Lipophilic Cage Ligands Containing Two Tightly Connected 1,7-Dioxa-4,10-diazacyclododecane Rings: Synthesis and X-ray Structure of a Sodium Perchlorate Complex

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Sodium perchlorate complexes **2** of lipophilic macrotricyclic receptors **1** were obtained in high yield by following a synthetic route in which sodium cation acts as the templating agent in the last step. Complexes with several inorganic salts were directly prepared from the free ligands **1**, obtained by decomplexation of **2**, or via anionic exchange from the complexes **2**. Extraction data of alkali halides under two-phase conditions (H_2O–$CHCl_3$) with ligand **1a** showed a cation extraction selectivity order $Na^+ \gg K^+ > Li^+$. Under liquid–liquid two-phase conditions, ligands **1** proved to be effective phase-transfer catalysts in hydroxide ion initiated carbanion formation from very weak carbon acids. The sodium complex **2a** was crystallographically characterized. The sodium cation is in a nonsymmetric cubic environment of four oxygen (Na···O 2.46 Å) and four nitrogen (Na···N 2.79 Å) atoms.

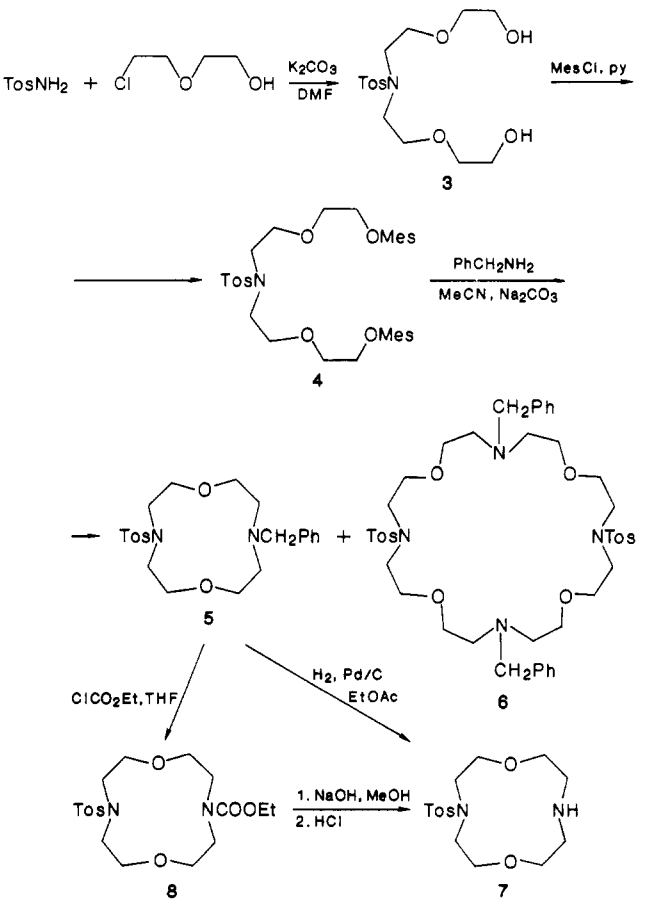
Although many examples of macrocyclic and macropolycyclic synthetic ligands capable of complexing metal cations are known,[1] the search for new receptors featuring greater complex stabilities or higher selectivities is still very active. Lipophilic macropolycyclic ligands are of particular interest due to their capability of dissolving inorganic salts in nonpolar organic solvents. They can be used as phase-transfer catalysts or, more generally, as anion activators.[2]

In the present paper, we describe the synthesis of lipophilic cage ligands **1a,b** in which two 1,7-dioxa-4,10-diazacyclododecane rings are held together by two short bridges.[3] This promotes cooperation of the macrocyclic binding subunits in the complexation, thus allowing formation of only mononuclear inclusion complexes.[4] The X-ray structure of the sodium perchlorate complex **2a**, the extraction constants for alkali halides by receptor **1b**, and some examples of the application of ligands **1a,b** as phase-transfer catalysts in base-promoted reactions are also reported.

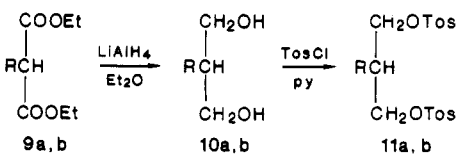
Results and Discussion

Synthesis. Bisalkylation of *p*-toluenesulfonamide with 2-(2-chloroethoxy)ethanol and K_2CO_3 in DMF afforded diol **3**, which was converted into the corresponding bis(methylsulfonyl) derivative **4** (Scheme I). Condensation of **4** with benzylamine in refluxing acetonitrile and Na_2CO_3 gave the coronands **5** and **6** in 51% and 5% yields, respectively. Debenzylation of **5** by catalytic hydrogenation with 10% Pd/C in ethyl acetate afforded **7** in quantitative yield. Alternatively **5** was reacted with ethyl chloroformate leading to the urethane **8**, which after alkaline hydrolysis and decarboxylation with concentrated HCl gave **7** in 80% overall yield.

Scheme I



Reduction of diethyl 2-benzylmalonate or diethyl 2-hexadecylmalonate (**9a,b**) with $LiAlH_4$ gave diols **10a,b**, which were tosylated to afford **11a,b** (eq 1).



(1)

a, R = $PhCH_2$; **b**, R = n-$C_{16}H_{33}$

Condensation of bis-*p*-toluenesulfonates **11a,b** with **7** in refluxing acetonitrile and Na_2CO_3 allowed the insertion of

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(2) (a) Lehn, J.-M. *Science (Washington, D.C.)* **1985**, *227*, 1849 and references therein. (b) Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147 and references therein.

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(4) Stoichiometry and stability of the complexes of macrotricycles containing two diazacrown rings is regulated by the length of the bridging chains.[5] An example of a very stable sodium complex with a structure similar to that of **1a,b** has been previously reported.[6]

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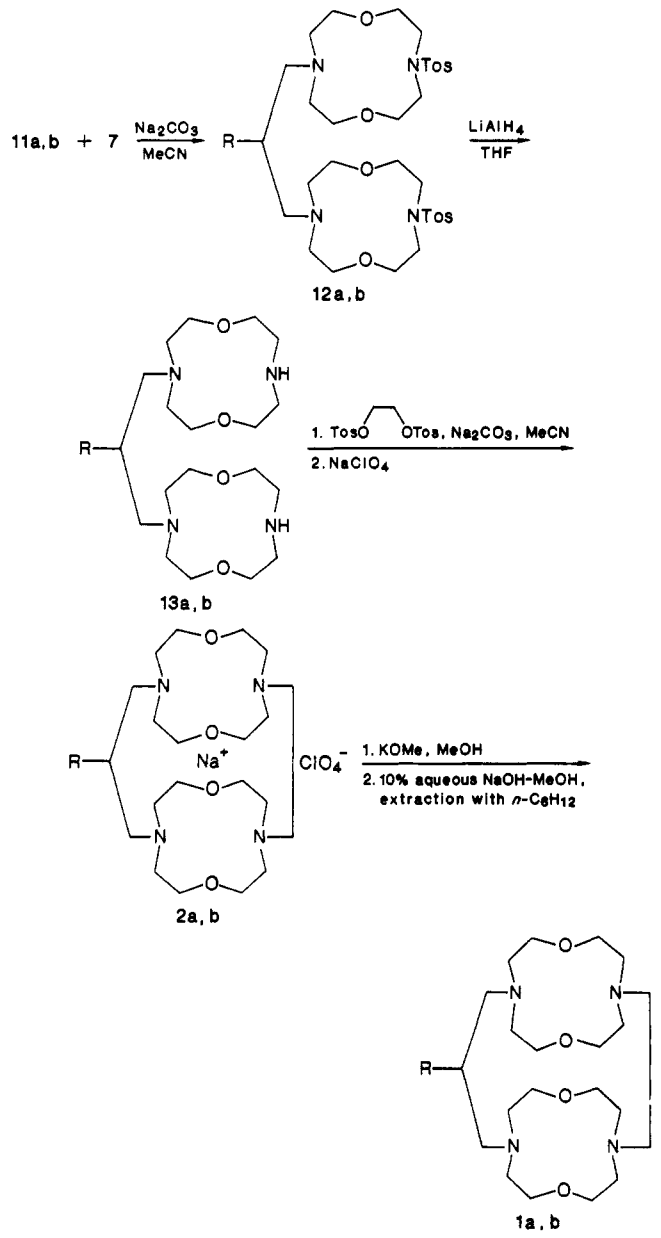
Scheme II[a]



[a] a, R = $PhCH_2$; b, R = n-$C_{16}H_{33}$.

the first bridge, leading to bis macrocycles **12a,b** (Scheme II). Cleavage of *p*-tolylsulfonyl groups of **12a,b** with $LiAlH_4$ gave the amines **13a,b**, which were reacted with ethylene glycol bis(*p*-toluenesulfonate) in acetonitrile and Na_2CO_3, affording the final macrotricyclic sodium complexes. These latter were isolated in 60–70% yield as perchlorates **2a,b** after treatment of reaction crudes with aqueous $NaClO_4$.

The template effect of the sodium cation accounts for the high yield obtained in the final ring closure. When lithium or potassium cations were used as templating agents in the final ring closure, followed by treatment with $LiClO_4$ and KPF_6, respectively, mixtures of $[Li \subset \mathbf{1a}]^+ClO_4^-$ and $[Na \subset \mathbf{1a}]^+ClO_4^-$ in the case of Li^+, and of $[K \subset \mathbf{1a}]^+PF_6^-$ and $[Na \subset \mathbf{1a}]^+PF_6^-$ in the case of K^+, were isolated in 32% and 38% yields after column chromatography (see Experimental Section). Most likely the exchanges of Li^+ and K^+ for Na^+ occur during chromatography, due to the very high selectivity of receptor **1a** for sodium.

Treatment with aqueous $NaClO_4$ of the mixtures of complexes dissolved in $CHCl_3$ afforded in both cases pure **2a** in quantitative yields.

Decomplexation and Synthesis of Other Complexes. Metal cation templated syntheses of macropolycyclic receptors occur through a metal-coordinated intermediate which favors the intramolecular cyclization. The final product can be either the free ligand,[7] when the coordination is weak, or the complex if the metal–receptor interaction is sufficiently strong, as for **2a,b**.[6,8]

Free ligands **1a,b** were obtained by the continuous extraction of a solution of the corresponding sodium methoxide or sodium fluoride complex (see below) in methanol–10% aqueous KOH (or KF) with *n*-hexane for several days. The extraction equilibrium is depicted in eq 2.

$$[Na \subset 1]^+X^-_A \rightleftarrows 1_{hexane} + Na^+_A + X^-_A \qquad (2)$$

A = MeOH–10% aqueous KOH (or KF), 1:3 (v/v)

Two main conditions are required to obtain the free ligand by using this technique: (i) high lipophilicity of the ligand; the more lipophilic ligand **1b** was quantitatively recovered after 2 days' extraction, whereas only 67% of **1a** was obtained after 2 weeks; (ii) high hydrophilicity of the anionic counterpart which destabilizes the complex; MeO^-, OH^-, or F^- are suitable anions for this purpose.

Starting from **1b**, KPF_6 and $AgNO_3$ complexes were prepared and fully characterized by ^1H and ^{13}C NMR spectroscopy.[9]

Sodium complexes **2a,b** were suitable starting materials for the preparation of many other sodium complexes via anionic exchange (eq 3). This reaction is driven by the

$$[Na \subset 1]^+ClO_4^- + KX \rightarrow [Na \subset 1]^+X^- + KClO_4 \qquad (3)$$

X = I, Br, Cl, OH, MeO, F

insolubility of $KClO_4$ and can occur due to the selectivity of the ligands **1a,b** for sodium.

Transmetalation (K^+/Na^+ exchange), which in principle can interfere, does not occur, as was confirmed by ^{13}C NMR analysis. Indeed, spectra of complexes prepared by this method showed only the resonances belonging to the sodium-complexed receptors.

Determination of Extraction Constants. The study of thermodynamic parameters ruling the complexation of lipophilic macropolycyclic receptors is limited by two main reasons: (i) these receptors are insoluble in aqueous solvents, generally used in the case of hydrophilic ligands; (ii) they show very high stability constants in low-polarity organic solvents, thus further reducing the possible methods of investigation.

We found that the picrate extraction method, which allows the direct determination of the association (K_a) and extraction (K_{ex}) constants of complexes in organic solvents,[10] cannot be used for receptors **1**, as reported by

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Table I. Extraction Constants (K_{ex}) for Alkali Halides Complexed by Ligand 1b[a]

	K_{ex}[b]		
M^+	I^-	Br^-	Cl^-
Li^+	670	–[c]	–[c]
Na^+	>10^7[d]	51.000	3.000
K^+	5200	61	–[c]
Rb^+		–[c]	
Cs^+	–[c]	–[c]	

[a] Solutions (5×10^{-2} M) of **1b** in $CHCl_3$ and of alkali halide in H_2O equilibrated at 20 °C for 24 h. [b] Values (±10%) are the average of at least four experiments. [c] The halide concentration in the aqueous phase was comparable with that of the starting solution. [d] Estimated by using 5×10^{-3} M solutions.

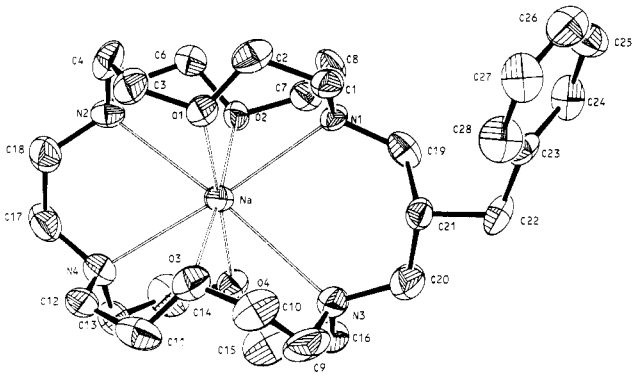

Figure 1. Perspective view of the **2a** cation.

Cram et al. in the case of cryptands and cryptahemispherands.[11] In fact, after equilibration of a 10^{-3} M aqueous solution of alkali picrates with a 10^{-3} M solution of **1** in $CDCl_3$, the picrate was entirely extracted in the organic phase, independently of the cation: this indicates very high K_a values.

An original procedure was used for the evaluation of the extraction constants (K_{ex}) for alkali halides with **1b**, eq 4.

$$M^+_{H_2O}X^-_{H_2O} + \mathbf{1b}_{CHCl_3} \overset{K_{ex}}{\rightleftharpoons} [M \subset \mathbf{1b}]^+X^-_{CHCl_3} \quad (4)$$

A solution of ligand **1b** in $CHCl_3$ was equilibrated for 24 h at 20 °C with equimolar aqueous solutions of alkali halides. The concentrations of the species at the equilibrium were determined by potentiometric titration of the halide in the aqueous phase. Results of the extraction experiments (Table I) show the high selectivity of ligand **1b** for Na^+.

In the case of Br^- and I^-, the extractability of Na^+ is more than 10^3 times that of K^+, whereas those of Li^+, Rb^+, and Cs^+ are undetectable. In the case of I^-, the extractability of Na^+ is more than 10^3 and more than 10^4 those of K^+ and Li^+, respectively, that of Cs^+ being again undetectable. Within the series of alkali chlorides, NaCl was the only salt extracted. These data indicate that the softer the anion, the higher the extractability of the salt, and once again stress the influence of the anion on the extraction of inorganic salts by lipophilic ligands into low-polarity organic solvents.[12]

X-ray Analysis of 2a. In order to ascertain the way of coordination of the Na^+ cation and the conformation of the receptor, we have performed a single-crystal X-ray diffraction experiment on **2a**.

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Table II. Bonding Parameters within 2a

	C–C Bond Lengths, Å		
C1–C2	1.510 (13)	C20–C21	1.524 (12)
C3–C4	1.490 (11)	C21–C22	1.552 (11)
C5–C6	1.518 (11)	C22–C23	1.517 (11)
C7–C8	1.473 (11)	C23–C24	1.379 (11)
C9–C10	1.441 (14)	C23–C28	1.364 (11)
C11–C12	1.417 (13)	C24–C25	1.340 (13)
C13–C14	1.480 (14)	C25–C26	1.335 (15)
C15–C16	1.428 (14)	C26–C27	1.353 (13)
C17C18	1.502 (13)	C27–C28	1.368 (13)
C19–C21	1.501 (11)		
	C–N Bond Lengths, Å		
C1–N1	1.459 (9)	C9–N3	1.434 (13)
C8–N1	1.488 (9)	C16N3	1.508 (11)
C19–N1	1.482 (11)	C20–N3	1.499 (11)
C4–N2	1.434 (11)	C12–N4	1.499 (12)
C5–N2	1.465 (10)	C13–N4	1.416 (13)
C18–N2	1.443 (10)	C17–N4	1.472 (12)
	C–O Bond Lengths, Å		
C2–O1	1.392 (11)	C10–O3	1.453 (12)
C3–O1	1.423 (11)	C11–O3	1.385 (10)
C6–O2	1.412 (10)	C14–O4	1.433 (12)
C7–O2	1.421 (9)	C15–O4	1.375 (12)
	Na···O and Na···N Interactions, Å		
Na···O1	2.596 (6)	Na···N1	2.745 (6)
Na···O2	2.415 (6)	Na···N2	2.724 (8)
Na···O3	2.331 (6)	Na···N3	2.953 (8)
Na···O4	2.503 (6)	Na···N4	2.745 (8)

Dihedral Angles of the Two 1,7-Dioxa-4,10-diazacyclododecane Rings, deg

C3–O1–C2–C1	–172	C10–O3–C11–C12	–177
O1–C2–C1–N1	54	O3–C11–C12–N4	55
C2–C1–N1–C8	71	C11–C12–N4–C13	73
C1–N1–C8–C7	–153	C12–N4–C13–C14	–142
N1–C8–C7–O2	67	N4–C13–C14–O4	60
C8–C7–O2–C6	79	C13–C14–O4–C15	81
C7–O2–C6–C5	–171	C14–O4–C15–C16	–178
O2–C6–C5–N2	61	O4–C15–C16–N3	56
C6–C5–N2–C4	69	C15–C16–N3–C9	74
C5–N2–C4–C3	–153	C16–N3–C9–C10	–133
N2–C4–C3–O1	64	N3–C9–C10–O3	60
C4–C3–O1–C2	86	C9–C10–O3–C11	84

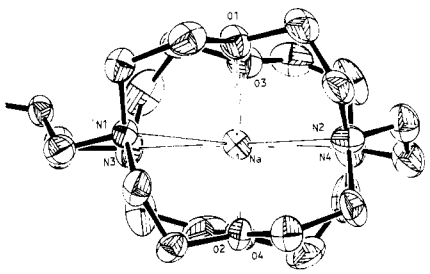

Figure 2. Perspective view of the cage projected on the idealized mirror plane.

In Figure 1 is reported a view of the complex, in Table II a list of the most significant bonding parameters. The structure consists of bulky $[Na \subset \mathbf{1a}]^+$ cations and ClO_4^- anions. The shortest distance between the center of the anion and Na^+ is 6.7 Å. The two 1,7-dioxa-4,10-diazacyclododecane rings are held together by two bridges of different lengths (two and three carbon atoms, respectively), and the resulting cage resembles a truncated cone. In fact, the distance between the two 12-membered rings increases on going from left to right in Figure 1, as indicated by the following intramolecular distances: N2···N4 (3.01 Å) < O1···O3 (3.24 Å) < O2···O4 (3.29 Å) < N1···N3 (3.52 Å).

The cage has an idealized C_s symmetry in the crystal, the mirror being the plane of Figure 2. This can be related

Table III. Hydroxide Ion Initiated Oxidation of Diphenylmethane Catalyzed by 1b under Liquid-Liquid Phase-Transfer Conditions

entry	1b, mequiv	aqueous NaOH, %	T, °C	time, h	yield, %
1[a]	0.20	40	70	1	94
2[a]	-	50	70	24	3
3[a]	0.05	50	70	1	96
4[b]	0.10	50	25	23	89
5[c]	0.075	63	60	1.5	91
6[c]	0.05	63	80	1.5	91

[a] Without organic solvent. [b] Solution (0.5 M) of diphenylmethane in chlorobenzene. [c] Solution (0.05 M) of diphenylmethane in chlorobenzene.

to the behavior of **2a** in solution, where only half of the expected ^{13}C NMR resonances are observed.[13]

The conformation of the two 1,7-dioxa-4,10-diazacyclododecane rings is close to the quadrangular [3 3 3 3] of C_4 symmetry[14] that has been found in the solid state[12] and has been calculated to be the most stable[15] for cyclododecane. The presence of two nitrogen and two oxygen atoms in the cycle, the linking of two such cycles in a cage, and perhaps the coordination to a sodium atom reduce the idealized symmetry to C_2, as is evident from the list of the pertinent dihedral angles reported in Table II. A similar lowering of the symmetry has been found in the two analogous rings of the 7,16,21,26-tetraoxa-1,4,10,13-tetraazatricyclo[11.5.5.5^{4,10}]octacosane sodium tetrafluoroborate.[16] A measure of the $C_4 \rightarrow C_2$ symmetry distortion can be the difference between the N···N and O···O intracycle nonbonding distances (that should be equal in C_4 symmetry), which are 4.45 (N1···N2) and 3.80 (O1···O2) Å in one cycle and 4.62 and 3.57 Å in the other.

The cubic geometry of the donor atoms is dictated by the organic skeleton, but the particular cation can drive the cage conformation. In the present compound, the four oxygen atoms are closer (mean 2.46 Å) to the Na^+ cation than the four nitrogen atoms (mean 2.79 Å), similarly to what is found in the 7,16,21,26-tetraoxa-1,4,10,13-tetraazatricyclo[11.5.5.5^{4,10}]octacosane $NaBF_4$ complex, while in the KSCN derivative the K···N and the K···O distances are more similar.[17]

Ligands 1a,b as Anion Activators. Under homogeneous conditions, the reactivity of $[Na \subset 1]^+X^-$ (X = I, Br, Cl) in nucleophilic substitution reactions on *n*-octyl methanesulfonate was shown to be very high and comparable with that of $[K \subset (2,2,2\text{-}C_{14})]^+X^-$.[3,7b] The sodium complexes of ligands **1a,b** can be used as catalysts in carbanion formation from very weak carbon acids in liquid–liquid two-phase conditions with highly concentrated aqueous alkali hydroxides.

Diphenylmethane (pK_a = 32.2)[18] was 50% deuteriated in an inert atmosphere with 40% NaOD in D_2O at 70 °C for 5 h in the presence of 0.2 molar equiv of **1a** as catalyst. When carbanions were formed with aqueous NaOH in an oxygen atmosphere, ketones were the reaction products. As reported in Table III, diphenylmethane gave benzophenone in good yield under a wide range of conditions: temperature (25–80 °C), NaOH concentration (40–63%), amount of catalyst (0.05–0.2 molar equiv), and with or without solvent.[19] In the absence of catalyst, only 3% of benzophenone was detected after 24 h at 70 °C. 3-Benzoylpyridine was obtained in 96% yield from 3-benzylpyridine (pK_a = 30.1)[20] in chlorobenzene–60% aqueous NaOH for 6 h at room temperature and in the presence of 0.1 molar equiv of **1b** as catalyst.

It has to be stressed that triphenylmethane (pK_a = 31.5),[15,18] in these same conditions, affords triphenylcarbinol very slowly. It is most likely that the anion of the latter remains in the organic phase associated with the sodium cation complex, thus slowing down the catalytic process. This compares with previous observations that the extraction of the hydroxide ion in nonpolar organic solvents is inhibited by the presence of even very small amounts of softer anions.[21]

In conclusion we would like to point out the following: (i) the efficiency of the sodium cation in templating the final ring closure leading to lipophilic macrotricyclic receptors; (ii) the remarkable selectivity of receptors **1** for Na^+ over K^+ and Li^+; (iii) the importance of the lipophilicity of the ligand and the hydrophilicity of the anion associated with the sodium cation complex in driving the decomplexation process; and (iv) the high catalytic activity of receptors **1** in the hydroxide ion initiated carbanion formation from very weak carbon acids under phase-transfer conditions.

Experimental Section

^1H NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer with Me_4Si as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 377 spectrometer. Melting points were measured on a Büchi 510 apparatus and are uncorrected. GLC analyses were performed on a Hewlett-Packard Model 5840 flame-ionization instrument (2 ft × 0.125 in. OV 17 10% on Chromosorb W column). Potentiometric titrations were performed with a Metrohm Titroprocessor E 636 and Metrohm Dosimat E635. Satisfactory combustion analyses (±0.40% for C, H, and N) were submitted for all new compounds. Organic and inorganic reagents, ACS grade, were used without further purification. Ethylene glycol bis(methanesulfonate) was prepared according to ref 22.

***N,N*-Bis[2-(2-hydroxyethoxy)ethyl]-4-methylbenzenesulfonamide (3).** A mixture of 34.2 g (0.2 mol) of *p*-toluenesulfonamide, 64.5 g (0.52 mol) of 2-(2-chloroethoxy)ethanol, and 138.2 g (1.0 mol) of anhydrous K_2CO_3 in 500 mL of DMF was refluxed for 4 days with vigorous stirring. After cooling at room temperature, the reaction mixture was filtered and the precipitate washed with CH_2Cl_2 (2 × 100 mL). The solvent was evaporated in vacuo and the residue (72 g) purified by column chromatography (silica gel; EtOAc), affording 54.0 g (77%) of **3** as a colorless thick oil and 7.15 g (14%) of *N*-[2-(2-hydroxyethoxy)ethyl]-4-methylbenzenesulfonamide as a colorless thick oil. Compound **3**: n^{20}_D 1.5219; IR (film) (cm^{-1}) 3400, 1335, 1155, 1120, 1085, 1060; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.00 (br s, 2 H, D_2O exchange), 3.25–3.80 (m, 16 H), 7.20 and 7.60 (AA'XX', q, 4 H). *N*-[2-(2-Hydroxyethoxy)ethyl]-4-methylbenzenesulfonamide: n^{20}_D 1.5306; IR (film) (cm^{-1}) 3400, 1325, 1155, 1120, 1085, 1060; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.9 (br s, 1 H, D_2O exchange), 3.15 (q, 2 H), 3.30–3.85 (m, 6 H), 6.1 (t, 1 H, D_2O exchange), 7.20 and 7.60 (AA'XX', q, 4 H).

6-[(4-Methylphenyl)sulfonyl]-3,9-dioxa-6-aza-1,11-undecanediol Bis(methanesulfonate) (4). Methanesulfonyl chloride (13.74 g, 0.12 mol) was added in 30 min to a solution of 18.7 g

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(0.054 mol) of **3** in 80 mL of pyridine, the temperature being kept below 0 °C. The reaction mixture was maintained at 0 °C for a further 2 h and then left overnight in the refrigerator. The mixture was poured into 200 g of ice and 100 mL of 37% aqueous HCl, extracted with CH_2Cl_2 (3 × 80 mL), washed with brine (2 × 50 mL), and dried over $MgSO_4$. Evaporation of the solvent afforded 26.2 g (96%) of **4** as a thick oil: ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 3.06 (s, 6 H), 3.40 (t, 4 H), 3.60–3.87 (m, 8 H), 4.25–4.41 (m, 4 H), 7.20 and 7.60 (AA'XX', q, 4 H).

10-Benzyl-4-[(4-methylphenyl)sulfonyl]-1,7-dioxa-4,10-diazacyclododecane (5). A mixture of 63.4 g (0.126 mol) of **4**, 13.5 g (0.126 mol) of benzylamine, and 40.1 g (0.378 mol) of anhydrous Na_2CO_3 in 1200 mL of MeCN was refluxed for 40 h with vigorous stirring. The reaction mixture, cooled at room temperature, was filtered; the solid precipitate was washed with CH_2Cl_2 (2 × 100 mL) and the solvent evaporated in vacuo. The oily residue was stirred at room temperature with 100 mL of EtOH, affording 34.0 g of a white solid. After crystallization from CH_2Cl_2–*n*-hexane, 26.9 g (51%) of pure **5** was obtained: mp 92–95 °C; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.70 (t, 4 H), 3.30 (t, 4 H), 3.50 (t, 4 H), 3.65 (s, 2 H), 3.85 (t, 4 H), 7.15–7.35 (m, 7 H), 7.65 (d, 2 H). After evaporation of the crystallization solvent, the residue was crystallized twice from EtOH, affording 2.5 g (4.7%) of **6**: mp 128–130 °C; ^1H NMR ($CDCl_3$) δ 2.35 (s, 6 H), 2.65 (t, 8 H), 3.20–3.70 (m, 28 H), 7.00–7.25 (m, 14 H), 7.40 (d, 4 H); mass spectrum, *m/z* 836 (M^+).

4-Carbethoxy-10-[(4-methylphenyl)sulfonyl]-1,7-dioxa-4,10-diazacyclododecane (8). A solution of 8.68 g (0.080 mol) of ethyl chloroformate in 20 mL of anhydrous THF was added within 20 min to a stirred solution of 16.74 g (0.040 mol) of **5** in 80 mL of THF. The reaction mixture was heated to 60 °C and stirred for a further 2 h. The small amount of a light white precipitate formed was filtered over Celite. Evaporation of the solvent and treatment of the residue with petroleum ether (100 mL) afforded 14.4 g (90%) of **8** as a white solid: mp 89–92 °C; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.45 (s, 3 H), 3.25–3.80 (m, 16 H), 4.10 (q, 2 H), 7.20 and 7.60 (AA'XX', q, 4 H).

4-[(4-Methylphenyl)sulfonyl]-1,7-dioxa-4,10-diazacyclododecane (7). Method A. A sample of 33.48 g (0.080 mol) of **5** dissolved in 250 mL of EtOAc was hydrogenated for 24 h at room temperature in the presence of 6.6 g of 10% Pd/C. Filtration of the catalyst and evaporation of the solvent in vacuo afforded **7** as a white solid in quantitative yield: mp 108–110 °C (EtOAc); ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.65 (s, 1 H, D_2O exchange), 2.8 (t, 4 H), 3.25 (t, 4 H), 3.40–3.65 (m, 8 H), 7.20 and 7.60 (AA'XX', q, 4 H).

Method B. A solution of 13.7 g (0.342 mol) of NaOH in 30 mL of H_2O was added to a solution of 13.7 g (0.0342 mol) of **8** in 150 mL of EtOH. The reaction mixture was stirred and refluxed for 3 days. The solvent was evaporated, and the residue was taken up with 100 mL of H_2O. This mixture was cooled to 0 °C with an ice bath, and with vigorous stirring, concentrated HCl was slowly added until the pH was <1. The aqueous phase was extracted with Et_2O (2 × 80 mL), and it was then made alkaline with aqueous 30% NaOH and extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated to give 11.3 g of a slightly beige solid, which was treated with isopropyl ether, affording 10.05 g (89%) of **7**.

Diethyl 2-Hexadecylpropane-1,3-dicarboxylate (9b). A mixture of 3.2 g (0.020 mol) of diethyl malonate, 9.15 g (0.030 mol) of hexadecyl bromide, 8.28 g (0.060 mol) of K_2CO_3, and 0.322 g (0.001 mol) of tetrabutylammonium bromide in 60 mL of MeCN was stirred and refluxed for 3 days. After cooling to room temperature, the mixture was filtered, the solid precipitate carefully washed with CH_2Cl_2, and the solvent evaporated. The residue was dissolved in 100 mL of CH_2Cl_2, washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and evaporated to afford 13.17 g of crude product. Column chromatography (silica gel, petroleum ether–Et_2O) afforded 7.33 g (95%) of **9b** as a colorless thick oil: IR (film) ν_{CO} 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–2.20 (m, 36 H), 3.30 (t, 1 H), 4.20 (q, 4 H).

2-Benzylpropane-1,3-diol (10a). A solution of 25.0 g (0.1 mol) of diethyl 2-benzylpropane-1,3-dicarboxylate in 70 mL of Et_2O was added to a stirred suspension of 5.3 g (0.14 mol) of $LiAlH_4$ in 50 mL of Et_2O at a rate so as to maintain a gentle reflux of the solvent. The reaction mixture was stirred at room temperature for an additional 2.5 h. The excess of $LiAlH_4$ was destroyed with EtOAc and H_2O. The precipitated hydroxides were dissolved with 100 mL of aqueous 10% H_2SO_4, and the organic phase was separated. The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phase was dried over $MgSO_4$ and the solvent evaporated to afford 17.6 g of crude product. Column chromatography (silica gel, Et_2O) gave 12.0 g (72%) of **11** as a white solid: mp 66–68 °C (lit.[23] mp 68–70 °C); ^1H NMR ($CDCl_3$) δ 1.95–2.25 (m, 1 H), 2.65 (d, 2 H), 3.10 (br s, 2 H, D_2O exchange), 3.50–3.95 (m, 4 H), 7.25 (m, 5 H).

2-Hexadecylpropane-1,3-diol (10b) was prepared from **9b**, as described for **10a**, in 91% yield: mp 82–84 °C; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H); 1.10–1.20 (m, 31 H); 2.20 (br s, 2 H, D_2O exchange), 3.50–3.90 (m, 4 H).

2-Benzylpropane-1,3-diol Bis(4-methylbenzenesulfonate) (11a). A solution of 30.22 g (0.159 mol) of *p*-toluenesulfonyl chloride in 70 mL of pyridine was added dropwise to a stirred solution of 12.0 g (0.072 mol) of **10a** in 50 mL of pyridine, the temperature being kept below 0 °C. The reaction mixture was stirred at 0 °C for a further 4 h and left overnight in the refrigerator, and then it was poured into ice-cold aqueous 3 N HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL); the organic phase was washed with water (2 × 100 mL), dried over $MgSO_4$, and evaporated to afford 33.8 g of a solid crude product, which was crystallized from 130 mL of absolute EtOH to give 28.5 g (83%) of **11a** as a white solid: mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 2.00–2.65 (m, 9 H), 3.75–4.10 (m, 4 H), 6.80–7.40 (m, 9 H), 7.80 (d, 4 H).

2-Hexadecylpropane-1,3-diol Bis(4-methylbenzenesulfonate) (11b). A solution of 12.35 g (0.065 mol) of *p*-toluenesulfonyl chloride in 30 mL of CH_2Cl_2 was added, at room temperature and within 30 min, to a stirred solution of 6.5 g (0.022 mol) of **10b** and 10.9 g (0.108 mol) of Et_3N in 100 mL of CH_2Cl_2. The reaction mixture was stirred overnight at room temperature, and then it was washed with aqueous 3 N HCl (2 × 50 mL) and with water (2 × 100 mL) and the organic phase dried over $MgSO_4$. Evaporation of the solvent afforded 17.3 g of crude product as a thick oil. Column chromatography (silica gel, petroleum ether–Et_2O) afforded 11.2 g (85%) of **11b** as a white solid: mp 50–51 °C; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–2.20 (m, 31 H), 2.50 (s, 6 H), 3.95 (d, 4 H), 7.20 and 7.60 (AA'XX', q, 8 H).

4,4'-(2-Benzyl-1,3-propanediyl)bis[10-[(4-methylphenyl)-sulfonyl]-1,7-dioxa-4,10-diazacyclododecane] (12a). A mixture of 9.24 g (0.028 mol) of **7**, 6.68 g (0.014 mol) of **11a**, and 14.95 g (0.140 mol) of Na_2CO_3 in 200 mL of MeCN was stirred and refluxed for 4 days. After cooling at room temperature, the reaction mixture was filtered, the precipitate carefully washed with CH_2Cl_2, and the solvent evaporated. The residue was dissolved in 200 mL of CH_2Cl_2 and washed with water (2 × 100 mL). Evaporation of the solvent and crystallization from EtOH afforded 10.3 g (93%) of **12a** as a white solid: mp 134–137 °C; ^1H NMR ($CDCl_3$) δ 2.20–2.80 (m, 21 H), 3.30 (t, 8 H), 3.80 (t, 8 H), 7.00–7.70 (m, 13 H).

4,4'-(2-Hexadecyl-1,3-propanediyl)bis[10-[(4-methylphenyl)sulfonyl]-1,7-dioxa-4,10-diazacyclododecane] (12b) was prepared from **11b** and **7** as described for **12a** in 75% yield: mp 113–115 °C; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.00–2.20 (m, 34 H), 2.20–2.50 (m, 10 H), 2.65 (t, 8 H), 3.30 (t, 8 H), 3.50 (t, 8 H), 3.85 (t, 8 H), 7.20 and 7.60 (AA'XX', q, 8 H).

4,4'-(2-Benzyl-1,3-propanediyl)bis(1,7-dioxa-4,10-diazacyclododecane) (13a). A solution of 9.44 g (0.012 mol) of **12a** in 100 mL of anhydrous THF was slowly added to a stirred suspension of 4.56 g (0.12 mol) of $LiAlH_4$ in 50 mL of THF in argon atmosphere. The reaction mixture was stirred and refluxed for 60 h. After cooling at room temperature, the excess of $LiAlH_4$ was destroyed by a dropwise addition of 30 mL of THF–H_2O, 2:1 (v/v). The mixture was filtered and the precipitate carefully washed with CH_2Cl_2. Evaporation of the solvent afforded 5.43 g (95%) of **13a** as a thick oil, which was used without further purification: ^1H NMR ($CDCl_3$) δ 2.00–2.80 (m, 23 H), 3.15 (br s, 2 H, D_2O exchange), 3.40–3.60 (m, 16 H), 7.00–7.25 (m, 5 H).

4,4'-(2-Hexadecyl-1,3-propanediyl)bis(1,7-dioxa-4,10-diazacyclododecane) (13b) was obtained as a thick oil in 96% yield

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by following the procedure described for **13a**: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.20–1.80 (m, 30 H), 2.00–2.90 (m, 23 H), 3.40–3.70 (m, 16 H).

[Na ⊂ 1a]$^+$ClO$_4^-$ (2a). Sodium-Templated Synthesis. A mixture of 5.43 g (11.3 mmol) of **13a**, 4.18 g (11.3 mmol) of diethylene glycol bis(*p*-toluenesulfonate), and 12.0 g (113 mmol) of Na_2CO_3 in 150 mL of MeCN was stirred and refluxed for 4 days. After cooling at room temperature, the reaction mixture was filtered, the precipitate was carefully washed with CH_2Cl_2, and the solvent was evaporated to dryness. The residue was dissolved in 100 mL of CH_2Cl_2 and stirred for 2 h with a solution of 6.1 g (50 mmol) of $NaClO_4$ in 30 mL of H_2O. The organic phase was evaporated and the residue purified by column chromatography (silica gel, $CHCl_3$–MeCN), affording 4.4 g (62%) of **2a** as a white solid: mp 244–246 °C. ^{1}H and ^{13}C NMR characterization of **2a** has been reported in ref 13.

Lithium-Templated Synthesis. Diethylene glycol bis(*p*-toluenesulfonate) and **13a** were reacted as described above by using Li_2CO_3 and $LiClO_4$. After column chromatography, a mixture of complexes [Li ⊂ **1a**]$^+$ClO$_4^-$ and **2a** in roughly 2:8 ratio (determined by ^{13}C NMR) was obtained in 32% yield. The mixture dissolved in $CHCl_3$ was stirred for 2 h with a large excess of a saturated aqueous $NaClO_4$ solution, quantitatively affording pure **2a**.

Potassium-Templated Synthesis. Diethylene glycol bis(*p*-toluenesulfonate) and **13a** were reacted, as described above, by using K_2CO_3 as a base. The crude product was treated with aqueous KPF_6 instead of $KClO_4$, which is slightly soluble in H_2O, and purified by column chromatography. A mixture of complexes [K ⊂ **1a**]$^+$PF$_6^-$ and [Na ⊂ **1a**]$^+$PF$_6^-$ in roughly 4:6 ratio (determined by ^{13}C NMR) was obtained in 38% yield. The mixture dissolved in $CHCl_3$ was stirred for 2 h with a large excess of a saturated aqueous $NaClO_4$ solution, quantitatively affording pure **2a**.

[Na ⊂ 1b]$^+$ClO$_4^-$ (2b) was prepared from **13b** as described in the sodium-templated synthesis of **2a**, in 66% yield: mp 180–182 °C. ^{1}H and ^{13}C NMR characterization of **2b** has been reported in ref 9.

[Na ⊂ 1a (or 1b)]$^+$X$^-$ (X = I, Br, Cl) by Anionic Exchange Starting from 2a (or 2b). General Procedure. A solution of the appropriate sodium salt (15 mmol) in MeOH was added to a stirred solution of 3 mmol of **2a** (or **2b**) in 50 mL of MeOH. The mixture was stirred at room temperature for 1 h and the solvent evaporated in vacuo. The residue was dissolved in 80 mL of CH_2Cl_2, filtered, and evaporated. This procedure was repeated three to 10 times, depending on the anion. Column chromatography (silica gel; $CHCl_3$–MeCN) of the crude complexes afforded compounds whose purity (95–100%) was tested by potentiometric titration of the halide ion.

12-Hexadecyl-7,17,22,27-tetraoxa-1,4,10,14-tetraazatricyclo[12.5.5.5^{4,10}]nonacosane (1b). A sample of 100 mL of a 0.5 M solution of KF (or KOMe) in MeOH was added to a stirred solution of 12.2 g (16 mmol) of **2b** in 150 mL of MeOH, immediately giving a precipitate of $KClO_4$, which was filtered. This procedure was repeated two more times. The full conversion of **2b** into the corresponding fluoride (or methoxide) was checked by TLC. The volume of the final solution was reduced to 50 mL by evaporation, and the concentrated solution was transferred into an apparatus for liquid–liquid extraction by upward displacement. After addition of 150 mL of 10% aqueous KF (or KOH), the resulting solution was continuously extracted at 50 °C with *n*-hexane over 2 days. Evaporation of the solvent afforded 9.75 g (93%) of **1b** as a white solid: mp 79–80 °C (MeOH). ^{1}H and ^{13}C NMR characterization of **1b** has been reported in ref 13.

12-Benzyl-7,17,22,27-tetraoxa-1,4,10,14-tetraazatricyclo[12.5.5.5^{4,10}]nonacosane (1a). Starting from **2a**, the same procedure used for **1b** gave, after 14 days, **1a** in 67% yield: mp 94–96 °C (*n*-pentane).

[K ⊂ 1b]$^+$PF$_6^-$. A solution of 208 mg (1.13 mmol) of KPF_6 in 5 mL of MeOH–H_2O, 4:1 (v/v), was added to a stirred solution of 723 mg (1.13 mmol) of **1b** in 8 mL of MeOH–$CHCl_3$, 1:1 (v/v). After evaporation of the solvent, the solid residue was crystallized from MeOH, affording 614 mg (66%) of the complex as a white solid: mp 133–135 °C.

Determination of Extraction Constants (K_{ex}) of Alkali Halides by 1b. Into a 20-mL centrifuge tube were introduced 5.0 mL of a 5×10^{-2} M solution of **1b** in $CHCl_3$, 5.0 mL of a 5×10^{-2} M aqueous solution of the appropriate alkali halide, and a small magnetic stir bar. The tube, stoppered to prevent evaporation, was stirred for 24 h at 20 °C and then centrifuged at 3000 rpm for 10 min. A 1.0-mL aliquot of the aqueous layer was diluted with 40 mL of H_2O, acidified with 1 mL of 6 N HNO_3, and potentiometrically titrated with 1×10^{-2} N aqueous $AgNO_3$. Extraction constants (K_{ex}),

$$K_{ex} = \frac{[(M \subset \mathbf{1b})^+X^-]_{CHCl_3}}{[M^+]_{H_2O}[X^-]_{H_2O}[\mathbf{1b}]_{CHCl_3}}$$

were calculated from the halide concentration in the aqueous phase $[X^-]_{H_2O}$ at the equilibrium:

$$[X^-]_{H_2O} = [M^+]_{H_2O}$$

$$[(M \subset \mathbf{1b})^+X^-]_{CHCl_3} = [X^-]^0_{H_2O} - [X^-]_{H_2O}$$

$$[\mathbf{1b}]_{CHCl_3} = [\mathbf{1b}]^0_{CHCl_3} - [(M \subset \mathbf{1b})^+X^-]_{CHCl_3}$$

where $[X^-]^0_{H_2O}$ and $[\mathbf{1b}]^0_{CHCl_3}$ are the initial concentrations. Results are reported in Table I.

Extractions of NaI were carried out with 5×10^{-3} M aqueous and organic solutions, and titrations were performed with 1×10^{-3} N aqueous $AgNO_3$. After 48-h equilibration, the I^- concentration was less then 5×10^{-4} M, thus indicating $K_{ex} > 10^7$.

Hydrogen–Deuterium Exchange of Diphenylmethane under Liquid–Liquid Phase-Transfer Conditions Catalyzed by 1b. A mixture of 84.1 mg (0.5 mmol) of diphenylmethane, 1.0 mL of 40% NaOD in D_2O, and 50.5 mg (0.1 mmol) of **1b** was stirred at 70 °C for 5 h. After addition of 2 mL of H_2O and acidification with 3 N HCl, the mixture was extracted with CH_2Cl_2. Drying over $MgSO_4$ and evaporation of the solvent gave a residue, which was dissolved in 0.5 mL of $CDCl_3$. ^{1}H NMR analysis showed the 50% deuteriation of the diphenylmethane CH_2 signal.

Hydroxide Ion Initiated Oxidations under Liquid–Liquid Phase-Transfer Conditions Catalyzed by 1b. A mixture of 1 mmol of the appropriate substrate (neat or in chlorobenzene solution), 2 mL of 40–63% NaOH, and 0.05–0.2 molar equiv of **1b** was stirred in an oxygen atmosphere. Reactions were followed by GLC, and the results obtained are reported in Table III.

X-ray Crystallographic Analysis of 2a. Crystal data of **2a** are collected in Table IV. Diffraction intensies were measured on a Enraf-Nonius CAD4 diffractometer by using graphite-

Table IV. Crystal Data of 2a

formula	$C_{28}H_{48}ClN_4NaO_8$
formula wt	627.16
cryst system	monoclinic
a, Å	9.906 (2)
b, Å	10.150 (2)
c, Å	15.900 (2)
α, deg	–
β, deg	94.60 (1)
γ, deg	–
V, Å^3	1593.5
Z, ρ (calcd), g cm^{-3}	2, 1.307
space group	$P2_1$ (No. 4)
F(000)	672
radiation (graphite monochr)	Mo Kα (0.710 73)
diffractometer	Enraf-Nonius CAD4
μ(Mo Kα), cm^{-1}	1.81
2θ range, deg	$6 < 2\theta < 50$
scan method	ω
scan interval, deg	$0.90 + 0.347 \tan \theta$
scan speed, deg min^{-1}	1.0
collected octants	$\pm h,k,l$
no. of data collected (at room temperature)	2861
no. of data used ($I > 0$)	2373
crystal decay	no decay
crystal size, mm	0.34 × 0.19 × 0.06
weighting fudge p factor	0.030
R	0.126
R_w	0.065
GOF	1.367
no. of variable parameters	378
max peak in final diff Fourier, e A^{-3}	0.460

monochromatized Mo Kα radiation (λ = 0.71073 Å). A total of 2861 reflections was collected up to 2θ = 50°, among which 2373 were observed reflections.

The crystal structure was solved by the direct method (MULTAN)[24] and refined by the full-matrix least-squares method to the R_w index of 0.065.

The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were made ride at fixed C–H bond distances (0.95 Å) with fixed thermal parameters.

All the computations were performed on a PDP 11/34 computer by using the Enraf-Nonius Structure Determination Package (SDP) and the physical constants therein tabulated,[25] with ORTEP[26] being used for drawings.

(24) MULTAN, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (Germain, G.; Main, P.; Woolfson, M. M., *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1971**, *A27*, 368).

(25) SDP Plus, Version 1.0, from Enraf-Nonius, Delft, Holland, 1980.

(26) A Fortran thermal-ellipsoid-plot program for crystal-structure illustrations (Johnson, C. K. ORTEP; Oak Ridge National Laboratory: Oak Ridge, TN, 1971).

Registry No. **1a**, 115942-17-1; **1b**, 110668-29-6; **2a**, 96528-90-4; **2b**, 96528-89-1; **3**, 72358-83-9; **4**, 80639-61-8; **5**, 80639-62-9; **6**, 115942-18-2; **7**, 96563-15-4; **8**, 96563-14-3; **9a**, 607-81-8; **9b**, 41433-81-2; **10a**, 2612-30-8; **10b**, 91662-77-0; **11a**, 86103-46-0; **11b**, 96563-16-5; **12a**, 96563-18-7; **12b**, 96563-17-6; **13a**, 96563-20-1; **13b**, 96563-19-8; [Li ⊂ **1a**]$^+ClO_4^-$, 115942-20-6; [K ⊂ **1a**]$^+PF_6^-$, 115960-11-7; [Na ⊂ **1a**]$^+I^-$, 96528-95-9; [Na ⊂ **1a**]$^+Br^-$, 116003-24-8; [Na ⊂ **1a**]$^+Cl^-$, 96528-96-0; [Na ⊂ **1a**]$^+PF_6^-$, 116003-25-9; Li^+, 17341-24-1; Na^+, 17341-25-2; K^+, 24203-36-9; Rb^+, 22537-38-8; Cs, 18459-37-5; 2-(2-chloroethoxy)ethanol, 628-89-7; *p*-toluenesulfonamide, 70-55-3; diethyl malonate, 105-53-3; hexadecyl bromide, 112-82-3; diethylene glycol bis(*p*-toluenesulfonate), 7460-82-4; benzylamine, 100-46-9; diphenylmethane, 101-81-5.

Supplementary Material Available: The fractional atomic coordinates (Table V), the anisotropic thermal factors (Table VI), and the computed positions of the hydrogen atoms for the structure of **2a** (Table VII) (6 pages). Ordering information is given on any current masthead page.

Reactions of Trimethylsilyl Isocyanate and Isothiocyanate with 3-(Dialkylamino)-2*H*-azirines. A Facile Synthesis of 1-Unsubstituted 4-(Dialkylamino)imidazolin-2-ones and 4-(Dialkylamino)imidazoline-2-thiones[1]

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The reaction of azirines **3a,b,d,e** with trimethylsilyl isocyanate (**4**) or isothiocyanate (**5**) gives imidazolinones **6a,b,e** and thiones **7a,b,d,e**, respectively. However, in an alternate reaction course, azirine **3c** leads to amidinium salts **9**. The potential of the products for chemical modification is shown by hydrolysis of **7a** to give **12** and by the oxidative desulfurization of **7a,d** to furnish **6a,d**.

Introduction

A variety of synthetic approaches to hydantoins and related compounds have been devised.[2] Because of the therapeutic value of some 5,5-diarylhydantoins[3] and the 2-thio analogues,[4] we report here a new approach to some 5-substituted hydantoin derivatives using the cycloadditon of 3-(dialkylamino)-2*H*-azirines **3** with trimethylsilyl isocyanate (**4**) and isothiocyanate (**5**). Previous investigations on the reaction of the highly nucleophilic azirines **3** with alkyl,[5] phenyl,[6] or tosyl isocyanate[7] or with isothiocyanates[8] had provided a host of heterocyclic systems, resulting from opening of either the 1,2- or the 1,3-bond in **3**.

(1) Part 9 in the series "Heterocyclic Ring-Closure Reactions." Part 8: Khattak, I.; Ketcham, R.; Schaumann, E.; Adiwidjaja, G.; *J. Org. Chem.* **1985**, *50*, 3431.

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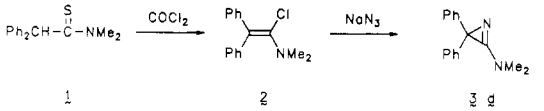
Results and Discussion

Azirines **3a–d** were prepared from the chloro enamines and sodium azide according to the method of Ghosez.[9] The carbamoyl azirine **3e** was prepared by the photolysis of the isoxazole following Viehe's method.[10,11] Only the diphenyl azirine **3d** had not been previously reported and was prepared from thioamide **1** via the chloro enamine **2** by the following reaction sequence.



1 2 3 d

In contrast to other chloro enamines **2** and 2,2-disubstituted azirines **3** the diphenyl compounds **2**, **3d** were both solids. Azirine **3d** gave the typical IR band at 1775 cm^{-1} associated with the amidine moiety.[9] Because of its reactivity and sensitivity to moisture, the chloro enamine was not fully characterized but was reacted after distillation with sodium azide to give the azirine **3d**.

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