All of the cryptands shown in Figure 1 gave the same unusual TLC spot with fronting with R_f = 0.2–0.3 (silica gel; CH_3OH/30% aqueous NH_4OH, 10/1) as previously reported for other cryptands,[35] while bis-crown 13 gave the usual spot with tailing with R_f = 0.42.

The NMR spectra of 30 would be similar to those of cryptands 7 and 11. Acetal methylene protons (OCH_2O) of cryptands 7 and 11 gave a singlet at δ 4.62 and 4.55, respectively, while acetal methylene protons of bis-crown 13 gave two doublets at δ 4.80 and 4.69. The two methylene protons in each dioxazocine ring of 13 are not in the same chemical environment because of the conformation of the rigid eight-membered ring. Therefore, those protons couple each other to give the two doublets. The ^1H NMR spectra of 13 in $CDCl_3$ and in DMSO-d_6 were different, showing the solvent effects on ring conformation changes (see the Experimental Section). The acetal methylene peak in the ^{13}C NMR spectrum of 13 (δ 96.95) is shifted downfield compared to that in cryptands 7 (δ 94.80) and 11 (δ 94.71). The carbons connected to nitrogen atoms in 13 gave two peaks (δ 57.30 and 57.35) separated by only 0.05 ppm, while those carbons in cryptand 7 gave two peaks (δ 56.19 and 57.68) separated by 1.50 ppm and those carbons in cryptand 11 gave two peaks (δ 55.40 and 57.72) separated by 2.32 ppm. Most of the proton and carbon

Scheme IV. Other Methods To Prepare Cryptand 4



Scheme V. Preparation of Bis-crown Ether 14



peaks in the eight-membered rings of bis-crown 13 shifted downfield compared to the corresponding peaks in the big rings of cryptands 7 and 11. Similar downfield shifts of the NMR peaks were observed for benzo-9-crown-3 macrocycles as compared to the NMR peaks of dibenzo-18-crown-6.[41] All of these results indicate that the structure of bis-crown 13 is that shown.

Bis(2-methylenepropylene)-bridged cryptand 4 was proved by its independent synthesis using a different one-step method[35] (Scheme IV). Ditosylate 31[42] was first changed to its diiodide 32. 32, without characterization, was reacted with diamine 33 in a 2:1 cyclization reaction. Cryptand 4 obtained by this method had the same spectroscopic properties and the same TLC spot as 4 prepared as shown in Scheme II. Cryptand 4 also was obtained by the direct cyclization of ditosylate 31 and diamine 33 in a 2:1 fashion.

Bis-crown 14 (Scheme V) was prepared in order to confirm that cryptands 1, 4, and 8 were indeed prepared by the 2:1 cyclization process shown in Scheme II. Bis-crown 14 is a possible alternate product for the reaction of 17 with 25 wherein the dichloride would react with two alcohol functions attached to one amine of 17. Cyclization of ditosylate 31 with ethanolamine (34) gave lariat aza-crown 35.[43] Treatment of 35 with ditosylate 36 using NaH as the base gave bis-crown 14 in a 51% yield. The ^1H NMR spectral peaks attributable to the protons of the methylenes connected to the carbon atom with a double bond (C=CCH_2O) in bis-crown 14 (δ 4.21) are shifted downfield in comparison to the corresponding peaks for cryptands 1 (δ 4.10), 4 (δ 4.08), and 8 (δ 4.05). Ethylene protons (OCH_2CH_2O) in cryptands 4 and 8 exhibited a singlet at δ 3.64, while the peaks for the protons in bis-crown 14 were overlapped with other ethylene protons at δ 3.54–3.70. The peak for the quaternary carbon (C=CC) in bis-crown 14 shifted downfield to δ 146.41 as compared to the corresponding carbon in cryptands 1, 4, and 8. These results indicate that compounds 1, 4, and 8 belong to a different class of compounds than does bis-crown 14. All of the above results strongly suggest that new compounds 1–12 have the cryptand structure as shown and not

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Table I. log K Values[a] for the Interaction of a Series of New Cryptands and [2.2.1] and [2.2.2] with Alkali Metal Ions at 25 °C

cryptand	solvent[b]	Li^+	Na^+	K^+	Rb^+	Cs^+	selectivity factor[c]
1	D_2O	NR[d]	3.0 (1)	<2	<2		>12
1[e]	8M/2W		3.57 (4)	3.17 (5)			2.5
3	8M*/2W*	NR[d]		3.7 (1)	3.9 (2)	<2	
4	8M*/2W*	<2	4.0 (3)	3.8 (2)	3.7 (2)		1.8
5	8M*/2W*		2.8 (1)	4.7 (2)	3.62 (5)		0.013
6	8M*/2W*	<2	3.6 (1)	4.7 (2)		<2	0.09
7	8M*/2W*	<2	>5	2.2 (3)	<2	<2	>620
7[e]	8M/2W		5.5 (1)	2.42 (5)			1100
7	9.5M*/0.5W*		>5	3.0 (2)			>95
7	D_2O	NR[d]	2.6 (2)	NR[d]	NR[d]		>470
8	8M*/2W*	<2	3.01 (5)	4.1 (2)	3.5 (1)	3.5 (1)	0.07
9	8M*/2W*	NR[d]	2.0 (3)	4.3 (1)	2.9 (2)	2.6 (2)	0.005
11	8M*/2W*	NR[d]	2.2 (2)	3.8 (1)		<2	0.025
[2.2.1][f]	H_2O		5.40	3.95	2.55		28.28
[2.2.2][f]	H_2O		3.90	5.40	4.35		0.03

[a] Number in parentheses indicates the precision of the log K value. [b] 8M*/2W* is 80% CD_3OD + 20% D_2O (v/v); 8M/2W is 80% CH_3OH + 20% H_2O (v/v); 9.5M*/0.5W* is 95% CD_3OD + 5% D_2O (v/v). [c] K_{Na^+}/K_{K^+}. [d] No reaction. [e] Determined by a calorimetric method; the ΔH values measured for the interaction of 1 with Na^+ and K^+ are −14.2 and −12.2 (kcal/mol), respectively; the ΔH values for 7 with Na^+ and K^+ are −8.67 and −6.7 (kcal/mol), respectively. [f] Values taken from ref 2b.

that of the corresponding bis-crown.

Solid complexes of 4 with silver, thallium, and potassium perchlorates were prepared by dissolving equimolar amounts of 4 and the appropriate perchlorate salt in methanol and allowing the solution to evaporate. Unfortunately, the crystal structures of these complexes could not be solved.

The equilibrium constants (K) for the interaction of cryptands 1, 3–9, and 11 with alkali metal ions were determined at 25 °C using a ^1H NMR technique.[44] Some of the results were verified by a calorimetric titration technique.[45] All of the cryptands studied formed 1:1 complexes with the alkali metal cations. The log K values for the interaction of cryptands 1, 3–9, and 11 with Li^+, Na^+, K^+, Rb^+, and Cs^{2+} ions are listed in Table I. For comparison purposes, the log K values of cryptands [2.2.1] and [2.2.2] with these metal ions also are listed in the table.

As shown in Table I, the bismethylene-bridged cryptand 7 exhibited a high selectivity for Na^+ over K^+. The log K value for the interaction of 7 with Na^+ was greater than 5 while that for the interaction of 7 with K^+ was 2.2 in the 80% CD_3OD and 20% D_2O solvent system. A calorimetric determination in 80% CH_3OH/20% H_2O gave log K values of 5.5 and 2.42 for the interaction of 7 with Na^+ and K^+ ions, respectively, showing a selectivity factor of over 1000. The selectivity of Na^+ over K^+ by 7 also was observed in pure D_2O and in a 95% CD_3OD/5% D_2O mixture. Comparable selectivities for Na^+ over K^+ were reported for the cryptohemispherands in $CDCl_3$ saturated with D_2O.[46,47] The selectivity of Na^+ over K^+ by cryptand [2.2.1] in H_2O is much lower than that by 7 in D_2O (see Table I).[2] Although 7 structurally resembles cryptand [2.2.2], 7 is selective for Na^+ over K^+ while [2.2.2] is selective for K^+ over Na^+ (see Table I). These results indicate that changing an ethyleneoxy unit in two bridges of [2.2.2] to methyleneoxy reduces the cavity size and flexibility of 7 causing it to be more selective for the smaller Na^+ ions. It is also possible that the cavity of 7 is smaller than that of [2.2.1].

In addition to 7, cryptand 1 also shows some selectivity for Na^+ over K^+. Cryptand 1 differs from [2.2.1] by having two $CH_2C(=CH_2)CH_2$ groups in place of two ethylene groups. Thus, 1 should have a slightly larger cavity than [2.2.1], causing a lower selectivity of Na^+ over K^+ as observed.

Cryptands 5, 6, 8, 9, and 11 show good selectivities for K^+ over Na^+ and Rb^+. It may be that the K^+ ion fits best in these cavities compared to Na^+ and Rb^+. Cryptands 3 and 4 form stable complexes with Na^+, K^+, and Rb^+, but with little or no selectivity. None of the cryptands studied show strong interactions with Li^+ ions, and the cryptands do not interact appreciably with Cs^+, except for 8 and 9. It is likely that Li^+ is too small for the cavities and it is too strongly solvated. Thus, as a free ion, Li^+ is too small to form complexes with cryptands having large cavities, and as a solvated ion, Li^+ is too large to fit in the cavities of the reported cryptands. It is possible that free Cs^+ is too large for most of the cavities. Also, Cs^+ ion is less solvated than K^+ and Na^+. In addition, because of the size of the Cs^+ ion and its lower charge density, Cs^+ should have weaker electrostatic interactions than K^+ and Na^+ with ether oxygen donors. It is not clear at present why 8 forms a stronger complex with Cs^+ than does 9.

Experimental Section

Proton and carbon NMR spectra were obtained at 200 MHz in $CDCl_3$. Molecular weights were determined by electron-impact HRMS. Log K values were measured by a ^1H NMR technique at 500 MHz[44] and by a titration calorimetric method.[45] Di-, tri-, and tetra(ethylene glycol) ditosylates (**36**, **23**, and **24**) (now sold by Aldrich), 2,6-pyridinediyldimethyl ditosylate (**26**) and glycol ditosylate **31** were prepared from the corresponding diols and *p*-toluenesulfonyl chloride according to the reported procedure.[42,48–50] Ligand **35** was prepared as reported.[43] Macrocycles 1–14 were dissolved in toluene and filtered through a glass filter before they were analyzed. Other organic and inorganic starting materials were used as purchased.

3,9-Bis(2-hydroxyethyl)-6-oxa-3,9-diaza-1,11-undecanediol (15) (Scheme I). To a mixture of 11.0 g (0.1 mol) of diethanolamine (**19**) and 10.2 g (0.1 mol) of triethylamine in 450 mL of $CHCl_3$ was added a solution of 8.6 g (0.05 mol) of diglycolyl dichloride (**20**) in 100 mL of $CHCl_3$ at 0–5 °C with stirring over a period of 2 h. The resulting mixture was stirred for an additional 12 h at rt. The solvent was evaporated, and 200 mL of DMF was

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added at rt to dissolve part of the residue. The white solid was filtered and washed with DMF. The filtrate was evaporated under reduced pressure to give crude **18** which was reduced without further purification. A mixture of the residue, 11.0 g (0.280 mol) of $LiAlH_4$, and 250 mL of *p*-dioxane was stirred under reflux for 2 days. Aqueous NaOH (5%; 10 mL) was very slowly dropped into the stirred mixture at 0–5 °C to destroy the excess $LiAlH_4$. After being stirred for 1 h, the mixture was filtered and washed several times with hot THF. The filtrate was evaporated, and the residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 80/1 and 5/1, as eluents. Evaporation of the solvent gave 14.01 g (68%) of **15** as a pale yellow oil: ^1H NMR δ 2.50–2.70 (m, 12 H), 3.52–3.75 (m, 12 H), 4.10–4.40 (b, 4 H, disappeared in D_2O); IR 3404 (broad), 1461, 1366, 1072 cm^{-1}; MS *m/e* 262 (M^+ – 18), 249 (M^+ – 31). The cryptands prepared from this material gave satisfactory elemental analyses.

3,12-Bis(2-hydroxyethyl)-6,9-dioxa-3,12-diaza-1,14-tetradecanediol (16) (Scheme I). A mixture of 37.4 g (0.20 mol) of 1,2-bis(2-chloroethoxy)ethane (**21**), 44.2 g (0.42 mol) of diethanolamine (**19**), 120 g (1.1 mol) of anhyd Na_2CO_3, and 500 mL of xylene was stirred under reflux for 2 days using a Dean–Stark trap to remove water. The cooled reaction mixture was filtered, and the solid was washed with $CHCl_3$. The filtrate was evaporated, and the residue was dissolved in 600 mL of water and extracted three times with 100-mL portions of CH_2Cl_2. The aqueous solution was evaporated under reduced pressure. $CHCl_3$ was added to dissolve the product, and the solid was filtered and washed with $CHCl_3$. The organic solution was evaporated under reduced pressure, and the excess **19** was collected at 100 °C (1.0 mm), leaving 65 g (100%) of **16** as a pale yellow oil: ^1H NMR δ 2.50–2.70 (m, 12 H), 3.40–3.65 (m, 16 H), 4.30–4.55 (b, 4 H, disappeared in D_2O); IR 3400 (broad), 1470, 1350, 1090 cm^{-1}; MS *m/e* 323 (M^+ – 1), 293 (M^+ – 31). **16** was prepared from ditosylate **23** but at a lower yield. **16** also was prepared by another method in a 71% yield.[40] The cryptands prepared from this material gave satisfactory elemental analyses.

3,15-Bis(2-hydroxyethyl)-6,9,12-trioxa-3,15-diaza-1,17-heptadecanediol (17) (Scheme I). Tetraalcohol **17** was prepared as above for **16** from 19.1 g (0.18 mol) of **19**, 20 g (0.086 mol) of di(ethylene glycol) bis(2-chloroethyl) ether (**22**), and 60 g (0.57 mol) of anhyd Na_2CO_3 in 500 mL of xylene. Product **17** (28.5 g, 90%) was a pale yellow oil: ^1H NMR δ 2.60–2.78 (m, 12 H), 3.48–3.72 (m, 20 H), 3.80–4.00 (b, 4 H, disappeared in D_2O); IR 3420 (broad), 1480, 1360, 1090 cm^{-1}; MS *m/e* 365 (M – 3), 337 (M – 31). **17** was prepared from ditosylate **24**, but at lower yield (lit. yield 79%[40]). The cryptands prepared from this material gave satisfactory elemental analyses.

6,16-Dimethylene-4,8,14,18,23-pentaoxa-1,11-diazabicyclo[9.9.5]pentacosane (1) (Scheme II). DMF (50 mL) was added dropwise into a flask containing 0.8 g (0.033 mol) of NaH and 0.3 g (0.037 mol) of LiH under N_2. A solution of tetraalcohol **15** (1.50 g, 5.3 mmol) in 150 mL of DMF was added to the stirred mixture. The resulting mixture was stirred for 2 h at 60 °C. A solution of 3-chloro-2-(chloromethyl)-1-propene (**25**) (1.35 g, 10.6 mmol) in 50 mL of DMF was added at 40 °C. The reaction mixture was stirred for 12 h at rt and 36 h at 60–70 °C. The solvent was evaporated under reduced pressure, and the residue was dissolved in 50–70 mL of water. The mixture was extracted several times with $CHCl_3$. The extract was dried (Mg_2SO_4) and evaporated. The residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents. Evaporation of the solvent gave 0.58 g (28%) of cryptand **1** as a pale yellow oil: ^1H NMR δ 2.55–2.68 (m, 12 H), 3.45–3.58 (m, 12 H), 4.10 (s, 8 H), 5.10 (s, 4 H); ^{13}C NMR δ 57.04, 57.33, 70.11, 72.61, 113.85, 144.78; IR 3077, 1446, 1352, 1127 cm^{-1}. Anal. Calcd for $C_{20}H_{36}N_2O_5$: C, 62.47; H, 9.43; MW 384.51. Found: C, 62.54; H, 9.40; MW 384.

4,12,18,26,31-Pentaoxa-1,15,34,35-tetraazatetracyclo[13.13.5^{1,15}.1^{6,10}.1^{20,24}]pentatriaconta-6(34),7,9,20(35),21,23-hexaene (2) (Scheme II). Cryptand **2** was synthesized as above for **1** from 1.0 g (3.5 mmol) of **15**, 0.60 g (0.025 mol) of NaH, 0.20 g (0.025 mol) of LiH, and 3.1 g (6.9 mmol) of 2,6-pyridinediyldimethyl ditosylate (**26**) in 170 mL of DMF. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents gave 0.18 g (11%) of **2** as a pale yellow oil: ^1H NMR δ 2.57 (t, 4 H, J = 6.2 Hz), 2.70 (t, 8 H, J = 6.2 Hz), 2.85 (b, 2 H, H_2O), 3.24 (t, 4 H, J = 6.2 Hz), 3.55 (t, 8 H, J = 6.2 Hz), 4.63 (s, 8 H), 7.27 (d, 4 H, J = 8.3 Hz), 7.68 (t, 2 H, J = 8.3 Hz); ^{13}C NMR δ 55.37, 56.49, 69.11, 70.14, 74.52, 122.32, 137.59, 158.15; IR 3400 (broad), 3058, 1536, 1359, 1122 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_4O_5 \cdot H_2O$: C, 61.88; H, 7.98, MW 504.61. Found: C, 61.78; H, 7.74; MS *m/e* 486 (M^+ – H_2O).

4,13,19,28,23-Pentaoxa-1,16-diazatetracyclo[14.14.5^{1,16}.0^{6,11}.0^{21,26}]pentatriaconta-6,8,10,21,23,25-hexaene (3) (Scheme II). Cryptand **3** was synthesized as above for **1** from 1.0 g (3.5 mmol) of **15**, 0.5 g (0.02 mol) of NaH, 0.2 g (0.025 mol) of LiH, and 1.8 g (6.9 mmol) of α,α'-dibromo-*o*-xylene (**27**) in 150 mL of DMF. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 25/1 and 20/1, as eluents gave 0.14 g (8.3%) of **3** as a pale yellow oil: ^1H NMR δ 2.58–2.75 (m, 12 H), 3.44–3.68 (m, 12 H), 4.68 (s, 8 H), 7.18–7.40 (m, 8 H); ^{13}C NMR δ 56.69, 70.09, 70.56, 71.45, 127.96, 129.00, 137.42; IR 3027, 1454, 1358, 1125 cm^{-1}. Anal. Calcd for $C_{28}H_{40}N_2O_5$: C, 69.39; H, 8.32; MW 484.63. Found: C, 69.34; H, 8.21; MW 484.

6,16-Dimethylene-4,8,14,18,23,26-hexaoxa-1,11-diazabicyclo[9.9.8]octacosane (4) (Scheme II). Cryptand **4** was synthesized as above for **1** from 1.6 g (5.0 mmol) of **16**, 0.7 g (0.03 mol) of NaH, and 1.3 g (10 mmol) of **25** in 150 mL of DMF by stirring the reaction mixture for 24 h at rt and 3 h at 60–70 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents gave 0.8 g (37%) of **4** as a pale yellow oil: ^1H NMR δ 2.67–2.80 (m, 12 H), 3.49–3.60 (m, 12 H), 3.64 (s, 4 H), 4.08 (s, 8 H), 5.15 (s, 4 H); ^{13}C NMR δ 56.42, 56.91, 70.16, 70.87, 71.56, 72.42, 113.99, 144.30; IR 3070, 1450, 1350, 1110 cm^{-1}. Anal. Calcd for $C_{22}H_{40}N_2O_6$: C, 61.66; H, 9.41; MW 428.56. Found: C, 61.89; H, 9.26; MW 428.

6,16-Dimethylene-4,8,14,18,23,26-hexaoxa-1,11-diazabicyclo[9.9.8]octacosane (4) from Diamine 33 and Diiodide 32 (Scheme IV). A mixture of 4.9 g (10 mmol) of ditosylate **31**, 350 mL of CH_3CN, 4.5 g (30 mmol) of NaI, and 20 g of anhyd Na_2CO_3 was stirred under reflux for 18 h. A solution of diamine **33** (0.74 g, 5.0 mmol) in 20 mL of CH_3CN was added to the cooled reaction mixture. The resulting mixture was stirred under reflux for 48 h. The mixture was cooled, filtered, and evaporated. Water (80 mL) was added to the residue, and the mixture was extracted four times with 60-mL portions of $CHCl_3$. The aqueous layer was saturated with NaCl after the second extraction. The combined extracts were dried (Mg_2SO_4) and evaporated. The residue was purified by chromatography on alumina using THF/EtOH, 50/1 and 10/1, as eluents and then on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 10/1, as eluents. Evaporation of the solvent gave 0.42 g (20%) of cryptand **4** as a pale yellow oil which gave the same spectral properties as reported above. Anal. Calcd for $C_{22}H_{40}N_2O_6$: C, 61.66; H, 9.41; MW 428.56. Found: C, 61.44; H, 9.31; MW 428.

6,16-Dimethylene-4,8,14,18,23,26-hexaoxa-1,11-diazabicyclo[9.9.8]octacosane (4) from Diamine 33 and Ditosylate 31 (Scheme IV). Cryptand **4** also was prepared by refluxing a mixture of 10 g (20.6 mmol) of ditosylate **31**, 1.5 g (10 mmol) of diamine **33**, 20 g of anhyd Na_2CO_3, and 400 mL of CH_3CN under stirring for 5 days. Product **4** was isolated as above to give 1.16 g (27%) of a pale yellow oil which had the same spectral properties as reported above.

4,12,18,26,31,34-Hexaoxa-1,15,37,38-tetraazatetracyclo[13.13.8^{1,15}.1^{6,10}.1^{20,24}]octatriaconta-6(37),7,9,20(38),21,23-hexaene (5) (Scheme II). Cryptand **5** was synthesized as above for **1** from 1.4 g (4.1 mmol) of **16**, 0.3 g (0.012 mol) of NaH, 1 g (9.0 mmol) of potassium *tert*-butoxide, and 1.85 g (4.1 mmol) of **26** in 150 mL of DMF by stirring the reaction mixture for 2 days at 100 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1, 20/1, and 10/1, as eluents gave 0.15 g (14%) of **5** as a pale yellow oil: ^1H NMR δ 2.52–2.85 (m, 12 H), 3.25–3.70 (m, 16 H), 4.60 (s, 8 H), 7.25 (d, 4 H, J = 8.3 Hz), 7.62 (t, 2 H, J = 8.3 Hz); ^{13}C NMR δ 55.82, 56.27, 69.30, 70.09, 71.02, 74.60, 121.52, 137.48, 158.32; IR 3059, 1673, 1593, 1455, 1359, 1118 cm^{-1}. Anal. Calcd for $C_{28}H_{42}N_4O_6$: C, 63.37; H, 7.97; MW 530.66. Found: C, 63.16; H, 7.82; MW 530.

4,13,19,28,33,36-Hexaoxa-1,16-diazatetracyclo[14.14.8^{1,16}.0^{6,11}.0^{21,26}]octatriaconta-6,8,10,21,23,25-hexaene (6) (Scheme II). Cryptand **6** was synthesized as above for **1** from 2.6 g (8 mmol) of **16**, 1.2 g (0.05 mol) of NaH, and 4.4 g (0.016 mol)

of **27** in 350 mL of DMF by stirring the reaction mixture for 2 days at 70 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 80/1 and 30/1, as eluents gave 0.38 g (9%) of **6** as a pale yellow oil: ^1H NMR δ 2.70–2.85 (m, 12 H), 3.48–3.70 (m, 16 H), 4.62 (s, 8 H), 7.20–7.40 (m, 8 H); ^{13}C NMR δ 54.79, 55.14, 68.64, 69.17, 69.74, 126.23, 127.09, 155.42; IR 3033, 1454, 1354, 1100 cm^{-1}. Anal. Calcd for $C_{30}H_{44}N_2O_6$: C, 68.15; H, 8.39; MW 528.69. Found: C, 68.29; H, 8.27; MW 528. A second reaction gave 2.31 g (55%) of **6**.

4,7,13,15,20,22-Hexaoxa-1,10-diazabicyclo[8.7.7]tetracosane (7) (Scheme II). A mixture of 1.0 g (0.04 mol) of NaH, 2.0 g (6.0 mmol) of **16**, and 1.1 g (0.013 mol) of **29** in 200 mL of THF was gradually heated to 60 °C and stirred for 2 days. The cooled mixture was filtered, and the solid was washed with THF. The solvent was evaporated, and the residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 40/1 and 30/1, as eluents to give 0.8 g (59%) of **7** as a pale yellow oil: ^1H NMR δ 2.55–2.78 (m, 12 H), 3.43–3.74 (m, 16 H), 4.62 (s, 4 H); ^{13}C NMR δ 56.18, 57.68, 66.84, 70.53, 71.30, 94.80; IR 1449, 1359, 1114 cm^{-1}. Anal. Calcd for $C_{16}H_{32}N_2O_6$: C, 55.15; H, 9.25; MW 348.44. Found: C, 54.96; H, 9.18; MW 348.

18,27-Dimethylene-4,7,10,16,20,25,29-heptaoxa-1,13-diazabicyclo[11.9.9]hentriacontane (8) (Scheme II). Cryptand **8** was synthesized as above for **1** from 1.8 g (5.0 mmol) of **17**, 0.80 g (0.033 mol) of NaH, and 1.25 g (0.01 mol) of **25** in 120 mL of DMF by stirring the reaction mixture for 20 h at rt and 8 h at 60–70 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 25/1 and 20/1, as eluents gave 0.17 g (7%) of **8** as a pale yellow oil: ^1H NMR δ 2.68–2.81 (m, 12 H), 3.50–3.61 (m, 12 H), 3.64 (s, 8 H), 4.05 (s, 8 H), 5.14 (s, 4 H); ^{13}C NMR δ 55.91, 56.45, 69.96, 70.46, 71.32, 72.25, 114.20, 114.02; IR 3074, 1456, 1349, 1112 cm^{-1}; Anal. Calcd for $C_{24}H_{44}N_2O_7$: C, 60.99; H, 9.38; MW 472.62. Found: C, 60.97; H, 9.33; MW 472.

4,12,18,26,31,34,37-Heptaoxa-1,15,40,41-tetraazatetracyclo[13.13.11^{1,15}.1^{6,10}.1^{20,24}]hentetraconta-6(40),7,9,20(41),21,23-hexaene (9) (Scheme II). THF (50 mL) was added dropwise into a dry flask containing 1.0 g (0.04 mol) of NaH under N_2. A solution of 1.1 g (3.0 mmol) of **17** in 200 mL of THF was added into the stirred mixture. The resulting mixture was stirred for 2 h at 60 °C. A solution of 2.7 g (6.0 mmol) of **26** in 100 mL of THF was added, and the resulting mixture was stirred for 2 days at 60–70 °C. The cooled mixture was filtered and washed with THF. The solvent was evaporated, and the residue was purified by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 30/1 and 10/1, as eluents to give 0.30 g (17%) of **9** as a pale yellow oil which solidified on standing: ^1H NMR δ 2.60–2.80 (m, 12 H), 3.32–3.65 (m, 20 H), 4.60 (s, 8 H), 7.28–7.60 (m, 6 H); ^{13}C NMR δ 56.13, 56.60, 69.63, 70.31, 70.87, 70.95, 74.44, 120.84, 137.47, 158.49; IR 3061, 1455, 1348, 1119 cm^{-1}. Anal. Calcd for $C_{30}H_{46}N_4O_7$: C, 62.69; H, 8.07; MW 574.71. Found: C, 62.49; H, 8.11; MW 574.

4,13,19,28,33,36,39-Heptaoxa-1,16-diazatetracyclo[14.14.11^{1,16}.0^{6,11}.0^{21,26}]hentetraconta-6,8,10,21,23,25-hexaene (10) (Scheme II). Cryptand **10** was synthesized as above for **9** from 1.8 g (5.0 mmol) of **17**, 1.0 g (0.04 mol) of NaH, and 2.6 g (0.01 mol) of **27** in 200 mL of THF by stirring the reaction mixture for 4 days under reflux. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1, 10/1, and 5/1, as eluents gave 0.3 g (10%) of **10** as a pale yellow oil: ^1H NMR δ 2.70–2.90 (m, 12 H), 3.45–3.68 (m, 20 H), 4.50–4.65 (m, 8 H), 7.20–7.40 (m, 8 H); ^{13}C NMR δ 55.18, 55.54, 69.41, 70.49, 71.07, 71.42, 128.05, 128.85, 136.82; IR 3034, 1455, 1354, 1102 cm^{-1}. Anal. Calcd for $C_{32}H_{48}N_2O_7$: C, 67.14; H, 8.45; MW 572.74. Found: C, 67.42; H, 8.10; MW 572.

4,7,10,16,18,23,25-Heptaoxa-1,13-diazabicyclo[11.7.7]heptacosane (11) (Scheme II). Cryptand **11** was synthesized as above for **7** from 1.1 g (3.0 mmol) of **17**, 1.7 g (0.015 mol) of KO-*t*-C_4H_9, 0.70 g (2.0 mmol) of anhyd Cs_2CO_3, and 0.60 g (7.0 mmol) of **29** in 130 mL of THF by stirring the reaction mixture for 1 day at 60–70 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1 and 15/1, as eluents gave 0.47 g (40%) of **11** as a pale yellow oil: ^1H NMR δ 2.50–2.78 (m, 12 H), 3.38–3.65 (m, 20 H), 4.55 (s, 4 H); ^{13}C NMR δ 55.40, 57.71, 66.31, 69.79, 70.49, 71.40, 94.71; IR 1453, 1353, 1084 cm^{-1}. Anal. Calcd for $C_{18}H_{36}N_2O_7$: C, 55.08; H, 9.24; MW 392.49. Found: C, 55.18; H, 9.17; MW 392.

4,12,18,26,31,34,37-Heptaoxa-1,15-diazatetracyclo[13.13.11^{1,15}.1^{6,10}.1^{20,24}]hentetraconta-6(40),7,9,20(41),21,23-hexaene (12) (Scheme II). Cryptand **12** was synthesized as above for **10** from 1.8 g (5.0 mmol) of **17**, 1.0 g (0.04 mol) of NaH, and 2.6 g (0.01 mol) of **28** in 200 mL of THF. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 20/1, 10/1, and 5/1, as eluents gave 0.14 g (5%) of **12** as a pale yellow oil: ^1H NMR δ 2.65–2.90 (m, 12 H), 3.40–3.68 (m, 20 H), 4.48 (s, 8 H), 7.12–7.30 (m, 8 H); ^{13}C NMR δ 54.97, 55.11, 69.41, 70.30, 71.01, 73.53, 127.26, 128.90, 139.04; IR 3020, 1455, 1353, 1114 cm^{-1}. Anal. Calcd for $C_{32}H_{48}N_2O_7$: C, 67.14; H, 8.45; MW 572.74. Found: C, 66.95; H, 8.18; MW 572.

1,5-Bis(4,6-dioxa-1-azacyclooctyl)-3-oxapentane (13) (Scheme III). Bis-crown ether **13** was obtained following the same procedure as above for the preparation of cryptand **7** from 1.0 g (3.5 mmol) of **15**, 0.6 g (0.025 mol) of NaH, 0.2 g (0.05 mol) of LiH, and 0.6 g (7.0 mmol) of **29** in 200 mL of DMF by stirring the reaction mixture for 12 h at rt and for 36 h at 60–70 °C. Purification by chromatography on silica gel using CH_3OH/30% aqueous NH_4OH, 40/1, as the eluent and on neutral alumina using toluene/EtOH, 30/1, as the eluent gave 0.30 g (28%) of **13** as a colorless oil: ^1H NMR δ ($CDCl_3$) 2.77 (t, 4 H, J = 5.2 Hz), 2.84 (t, 8 H, J = 5.2 Hz), 3.57 (t, 4 H, J = 5.2 Hz), 3.74 (t, 8 H, J = 5.2 Hz), 4.69 (d, 2 H, J = 7.8 Hz), 4.80 (d, 2 H, J = 7.8 Hz); δ (DMSO-d_6) 2.70 (t, 4 H, J = 5.2 Hz), 2.78 (t, 8 H, J = 5.2), 3.50 (t, 4 H, J = 5.2 Hz), 3.64 (t, 8 H, J = 5.2 Hz), 4.66 (d, 2 H, J = 7.8 Hz), 4.57 (d, 2 H, J = 7.8 Hz); ^{13}C NMR δ 57.29, 57.35, 69.41, 69.76, 96.95; IR 1448, 1361, 1119 cm^{-1}. Anal. Calcd for $C_{14}H_{28}N_2O_5$: C, 55.24; H, 9.27; MW 304.38. Found: C, 55.10; H, 9.13; MW 304.

1,11-Bis(5-methylene-3,7-dioxa-1-azacyclodecanyl)-3,6,9-trioxaundecane (14) (Scheme V). A mixture of 0.4 g (16 mmol) of NaH and 0.44 g (2.1 mmol) of **35**[43] in 50 mL of THF was stirred under reflux for 2 h. A solution of 0.44 g (1.05 mmol) of **36** in 20 mL of THF was added at 50 °C. The resulting mixture was stirred under reflux for 2 days. The cooled mixture was filtered and evaporated. The residue was purified by chromatography on neutral alumina using toluene/EtOH, 100/1 was 80/1, as eluents. Evaporation of the solvent gave 0.25 g (51%) of bis-crown **14** as a pale yellow oil: ^1H NMR δ 2.77–2.81 (m, 12 H), 3.54–3.70 (m, 20 H), 4.21 (s, 8 H), 5.01 (s, 4 H); ^{13}C NMR δ 55.39, 56.69, 70.54, 70.87, 71.07, 71.32, 72.37, 113.68, 146.41; IR 3074, 1460, 1350, 1076 cm^{-1}. Anal. Calcd for $C_{24}H_{44}N_2O_7$: C, 60.99; H, 9.38; MW 472.62. Found: C, 60.84; H, 9.18; MW 472.

Silver Perchlorate Complex of Cryptand 4. Cryptand **4** (0.34 g, 0.7 mmol) and 0.15 g (0.7 mmol) of $AgClO_4$ were dissolved in 15 mL of hot CH_3OH. Single crystals of the complex were obtained without further recrystallization: mp 222–224 °C; ^1H NMR (DMSO-d_6) δ 2.70–2.92 (m, 12 H), 3.55–3.75 (m, 16 H), 4.10 (s, 8 H), 5.20 (s, 4 H); IR 3050, 1478, 1351, 1125 cm^{-1}. Anal. Calcd for $C_{22}H_{40}N_2O_{10}AgCl$: C, 41.55; H, 6.34; MW 635.88. Found: C, 41.55, H, 6.36; MS m/e 428 ($M^+ - AgClO_4$).

Thallium Perchlorate Complex of Cryptand 4. Cryptand **4** (0.34 g, 0.7 mmol) and 0.22 g (0.7 mmol) of $TlClO_4$ were dissolved in 20 mL/5 mL of hot CH_3OH/CH_3CN. Single crystals of the complex were obtained without further recrystallization: mp 214–215.5 °C; ^1H NMR (DMSO-d_6) δ 2.53–2.66 (m, 12 H), 3.42–3.60 (m, 16 H), 4.03 (s, 8 H), 5.20 (s, 4 H); IR 3082, 1479, 1354, 1074 cm^{-1}. Anal. Calcd for $C_{22}H_{40}N_2O_{10}TlCl$: C, 36.08; H, 5.51; MW 732.38. Found: C, 36.33; H, 5.65; MS m/e 428 ($M^+ - TlClO_4$).

Potassium Perchlorate Complex of Cryptand 4. Cryptand **4** (0.10 g, 0.23 mmol) and 0.03 g (0.22 mmol) of $KClO_4$ were each dissolved in hot CH_3OH and mixed together. Single crystals were obtained without further recrystallization: mp 210–212 °C; ^1H NMR (DMSO-d_6) δ 2.42–2.65 (m, 12 H), 3.38–3.62 (m, 16 H), 4.05 (s, 8 H), 5.20 (s, 4 H); IR 1479, 1355, 1093 cm^{-1}; MS m/e 428 ($M^+ - KClO_4$).

Determination of log K Values by the Direct ^1H NMR Method. The log K values listed in Table I were determined by a method similar to our reported procedure.[44] A sample containing a few milligrams of cryptand in a known volume of solvent was first loaded into the probe, and a spectrum was taken. The sample was then unloaded, added to the sample tube with 0.05 or 0.1 mL of a standard metal ion solution, and reloaded into the probe, and another spectrum was taken. This procedure was repeated until no significant change was observed in successive ^1H NMR spectra.

Usually, 8–12 spectra were taken for each log K determination. The original cryptand concentrations were about 0.04 M, and the variation of metal cation concentrations were from 0.00 to 0.08 M for each of the experiments. In such an experiment, an accurately weighed quantity of the cryptand was dissolved in a known volume of solvent. The concentrations of metal ions and cryptands were calculated according to the volume in the tube and the original concentration of each material. The log K values were obtained from the variation of the observed chemical shift with the metal cation/ligand mole ratio. It should be noted that the method becomes unreliable for very stable complexes (log K > 5.0).[51,52]

Determination of log K and ΔH Values by the Titration Calorimetric Method. Calorimetric titrations were carried out in a Tronac Model 450 isoperibol calorimeter using the reported method.[45]

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Chemoselective Ring Construction from Unsymmetrical 1,6-Dienes via Radical Addition of Sulfonyl Halides

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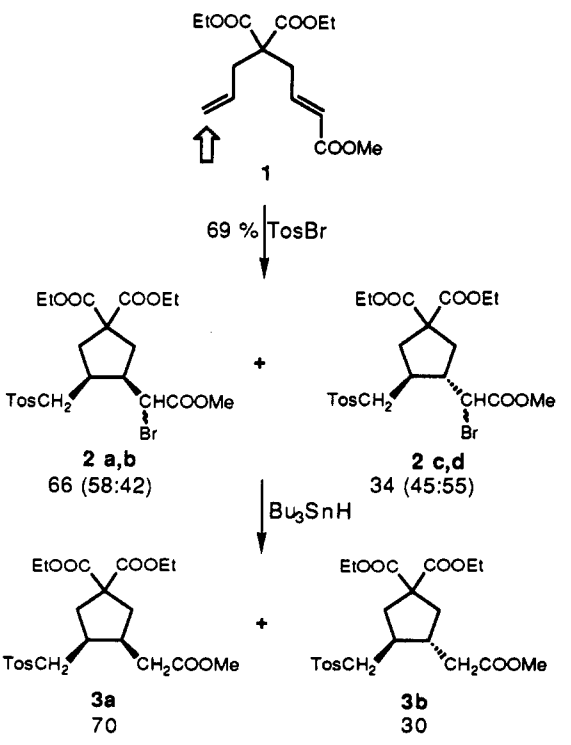
The sulfonyl radical-promoted cyclizations of 1,6-unsymmetrical dienes can be totally chemoselective. The addition of tosyl halides to various 1,6-dienes bearing both a nucleophilic and an electrophilic double bond clearly indicates that this attractive property is not related to the generally accepted electrophilic nature of tosyl radical. The chemoselectivity is likely to originate from the reversibility of the first step, i.e. tosyl radical addition to the double bond, which favors the formation of the adducts resulting from the one intermediate radical that cyclizes faster.

Sulfonyl radicals are generally recognized as useful intermediates in the synthesis of sulfones.[1] In previous papers,[2,3] we described the ability of the radical addition of sulfonyl halides to functionalize regio- and stereoselectively 1,6-dienes. Concurrently, other research groups have become interested in this strategy to prepare sulfonylated cyclic compounds from tosyl chloride,[4] tosyl iodide,[5] and allyl sulfones.[6,7]

From all these results it has appeared that the reaction with unsymmetrical 1,6-dienes could be highly stereoselective and moreover totally chemo- and regioselective. The synthetic aspects of the reaction have been illustrated by our experiments and those, previously mentioned, conducted simultaneously by other groups, whereas little attention has been paid to mechanistic aspects until very recently.[8] In order to investigate more thoroughly the reasons for such a high chemoselectivity, which we primarily ascribed to the reversibility of the initial addition of sulfonyl radical,[3] we studied the addition of TsBr to various 1,6-dienes bearing both a nucleophilic and an electrophilic double bond, thus trying to check the possibility of an influence of polar effects. The dienes 1 and 4 selected for this study contain both a monosubstituted

Scheme I



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